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AVERAGE EVOKED POTENTIALS

Methods, Results, and Evaluations

A conference held at

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AVERAGE EVOKED POTENTIALS

Methods, Results, and Evaluations

Edited by

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A conference organized by the American Institute of Biological Sciences under the sponsorship of the Behavioral Biology Program of the National Aeronautics and Space Administration, and held at San Francisco, California, September 10–12, 1968.

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Foreword

THIS DOCUMENT presents the proceedings of a conference sponsored by the National Aeronautics and Space Administration and the American Institute for Biological Sciences. The conference was held in San Francisco in September 1968 to discuss current problems in the study of average evoked potential. As can be seen from the list of participants, most laboratories, in this country and abroad, that actively use signal-averaging techniques in processing electroencephalographic records were represented at the conference. Our objective in organizing this conference was to provide a forum for discussing the problems involved in conducting these studies and in communicating the results of experiments.

For this purpose, the conference was organized in the following format. Six investigators were invited to prepare critical reviews of the literature—each on one of six assigned topics. The reviews were made available to all the conference participants 4 to 6 weeks before the conference. Each review was to serve as the text for one 3-hour session at the conference. The reviewer was allotted 20 minutes to restate some of the main points presented in his paper; then discussion was opened to all participants. The discussions were moderated in each case by an assigned discussant.

Chapters 2 through 7 present the review papers and the ensuing discussion. The remarks made by the reviewer were deleted since their substance is presented in the review.

All the principal speakers completed their assignment on time, and the reviews were sent to the participants. However Dr. Vaughan's report, as included in this volume, is substantially different from the document that he circulated to the participants. For this reason, the discussants ignore much of the material presented in his present chapter.

In addition to the working sessions of the conference, two evening sessions featured extended presentations. In the first one, Dr. Lindsley surveyed the evoked potential technique, its history, and achievements; in the second one, Dr. Frank Morrell discussed the neurophysiological mechanisms underlying the average evoked response. Dr. Lindsley's talk provided the material for Chapter 1. A supplement contains

reports that were submitted by participants to expand and elaborate upon some of the comments they made in the discussion.

The conference would not have been possible without the support of the Office of Space Science and Applications, NASA Headquarters and Dr. Orr Reynolds. Dr. Norman Weissman of NASA Headquarters was instrumental in providing support, both in the organization of the conference and in the publication of the Proceedings. His patience and understanding are deeply appreciated. Ames Research Center, where at the time I held a National Research Council Resident Research Associateship, provided much necessary help. Dr. Jorge Huertas was especially considerate. The organization of the conference down to the last detail was in the very capable hands of Mrs. Mary-Frances Thompson of the American Institute of Biological Sciences. Special thanks are due her for the magnificent job she has done.

Since we have deleted all the chairman's non-technical remarks, the Proceedings fail to underline the able chairmanship provided by Dr. D. B. Lindsley, who ran the meetings and regulated the discussions with a sage and firm hand.

In the preparation of these Proceedings, a great service was provided by Mrs. Pat Walter of the UCLA Brain Information Service, who verified most of the references. The BIS, however, is not responsible for any errors since many references were added to the list after their verification. My personal thanks are gratefully extended to my assistant, Miss Janice McMillin, whose help was exceedingly important in the preparation of this volume.

Finally, I would like to thank all the participants in the conference for their interest and help.

EMANUEL DONCHIN
NASA Ames Research Center

April 1969

Preface

AN UNDERSTANDING of the neural mechanisms underlying behavior has been of continuing interest to NASA. The ability to perform tasks during space flight depends ultimately on the capability of the nervous system to perform its vital control functions in the space environment. Thus, the influence of weightlessness and other spacecraft environmental variables on the central nervous system must be assessed carefully and thoroughly. Furthermore, techniques must be devised whereby the level of functioning of the nervous system can be assessed during flight without unduly interfering with the subject.

The electroencephalogram (EEG) has provided useful information on the state of the central nervous system in the clinical situation. The application of averaging techniques to the EEG may greatly expand its use. The average potential of the nervous system allows the evaluation of the neural responses to specific stimuli in human subjects with a minimum amount of interference with the subject. As such it has no equivalent.

Since averaging devices have become commonly available, the studies of the average evoked potential (AEP) have burgeoned, much of it with the support of NASA. The bibliography to this volume indicates that hundreds of papers have now appeared on this subject, and numerous laboratories are actively engaged in this research. As can be expected when investigators move into a new area of research, the literature is replete with different terminology and general differences in approach. This has made it difficult to compare, evaluate, and digest usefully much of this research.

Several investigators believed that the time was right to convene a meeting of evoked-response investigators to try to achieve a comprehensive picture of the state of the art, and to try to define the applications of this technique, as well as the pitfalls that must be avoided. Furthermore, a measure of uniformity in interlaboratory communication was sorely needed. The present volume summarizes the ensuing conference as a statement of the status of the evoked-potential research.

NORMAN W. WEISSMAN
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Acronyms

Average evoked potential reports are replete with acronyms. This book is no exception. The independent spirit of the participants in this conference has made it impossible to impose a uniform usage on all the reports. To assist the reader we have spelled out each acronym on its first appearance in a given context. A list of the acronyms defined is provided here.

AEP—Average Evoked Potentials
AER—Auditory Evoked Response
CNV—Contingent Negative Variation
EP—Evoked Potentials
EAP—Eye Artifact Potentials
EEG—Electroencephalogram
EKG—Electrocardiogram
ERG—Electroretinogram
ERP—Event-Related Potentials
EMG—Electromyogram
EOG—Electrooculogram
GSR—Galvanic Skin Response
MP—Motor Potential
RP—Readiness Potential
SEP—Somatic Evoked Potential
SER—Somatic Evoked Response
SPS—Steady Potential Shifts
VER—Visual Evoked Response
VEP—Visual Evoked Potential

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Welcoming Remarks

JORGE HUERTAS
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YOU ARE congregated here as members of a highly sophisticated group to discuss a subject that rates a very high priority in your interests. You are here to discuss, during the next 2 days, your current work on the evoked potentials of the electroencephalogram. It is my privilege to welcome you to this symposium on behalf of the National Aeronautics and Space Administration.

During this last decade, man has succeeded in escaping the physical constants that characterize his living and evolving milieu; the fleeting moments spent by man in the new environment have demonstrated his capability to survive, at least temporarily, in outer space. Also during this last decade, he has succeeded in sending automated man-made objects to Earth's immediate neighbors—the moon, Venus, and Mars. As a consequence of these two achievements—traveling in space and sending utensils to the planets—the enticement of getting there is a strong challenge to humanity.

The exploration of space has presented man with the possibility of looking upon himself from a new perspective, as well as the possibility of studying Earth from distant places at other evolutionary stages. The present-day status of science and technology is ripe for such an endeavor.

Next to survival, man's main concern has been to understand himself and to be able to attribute to himself a role in the universe. Today the challenge of space gives him the opportunity to travel to new frontiers. But this opportunity has also reminded him that he is an organism ecologically bound to Earth and more delicate than his own rockets, but more versatile than his own computers. For the exploration of space, evoked potentials are a unique method of studying the performance of the brain. They can be correlated with many variables such as intrinsic functions, metabolic functions, and behavioral patterns. The method to be discussed permits the correlation of the three main components that contribute to the information process of an organism—

the sensory input, the central neural processing expressed as an electrical potential (the evoked potential), and the performance of the organism.

The advances in methods and knowledge for the study of perception, conditioning, and learning have opened the door for more refined studies, such as the relationships between arousal and learning or vigilance and attention. The use of several species to obtain a more precise knowledge of the phenomena previously cited is mandatory, and a comparison of data from different species will be part of your deliberations. The differences in encephalization of cats, monkeys, and humans can be used, so to speak, as a dissection for the comparison of brain functions at different stages of phylogenesis.

Your interest in this subject assures your permanent attention during the symposium. Your suggestions concerning how evoked potentials can be used adequately as a means of studying the basic mechanisms of neuronal and brain performance as well as their permanence during space flight will be of importance to NASA. Your suggestions concerning how to continue using evoked potential techniques as a means of advancing further the understanding of the brain will fulfill the goal of this research applicable to space and will also be pertinent to scientific, industrial, and humanitarian purposes.

We hope that, at the end of this symposium, you consider that the time spent here was worthwhile and that you return to your laboratories with new enthusiasm and new ideas. The symposium proceedings will be the subject of a NASA Special Publication, the success of which is in your hands because its contents will be your contributions. The caliber of the invitees makes it easy to predict that this meeting will be a success.

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CHAPTER 1

Average Evoked Potentials—Achievements, Failures and Prospects

DONALD B. LINDSLEY
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DR. BRAZIER and guests: It is a great pleasure for me to welcome you to this meeting. I hope that at the end you will all feel well repaid for coming, and I believe that you will. Let me say at once that it was Dr. Emanuel Donchin, a former student and colleague of mine, who brought all of you here and that it was he who organized this program. I have been mainly an interloper sitting on the sideline, consulting a bit about it here and there. I find this workshop idea—a kind of question-and-answer procedure, in which we can informally try to find solutions to problems that bother us, or bring up problems that we feel others may be bothered by—very attractive.

We are all highly indebted to Dr. Orr E. Reynolds, Director, Biosciences Programs, NASA Headquarters in Washington, and to Dr. Norman W. Weissman, a member of his staff, who gave their enthusiastic sanction and support to this program and the publication of the proceedings. We also owe our sincere appreciation to Mrs. Mary-Frances Thompson of the American Institute of Biological Sciences, who through AIBS–NASA liaison has been very busy corresponding with many of you about this meeting and in making detailed arrangements for these sessions here in San Francisco.

My presentation this evening will be anything but a formal one. In fact, as you will observe later, I shall attempt to introduce a bit of levity and novelty into this opening session in an effort to prevent it from becoming too august, formal, and boring. I am afraid that I shall

not live up to the title assigned to me by Dr. Donchin, partly because I hesitate to preempt subjects assigned to later speakers and partly because I do not feel qualified to evaluate all that has been done in this field in terms of success and failure.

As I look around, I see that I am probably senior to most of you here, with the exception of Dr. Hallowell Davis, with whom I had the privilege of working at Harvard Medical School (Boston) 35 years ago when brain waves were first being recorded from human subjects in this country, both there and in Dr. Jasper's laboratory in Providence, Rhode Island, only 40 miles away. As you probably know, the first two American publications concerned with the EEG in human subjects appeared in the same year and came from those laboratories (Gibbs, Davis, and Lennox, 1935; Jasper and Carmichael, 1935). In 1933–34, I was working on electromyography in the Harvard laboratories under Hallowell Davis and the late Alexander Forbes, and was simply one of the subjects and an onlooker at these early EEG studies. However, I also knew Dr. Jasper, and he and I had been fellow graduate students under Dr. Lee Edward Travis at the University of Iowa. Hence, I was an occasional visitor to his laboratory at Bradley Hospital and Brown University. In this way, I became acquainted with the EEG work going on in both laboratories more or less concurrently. But I am getting ahead of my story; let me back up a bit.

I started out to say that in view of my age I might use it as a prerogative to review sketchily some of the history of brain potentials. Of course, as we all know, our Madam Chairman, Dr. Brazier, is an authoritative EEG and neurophysiology historian; so I must be careful. However, before coming to more contemporary matters, I would like to take a few brief glimpses backward.

EARLY HISTORY OF EVOKED POTENTIALS AND THE EEG

The first published recordings of evoked potentials were made by Caton (1875) nearly 100 years ago. I want to quote a paragraph from Caton's article because there seems to be ample indication from what he says that he was recording evoked potentials or currents in response to sensory stimulation, and possibly what we now know as spontaneous activity of the brain, or even the contingent negative variation (CNV) first described by Grey Walter (1964a).

> In every brain (of monkey or rabbit) hitherto examined, the galvanometer has indicated the existence of electric currents. The external surface of the grey matter is usually positive in relation to the surface of a section through it. Feeble currents of varying direction pass through the multiplier when the electrodes are placed on two points of the external surface, or one electrode on the grey matter, and one on the surface of the skull. The electric currents of the grey matter appear to have a relation to its function. When any part of the grey matter is in

a state of functional activity, its electric current usually exhibits negative variation. For example, on the areas shown by Dr. Ferrier to be related to rotation of the head and to mastication, negative variation of the current was observed to occur whenever those two acts respectively were performed. Impressions through the senses were found to influence the currents of certain areas; e.g., the currents of that part of the rabbit's brain which Dr. Ferrier has shown to be related to movements of the eyelids, were found to be markedly influenced by stimulation of the opposite retina by light.[1]

Below are some of the principal names of investigators of electrical activity of the brain and the dates of their publications. Following Caton there was a certain amount of work by investigators in Poland, Russia, Austria, and Germany—but nothing of any great significance until Berger (1929), whose monumental first communication and subsequent publications for the next 8 years gave us much of the story that we know today about spontaneous activity of the brain. I am afraid, unfortunately, that we don't know so very much more about the nature of the alpha rhythm or the other rhythms that Berger so ably described in that series of papers.

Some Early Publications On Brain Electrical Activity

Caton (1875)
Fleischl von Marxow (1890)
Beck (1890)
Danilewsky (1891)
Gotch and Horsley (1891)
Beck and Cybulski (1892)
Larinow (1898)
Trivus (1900)
Tchiriev (1904)
Kaufman (1912)
Prawdicz-Neminski (1913)
Cybulski and Macieszyna (1919)
Prawdicz-Neminski (1925)
Berger (1929)
Bartley and Newman (1930)
Bartley and Newman (1931)
Travis and Herren (1931)
Travis and Dorsey (1931)
Davis and Saul (1931)
Adrian (1931)
Adrian and Buytendijk (1931)
Bishop and Bartley (1932)
Travis and Dorsey (1932)
Fischer (1932)
Kornmüller (1932)
Perkins (1933)
Bartley (1933)
Gerard, Marshall, and Saul (1933)

Berger had been working since 1924 to record the human EEG and even before that in attempts to record electrical activity from the brains of animals. Very few people seemed to be aware of his efforts, and those that were paid relatively little attention to his publications (as evidenced by the fact that they did not refer to them) until Adrian and Matthews (1934) confirmed the fact that rhythmic potentials could indeed be recorded from the surface of the human scalp.

Apparently Adrian gradually had become convinced that slow potentials could be recorded from the central nervous system and from isolated insect ganglia although he and other classical neurophysiol-

[1] Caton, R.: The Electric Currents of the Brain. Brit. Med. J., 2, 278, 1875.

ogists of the day seemed reluctant to think of anything occurring in the nervous system other than the well known spike potentials accompanying neural discharges in nerve fibers. Adrian and Buytendijk (1931) recorded rhythmic slow potentials in the isolated brain stem of the goldfish, and Adrian (1931) found rhythmic changes in isolated ganglia of the water beetle. Earlier, Adrian (1930) had published a note on electrical activity in the nervous system of the caterpillar. In the goldfish, they found rhythmic slow potentials in the same frequency range as normal gill slit movements. Adrian (1932), in *The Mechanism of Nervous Action*, had this to say about it, which reflects the gradual change in his thinking and acceptance of the idea that another form of electrical activity other than the classical spike potential could be recorded from central nervous system structures:

> Since impulses cannot pass down nerve fibres without causing potential changes, the existence of a wave might mean no more than the existence of a discharge of impulses in the nerve tracts of the brain stem. But the form of the waves does not suggest that they are built up out of impulse potentials in the nerve fibres. They rise and subside slowly and are often quite free from the very rapid irregularities which would be present in a wave formed by the summation of impulse potentials. They suggest instead a slow change of potential taking place in the nerve cells or dendrites, the duration of the change in each cell being of the same order as the duration of the recorded wave.[2]

EARLY INVESTIGATIONS OF BRAIN POTENTIALS IN THE USA

What is little known and even less acknowledged (referring again to the previous list of early contributors) is the fact that in America some studies of electrical activity in the brain of animals were going on about the time Berger published his initial study of the human EEG. In Travis' laboratory at the University of Iowa, studies had been in progress since 1927 in which reflex time in humans and animals had been studied by electromyography. An excellent recording instrument (Westinghouse mirror oscillograph), with high-frequency capabilities but low sensitivity, was used with amplifiers having a transformer-coupled input and output. This was adequate for muscle potentials, but of course did not pass the slow, low-frequency potentials of the type Berger had been recording. At about that time, through annual visitations of Professor Raymond H. Wheeler to the Iowa campus during the summer sessions, Bartley, then a graduate student in psychology at the University of Kansas, became acquainted with the type of apparatus Travis and his colleagues were using and obtained a Westinghouse oscillograph and built his own amplifiers (also with a transformer-coupled input). Bartley and Newman (1930a, b), fel-

[2] Adrian, E. D.: The Mechanism of Nervous Action. Philadelphia: University of Pennsylvania Press, 1932, pp. 82–83.

low graduate students at Kansas, then published the first two notes concerned with cerebral potentials in the dog, followed by more extensive studies (Bartley and Newman, 1931; Bartley, 1933a, b; also Perkins, 1933).

Travis and his associates at Iowa, following their interest in reflex activity, began to explore the electrical activity of the brain in search of higher level reflex manifestations in the dog and rat (Travis and Herren, 1930, 1931; Travis and Dorsey, 1931, 1932). Variations in the background high-frequency activity were found to be associated with sensory stimulation, reflex elicitation, and motor activity; however, little of significance could be interpreted from these records, and there were no slow potential changes observed because the transformer-coupled input and output passed only the higher frequencies. In none of these studies was there reference to the work of Berger; therefore, it seems apparent that they were not aware of his published work at that time. The same was true of the early studies of Davis and Saul (1931) and Saul and Davis (1933). These investigators, following up the Wever-Bray effect recorded in the eighth nerve, began to push on into the brain stem and more rostral regions of the auditory pathways, including the cortex, in search of auditory potentials. Although these investigators used resistance-capacity-coupled amplifiers without transformer-coupled input and output, their goal seemed mainly to determine how well auditory pathways in the brain responded to higher frequencies of stimulation. From the limited records presented, it appears that they found evoked potentials to auditory stimulation within the auditory pathways of the brain stem, and they reported similar effects in auditory radiations and cortex. If, indeed, there were any slow-wave manifestations, they didn't mention them, nor did they comment on the slower-than-spike potential characteristics of the evoked potentials.

It is interesting that in all of these early studies, except for Berger's, it was almost an anathema to mention slow-wave activity—if indeed any had been observed—so fixed was the idea that the only electrical activities that could occur in nervous tissue were spike potentials. This is reflected in an article by Gasser and Graham (1933), who, in studying reflex activity at the spinal cord level beyond the dorsal roots, found that there were slow negative and positive potentials that they rather reluctantly admitted could not be accounted for in terms of classical spike potential phenomena. For want of a better name, and because they could find no reason to include them with nerve after-potentials, they called them intermediary potentials and suggested the internuncial neurones as their probable origin. That they were beginning to think that these slow potentials might represent something

different is indicated in the following quote from the discussion section of their paper:

> The most interesting feature of the cord electrogram is the prolonged potentials which, provided there is sufficient depth of narcosis, present a perfectly smooth contour. Their duration and freedom from oscillations place them in the group of potentials which have from time to time been described as occurring in the central nervous system. Potentials of a duration longer than the spikes of peripheral nerve impulses have been recorded in recent years from the cerebral cortex by Prawdicz-Neminsky, Berger (who reviews the older literature), Bartley and Newman, and Fischer. (Note the first reference to Berger's work in any of these early studies!) As recently described by Bishop and Bartley, the waves in the rabbit have a duration of 30 to 100 sigma (msec) and are free from oscillations. Waves of similar type have been derived from the optic lobes of the goldfish by Adrian and Buytendijk. They have the rhythm of the respiration and durations up to ¼ second. All the authors are in agreement in holding that the waves in question are long potential changes rather than a summation of shorter ones.[3]

SOURCES OF THE EEG

Spontaneous slow rhythms from the brains of animals (rabbit, cat, monkey) as well as localized evoked responses to visual, auditory, and other kinds of sensory stimulation were soon described by Fischer (1932) and Kornmüller (1932) in Germany and by Gerard, Marshall, and Saul (1933) in the United States. So, spontaneous and evoked potentials were gradually becoming accepted. With the verification of Berger's findings in human subjects by Adrian and Matthews (1934), the acceptance of a new type of neural electrical activity, the slow, spontaneous or autonomous potentials, often rhythmic in nature, was established. The flood-gates were opened, and the next 5 to 10 years witnessed a slightly mad rush to be first to identify some kind of psychological or physiological correlate of the ubiquitous alpha rhythm, or other rhythmic variants. Some studies were done quickly and carelessly; others were more systematic. The early promise of the EEG in clinical neurology and related fields diverted much energy into the study of pathological phenomena, and not without benefit. However, the fact that we still know so little about the source, nature, and regulation of alpha and other spontaneous rhythms after all of these years makes one pause as we now find ourselves hurtling into the field of average evoked potentials and other slow potential shifts (CNV). It is not that we should not do so, but that we should do so with caution and due consideration for what has gone on before and with as clear vision as possible as to where we want to go and what the most critical problems are that we must solve in order to get there. That, of course, is one of the reasons for this conference.

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[3] Gasser, H. S. and Graham, H. T.: Potentials Produced in the Spinal Cord by Stimulation of Dorsal Roots. Amer. J. Physiol., 1933, 103, 303–320.

After Adrian and Matthews had confirmed Berger's results, Adrian and Yamagiwa (1935) studied the distribution of potentials on the human head, very much as we are doing now in relation to the locus and possible source of average evoked potentials. They were curious about the topographical distribution of potentials over the head and tried to determine the best way to localize the source by phase reversal techniques as well as by frequency and amplitude comparisons. After they established some of these localizing characteristics over the scalp of living persons, they tried to duplicate them by placing a potential generator inside the skull of a cadaver filled with material calculated to resemble the brain in the hope that there would be some clues as to the possible source of the generators in the living brain. Some of the more recent attempts to determine the source of evoked potentials and compare those recorded in the brain with those on the surface are suggestive of this sort of thing, although in the present day context there have been a limited number of opportunities to place electrodes deep in the brains of living patients except when this seemed justified for other reasons.

The spontaneous activity of the brain, the so-called autonomous activity, has given us much excitement over the years, and, I suppose one should add, many disappointments. Methodologically, it has taken many years to standardize even partially such aspects of EEG practice as electrode placements and input recording conventions, such as scalp-to-scalp, and scalp-to-ear, or other reference locations. Not the least of disappointments have been frequency analysis methods such as Fourier transforms or other time-voltage plots. Theoretically, many of these notions seemed ideal, but practically they appeared to be lacking in desired benefits; in any event, they do not seem to have moved us much forward in our thinking and conceptualization. Often the purpose to which they were put led only to more and more complex accumulations of frequency spectra that could not be resolved easily in connection with the set goals. Perhaps this was less a matter of the efficacy of the method or its theoretical soundness than of the perspicacity of those who sought to employ it. Perhaps the right questions were not being asked, and accordingly the solutions were diffuse and hazy. Whatever the cause, our basic understanding of the EEG and its significance did not seem to have been advanced greatly by such methods. This raises a note of caution with respect to average evoked potentials and the various methods used to enhance their value to us, both in terms of neural mechanisms and our understanding of them and in terms of what general advances can be made by isolating and employing them in practical as well as theoretical ways. Certainly, we should attempt to learn from the mistakes that have been made

in our approaches to the analysis of spontaneous electrical activity of the brain—what we can avoid or what we can improve by our attempts to analyze and utilize evoked potentials.

As I indicated earlier, the nature of the spontaneous activity, especially the alpha waves, has not been resolved in terms of an understanding of just what are the specific generators of such potentials, and just what are and where are the pacemakers of the potential rhythms. We know something about generator potentials, graded synaptic potentials, local dendritic potentials, and the like, but we don't know precisely the origin of rhythmic, spontaneous, alpha waves or the locus and nature of the systems that play a part in their regulation. As rapidly as we seem to be moving along in the average evoked potential field, we must remember that there are many people who are still concerned with trying to get a basic understanding of the particular areas, layers, cell configurations, and contacts in the cortex that may be contributing spontaneous as well as evoked potentials, and the particular thalamo-cortical relations that may perpetuate or modify such rhythms and evoked potentials.

A book by Per Andersen and Sven A. Andersson is supposed to give us answers to such questions, for its title is *Physiological Basis of the Alpha Rhythm.* I hope that it does; however, I suspect, like so many other "solutions" that we have had, that it will not be a complete answer. (This book did appear following the conference (Andersen and Andersson, 1968) and seems to make a very substantial contribution to a number of the questions with which we have been concerned. Specifically, it attempts to document the role of thalamic generators of rhythms that control cortical generators giving rise to local potential changes. It is dominated by the point of view and experience of those, including the authors, who have sought to understand what happens in and around single cells by intracellular and extracellular microelectrode recordings and in terms of unitary EPSP and IPSP. These levels of understanding are often quite precise and clear so far as the individual unit is concerned, but are often a far-cry from revealing what a total population or aggregate of units may be doing. George Bishop once told me "Nothing happens in the CNS in terms of a single unit." Nevertheless, very important clues have been provided by microelectrode studies in many areas, and I think that this book will be of great value to all of us as we think about and work with spontaneous and evoked potentials, whatever our mode of approach may be. One criticism of the book is its somewhat spotty selection of studies bearing on grossly recorded potentials and rhythms against which to compare and analyze the results of unit studies. Another is that the authors sometimes plunge *de novo* into areas that have been well trod by others, as if nothing counted but their own

purview of the territory with their own approaches. There are of course certain advantages in this, and the authors do apologize for the overwhelming devotion in the book to their own data at the expense of those of others. But let me return to my historical theme. I mentioned that Adrian and Matthews finally convinced classical neurophysiologists and others of the verity of Berger's findings.

A TRIBUTE TO HANS BERGER

Berger, in whose honor I think we should often dedicate meetings such as this, was not a neurophysiologist in the traditional sense; however, were it not for Berger's persistence in the face of repeated failure, I suspect it would have been some time before the basic fact of spontaneous electrical activity of the brain was discovered, even though people were getting close to establishing that there were wave-like rhythmic activities of a slower nature than the classical spike potential found in peripheral nerves and in central neural pathways. A considerable period of time might have elapsed before his findings would have been duplicated by others, especially with respect to the human EEG.

Figure 1–1 is a photograph of Berger, presented to some of us, who, at the instigation of Fred and Erna Gibbs, contributed small sums to a fund for Mrs. Ursula Berger, in the difficult days following Berger's death. With the rise of Hitler and the approach of World War II, Berger found it more and more difficult to carry on his work; eventually his health broke, and he died on June 7, 1941. The following is a brief note that appeared in the *New York Times* on June 10, 1941:

Hans Berger

Discoverer of Electrical "Brain Waves" in Humans Was 68

Berlin, June 7—Professor Hans Berger of the University of Jena, who discovered the effects of electrical manifestation on the human brain, died today at the age of 68.

About sixteen years ago Dr. Berger attached small electrodes to the skull and wired them to a modified radio receiver in which were tubes that could amplify feeble currents a million times. Thus were so-called "brain waves" discovered. They were later called "Berger's rhythms." Knowledge of them has been particularly helpful in the study of the disease of epilepsy.

Dr. and Mrs. Frederic A. Gibbs, who early made the acquaintance of Dr. and Mrs. Berger and visited Berger's laboratory in the mid-thirties, were some of the first to read and abstract the numerous articles of Berger and publish them informally in 1936, which they distributed to their friends then working in the field. Jasper's (1936)

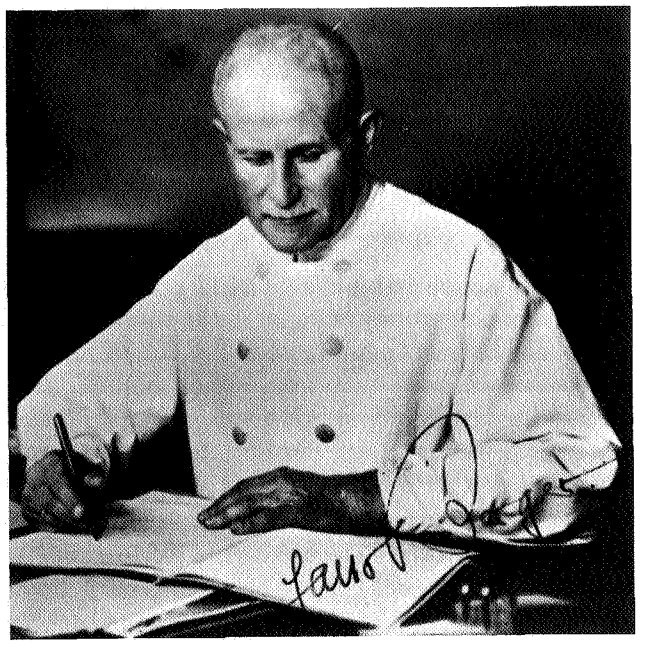

FIGURE 1–1.—Professor Hans Berger (1873–1941), neuropsychiatrist, University of Jena, Jena, Germany, first to discover and describe in 1929 a unique kind of electrical activity recorded from the brain of man, which he named the electroencephalogram (Elektrenkephalogramm).

early review of that time was an important landmark in bringing the work of Berger and others to the awareness of many people.

Following Berger's initial publication in 1929, as his discoveries became known, Adrian, Bishop and Bartley, Bremer, Fischer, Kornmüller, and others began to look for sources of these potentials in the brains of animals. But this is along story, and time will not permit discussing all of its ramifications now. I shall do so only briefly in order to stress the similarity that existed then with respect to problems related to the origin of spontaneous rhythms and that which exists now with respect to average evoked potentials. In the case of the latter, except under unusual circumstances at the time of operation, we cannot penetrate the brains of humans in search of potential sources; therefore, animal experiments are exceedingly important to us now as they were in the early 1930's.

In looking back over the progress that was made, it seems to me that it has not been primarily the specific techniques that were important, i.e., the types of electrodes, their placement, the types of amplifiers and recording systems, and all of the rest, but rather the conceptual think-

ing along certain system lines of approach that provided the greatest forward movement. For example, Bremer's (1935) sectioning of the brain stem and observation of the behavioral and electrophysiological state of the organism after his famous encephale isolé and cerveau isolé preparations had great importance. The work of Morison and Dempsey (1942), through electrical stimulation of midline thalamic nuclei, opened up a whole new realm of conceptions relative to thalamocortical relationships, involving recruiting and augmenting responses. Moruzzi and Magoun (1949), in discovering the functional role of the reticular formation by its electrical stimulation, brought forth a tremendously stimulating concept of ascending activation and its effect on electrocortical activity and behavior.

It seems to me that as one looks back over these early, and more recent, periods, it may be observed that the thing of greatest utility in probing the nervous system was often a non-naturally occurring event in the nervous system, such as electrical stimulation, or the specific interruption of certain pathways. Certainly recruiting responses are generated by non-natural electrical stimulations of nonspecific thalamic nuclei at about 8 per second; electrical stimulation of the reticular formation at 100 or 300 per second is another example. In each case, something quite reproducible and reliable could be effected in the nervous system and then studied in relation to other events and circumstances. In almost every area, we can discern evidences of artificial experimental procedures that have led to significant advances.

SOME FURTHER HISTORICAL NOTES

I will hastily finish this historical introduction and get on with the subject of average evoked potentials. Figure 1–2 shows one of the first human EEG records taken in this country by Jasper and Carmichael (1935) at Bradley Hospital and Brown University in 1934. Carl Pfaffmann, one of our psychologist friends and now Vice President of Rockefeller University, was the subject.

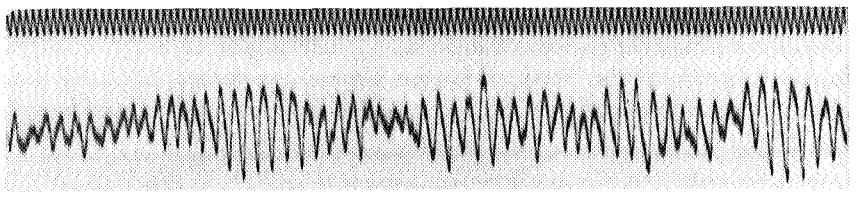

FIGURE 1–2.—Sample of the first EEG tracing taken at the Bradley Hospital, E. Providence, Rhode Island, by H. Jasper and L. Carmichael. Subject: Carl Pfaffmann. Date: July 9, 1934. Record, which shows prominent alpha rhythm of about 11.5 per second, was made with a Westinghouse, galvanometer-type, mirror oscillograph. Time line above: 25 Hz.

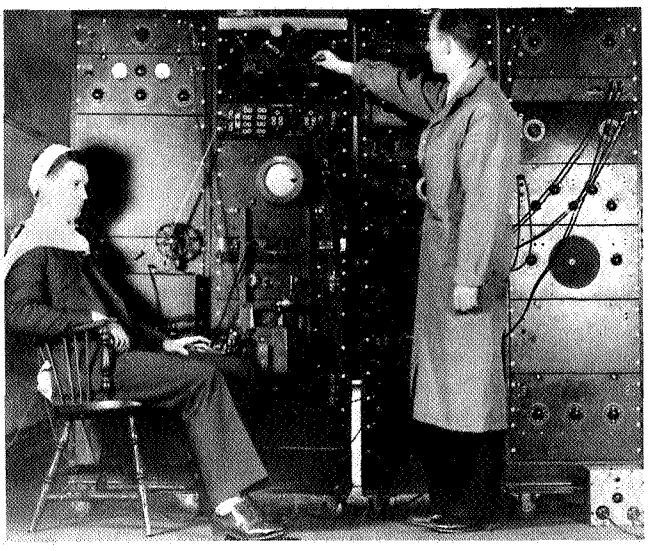

FIGURE 1–3.—Electrophysiological equipment used in auditory research and initial EEG studies in the laboratory of Hallowell Davis, Department of Physiology, Harvard Medical School, Boston, Massachusetts. First animal and human electroencephalograms recorded in this laboratory in 1934 with cathode-ray oscillograph (center) and Western Union "undulator" (above center), an inkwriting pen oscillograph. Subject: D. B. Lindsley; operator adjusting undulator, A. J. Derbyshire.

Figure 1–3 shows that another psychologist (myself) was a subject for Gibbs, Davis, and Lennox (1935) and others who were pursuing this problem at the same time at Harvard Medical School. The operator of the apparatus in this particular picture is A. J. (Bill) Derbyshire, who has spent much of his professional life in EEG work. Most of this equipment was for auditory studies carried on by Hal Davis, Bill Derbyshire, S. S. Stevens, and others, but it was also used for recording brain waves. They could be recorded on the oscilloscope, but for continuous recordings were traced on ½-inch paper tape by a single inkwriting pen of the Western Union Undulator device mounted just above the oscilloscope. E. L. Garceau had built most of this equipment for Hal Davis' group (see Garceau and Davis, 1935), but Albert Grass, an engineer from Massachusetts Institute of Technology, was soon to supply the first especially built EEG for Gibbs and Lennox at Boston City Hospital (Fall of 1935) and for the Davises and others at Harvard Medical School. Jasper, with the help of Howard Andrews, a physicist, designed and built his own equipment at Bradley Hospital; they used a Westinghouse multi-element mirror oscillograph

as their recording instrument, and subsequently an Offner-type crystograph inkwriter driven by rochelle salt crystals across which the amplified potentials were applied. This they also made themselves. Offner, a physicist, was beginning to develop amplifiers and recording equipment for Ralph Gerard at the University of Chicago; however, Wade H. Marshall was responsible for the design and construction of amplifiers used by Gerard, Marshall, and Saul (1933, 1934, and 1936). Theodore A. Hunter and Paul E. Griffith, radio engineers, built most of the early equipment used by the Travis group at Iowa.

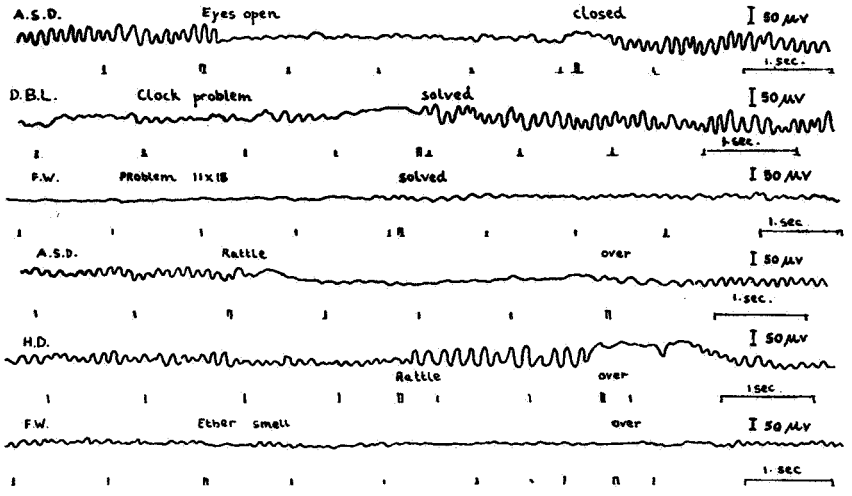

FIGURE 1–4.—Alterations in the electroencephalograms of normal subjects by sensory stimulation and by mental effort. From Gibbs, Davis, and Lennox (1935). A.S.D. (A.S. "Bill" Derbyshire; D.B.L. (D. B. Lindsley); F. W. (Fred Waite); H. D. (Hallowell Davis). Recordings made in summer of 1934.

Figure 1–4 shows some of the tracings recorded by Gibbs, Davis, and Lennox (1935) from Derbyshire (ASD), myself (DBL), Hal Davis (HD), and Fred Waite (FW), a laboratory technician. These were recorded with the Undulator. One can observe in these single-pen tracings the blocking of the alpha rhythm during eyes open, mental arithmetic, or solving the clock problem and so on. These maneuvers were characteristic of early investigations of the EEG that were done in those days in trying to find out what affected the alpha rhythm, what it meant, if anything, and in what relationship it stood not only to psychological events but to physiological states as well.

I am going to end this little historical prelude with a bit of levity. In 1939, Jasper was called to the Montreal Neurological Institute and McGill University by the neurosurgeon, Wilder Penfield, where he opened a laboratory and also established EEG recording facilities in

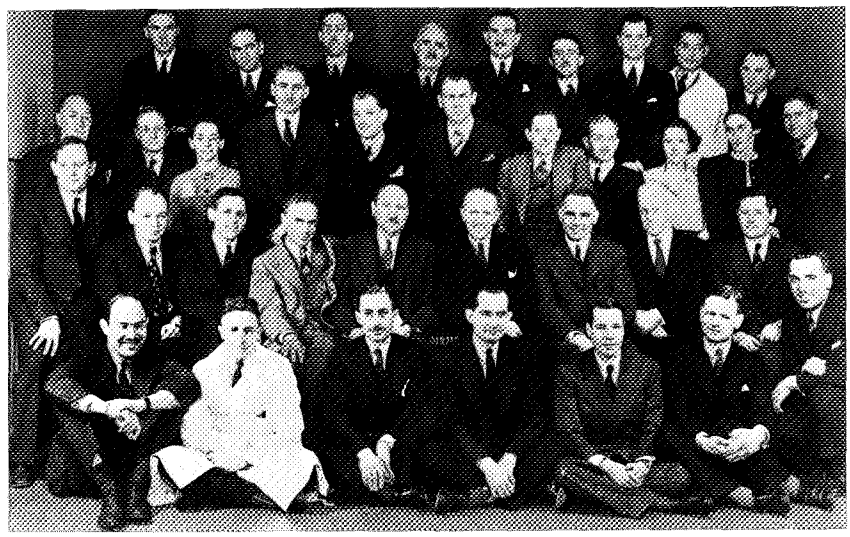

FIGURE 1–5.—Participants and invited guests at the opening of the Electrophysiological Laboratories in The Montreal Neurological Institute, February 24–26, 1939. First row; left to right: Robert S. Schwab, S. Humphreys, Herbert Jasper, A. Cipriani, Garret Hobart, N. Frazer, W. V. Cone. Second row: L. F. Nims, David P. C. Lloyd, Joseph G. Hughes, Stanley Cobb, E. Newton Harvey, Alfred L. Loomis, Alexander Forbes, Hallowell Davis. Third row: Colin Russel. (unidentified), Margaret Rheinberger, E. J. Baldes, G. E. Hall, Theodore C. Erickson, John E. Goodwin, Theodore J. Case, Molly R. Harrower-Erickson, Mrs. Robert S. Schwab, Arthur Elvidge. Fourth row: Howard L. Andrews, Joseph Evans, Donald Y. Solandt, (unidentified), John Kershman, J. Roy Smith, Donald B. Lindsley, Choh-Luh Li, Simon Dworkin.

the neurosurgical operating room with a glassed-in amphitheatre for observation. Figure 1–5 shows the group of people invited there for the opening of these new laboratories and a scientific program celebrating this occasion. Following the ceremonies, a fine banquet, and other festivities, those interested in skiing went to a resort in the Laurentian Mountains, which I believe was the forerunner of the Eastern EEG Society's subsequent annual ski meetings.

Following the banquet, a group of the younger neurological and neurosurgical workers put on a fine show for the visiting dignitaries, and some of them composed a little ditty about the EEG and the group assembled. I always thought it very funny and once gave a "benefit" performance of it before the American EEG Society in Atlantic City. My voice has not improved with age; on the other hand, I am not entirely sure it has gotten any worse! So, if you will bear with me for the next four slides I will try to sing it for you. In case you don't recognize the melody from my rendition, it was meant to be sung to the tune of "A Tisket, A Tasket."

A meeting! A meeting!
They're gonna have a meeting!
Electrophysiologists from all points of creation.
They'll wrangle and quibble
Such scientific dribble
Design new leads and coin those words that flabbergast the nation.

Wires were pulled down off the wall,
It was gonna be a free-for-all.
The epileptics ducked their heads
Beneath the covers of their beds.

"Cobb found one! Cobb found one!
Yes, on the wards he found one!"
They shaved her head and bound her to that instrument of Satan.

Did she scream? No, No, No.
Have a fit? No, No, No.
Bite her tongue? No, No, No.
Still they traced her undulations.

A brain wave! A brain wave!
The patient has a brain wave!
It's not an alpha, beta, gamma, delta, but a new one.
They found it! They found it!
Yes, in her bean they found it!
Their supercharger picked it up—they knew that it could brew one.

So Hallowell Davis grabbed the phone
From the clutches of Wee Willie Cone.
"Let's tell the papers tout de suite
So the world can learn of our great feat."

Colossal! Gigantic!
Stupendous and magnantic!
And if it doesn't bring us fame Harvard will suffer shame.

Said the News—No, No, No.
Said the Times—No, No, No.
Said the Star—No, No, No.
But it made the Hicktown Transcript.

The focus! The focus!
They had to find the focus!
Baldes said, "Now boys be calm; let's get down to essentials!"

We'll find it! We'll find it!
Said Robbie Schwab, "We'll find it!"
"If we just plug in all the leads and use reversed potentials!"

When the writers began their dizzy dance,
Herbie went into the usual trance.
The Chief said, "Herb! don't let us down
With all these potentates around."

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These brain wave dispensers
Then blew six condensers
Before they found this new rhythm that they were looking for.

Was it Bach? No, No, No.
Was it Liszt? No, No, No.
Was it Strauss? No, No, No.
It was just a swing-time rhythm.

To name it! To name it!
The boys had now to name it!
The Greeks must have a word for this astounding undulation!

They quarreled and quibbled
Saliva sprayed and dribbled.
Then Loomis said, "Let's all cool down and try some concentration."

Just when things had become an awful mess
Don Solandt said, "I must confess
These rhythms are not brain waves at all,
But the elevator in the hall."

"I found the connection
And have a recollection
That Arthur Elvidge did it as another boyish prank."

Were they pleased? No, No, No.
Shout with joy? No, No, No.
Laugh it off? No, No, No.
They electrocuted Arthur!

AVERAGE EVOKED POTENTIALS: PROBLEMS AND PROSPECTS

I thought that this little ditty would not only remind us of the past, but also would portend some of the problems of the future that we may have reason to discuss during the next few days. It may not be the elevator in the hall, but it may be gremlins in the computer with which we average our potentials! At any rate during the thirties and forties, there was much concern about how to separate the waves and rhythms of the spontaneous EEG. There were alpha, beta, gamma, delta, and theta waves, and eventually we got in a few additional Greek letters such as kappa and lambda waves. People who didn't like to categorize or name the waves nevertheless kept trying to fractionate the frequency spectrum by breaking it up into little packets of rhythms thought to have some special significance; e.g., 2–5, 5–8, 8–12, 12–18, 18–30, 30–50, and so on. It became quite a problem. And so it is today with average evoked potentials. Different investigators find and label different numbers of components, with different latencies and sometimes different polarities for supposedly the same components, depending upon the recording convention of whether negative or positive is up. This led Grey Walter not long ago to send out a questionnaire asking

the question, "Which way is up?" Apparently some don't know or at least don't label their published records so that the reader will know.

These and many other problems are reminiscent of the past; however, there are also many new ones, particularly since evoked potentials recorded on the surface of the scalp are relatively small signals compared with the background "noise" furnished by the much larger alpha and other ongoing activities. Certainly we must consider it a notable success and a "breakthrough" to have been able by means of computer technology to separate time-locked signals generated by a sensory stimulus from the ongoing or spontaneous background activity whose relationship to the stimulus onset is essentially random. In this way, we have been enabled to see not only the larger later components of the evoked potential, but also in some instances to identify the initial or primary components. However, we have not been able, with great clarity and reliability, to bring out the initial or primary response components to natural, receptor-initiated stimuli such as a flash of light to the eye. On the other hand, we do know from directly recorded evoked potentials on the visual cortex of the cat that a single suprathreshold pulse to the optic nerve or tract will cause not only a well demarcated surface positive primary response, but also three or four sharply defined initial components of that response, the first of which is a radiation response component, and the subsequent ones successive excitations up through the lower cell layers (Chang and Kaada, 1950; Bishop and Clare, 1952, 1953a). To a flash of light on the retina of the cat, the major surface-positive primary component is obtained but not the initial, rapid subcomponents. These seem to be washed out by a greater dispersion of impulses generated in the retina than when the optic nerve is stimulated directly. If greater dispersion and variability occur via receptor-initiated impulse discharges, it is understandable why the relatively short-lasting primary components of the average evoked response tend to get wiped out or reduced and occur with great variability. This seems to be true for both visual and auditory primary components of the average evoked response. On the other hand, somatosensory average evoked responses resulting from repeated stimulation of the median nerve provide much more clear and precise early components (Allison, 1962).

LOCUS, VARIABILITY AND COMPONENTS OF THE AEP

In order to illustrate further this point about the primary components of the average evoked response, as well as to examine the consistency of later components recorded from different topographical regions, I should like to present some data from a very interesting and important paper by Gastaut et al. (1967). Figure 1–6 illustrates some

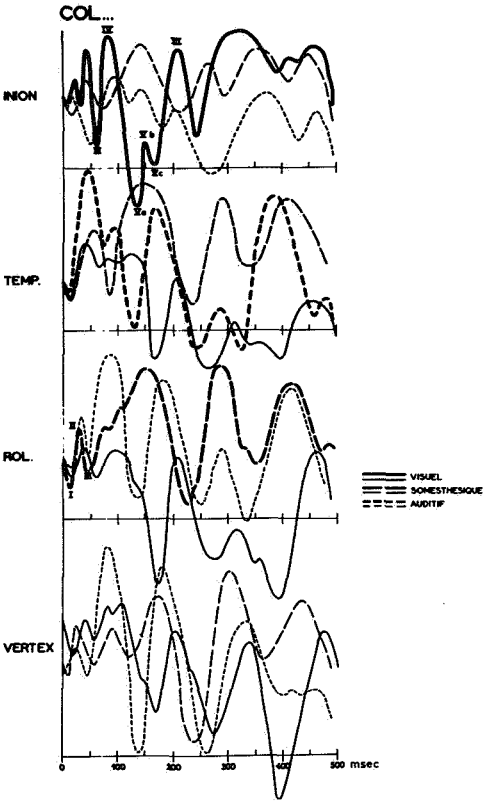

FIGURE 1–6.—Average evoked responses to visual, somatosensory, and auditory stimuli recorded at inion, temporal, rolandic, and vertex regions with contralateral ear reference. Positivity at active electrode downward; recording epoch 500 msec. All recordings from same subject. Heavy trace in top three sets represents sense mode corresponding to area of recording: visual-inion; auditory-temporal; somatosensory-rolandic. (From Gastaut et al., 1967, in: "The Evoked Potentials." Amsterdam: Elsevier, 1967, by permission of author and publisher.)

of these problems. Each set of three traces was recorded from a particular region of the head: inion, temporal, rolandic, and vertex. The heavy trace in each is for the specific modality represented in that area. In the top set, the heavy trace is the average evoked visual response in which, during the first 80 to 100 milliseconds, it is generally conceded that a primary component of specific character appears. For visual

and auditory areas, an early primary sensory response has not been considered a very reliable kind of response until recently. Even now it is dubious in the auditory area. Up to 80 or 100 msec, the early components in repeated averages for the same individual vary, but show some consistency; however, from individual to individual, they are exceedingly variable as we shall see in figures 1–7, 1–8, 1–9. Only the somatosensory average evoked response shows moderate consistency across individuals for these early primary responses.

From 100 to about 300 msec, there are major response components that most of us have been recording with some reliability. We call these "late" components, and in any given individual there is a certain amount of consistency; however, from individual to individual, there is much greater variability. Beyond 300 msec, there are the after potentials, the secondary potentials, and the after discharge, which some people have not observed because they have not extended their analysis epoch far enough. As Rémond points out, the epoch must extend at least 700 or 800 milliseconds in order to encompass the after discharge,

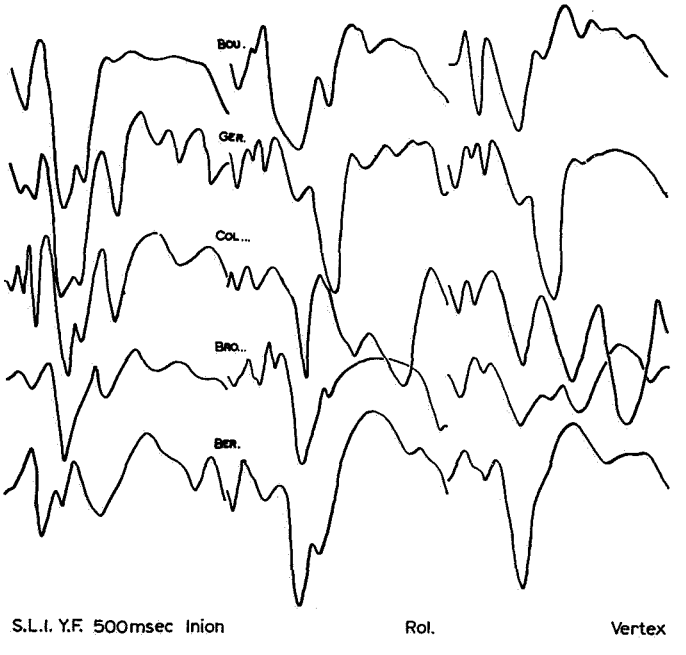

FIGURE 1–7.—Average visual evoked responses recorded at visual (inion), somatosensory (rolandic), and vertex regions in five different subjects. Positivity downward; 50-msec epochs. (From Gastaut et al., 1967, in: "The Evoked Potentials." Amsterdam: Elsevier, 1967, by permission of author and publisher.)

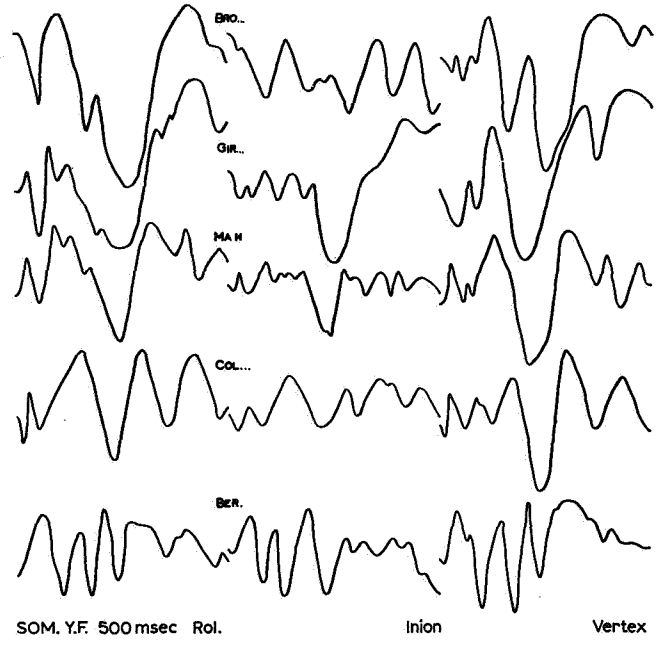

FIGURE 1–8.—Average somatosensory (median nerve) evoked responses recorded at rolandic, inion, and vertex regions in five different subjects. Positivity downward; 500-msec epochs. (From Gastaut et al., 1967, in: "The Evoked Potentials." Amsterdam: Elsevier, 1967, *by permission of* author and publisher.)

and perhaps even farther than that, which of course raises the question of how frequently can one stimulate without overlapping the preceding response in the train.

In the temporal region, there is no very characteristic early response to auditory stimulation, but one sees that there is one in the vertex recording, which oftentimes shows it better than the temporal region. Somatosensory stimulation, mainly because it has been given by electrical stimulation to the median nerve, tends to give a sharp, high-amplitude discharge in a large number of fibers, i.e., a concentrated volley, which tends to produce a much sharper evoked potential than one sees for visual or auditory stimulation in their respective cortical regions. Consequently, the somatosensory has been a favored region and a favored sense mode to use if one wants to investigate activities of primary or specific sensory nature as opposed to the nonspecific response associated with later components.

The very fact that there may be both specific and nonspecific components in the average evoked response is significant in that it sug-

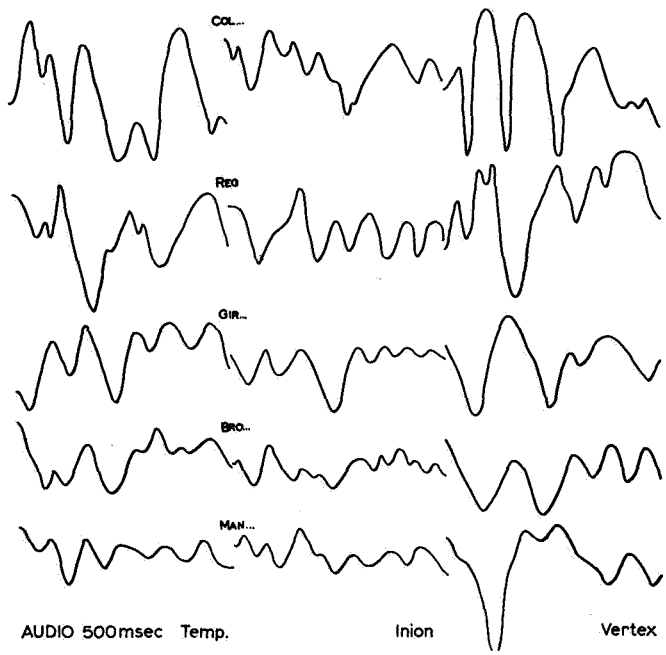

FIGURE 1–9.—Average auditory evoked potentials recorded at temporal, inion, and rolandic regions in five different subjects. Positivity downward; 500-msec epochs. (From Gastaut et al., 1967, in: "The Evoked Potentials." Amsterdam: Elsevier, 1967, by permission of author and publisher.)

gests that there may be ways of disentangling these components and identifying them with certain systems of operation within the brain, rather than simply relating them to a given stimulus mode or one particular state such as attention or arousal, and so on. In any case, I think that we need concurrent animal work, and, where neurosurgical considerations permit it, investigations of the relationship of deeper brain structures to human cortical evoked responses. It is even possible that through certain strategies in the use of computers the specific and nonspecific components of the average evoked potential can be separated, and at the same time spontaneous background activity and dc-shifts or CNVs separated or segregated as well.

In figure 1–6, one can certainly see by comparison of visual, somatosensory, and auditory responses in their respective areas, as well as in other zones, that there is a marked across-modality variation. Let us now look at across-individual variation for each of these three modalities as shown in figures 1–7, 1–8, and 1–9.

Figure 1–7 shows the average evoked potentials to visual stimulation at the inion, rolandic region, and vertex for five different subjects.

The response over the inion (first column) shows a fairly consistent, large, positive component in the 100- to 300-msec range in four of the five subjects. In front of it, there appears to be almost no consistency of the primary or specific components from person to person. If one looks next at the visual response recorded from the rolandic region (center) or the vertex (right column), it is difficult to see any consistency, although it may be that the same nonspecific, late positive component underlies another more general type of activity. Certainly the visual area gives the most reliable pattern of response to a visual stimulus.

Figure 1–8 shows averages for different subjects in rolandic, inion, and vertex regions for somatosensory (median nerve) stimulation. In the rolandic region, an early positive component is consistently present in four of the five subjects, and following it is a large negative-positive-negative complex of quite constant form. In the visual area (inion), these characteristic early responses are not seen; nor are the later ones. In contrast, and perhaps because of its relative proximity to the rolandic area, the vertex shows some of the early response components and quite similar large, late components. The reason I am showing these particular figures is that they raise a question about the topography or distribution of average evoked potentials on the head. The vertex, as most people have found, and as Gastaut and colleagues so ably pointed out, seems to show prominent later components with some consistency in response to all types of sensory stimulation, but seldom are there good early or primary components. Because the vertex responds so similarly to all types of stimulation, Gastaut et al. (1967) warn against its use as a common reference.

Figure 1–9 shows responses to auditory stimulation for five different subjects over temporal, inion, and vertex regions. Unlike visual and somatosensory stimulation, these auditory average evoked potentials defy any orderly classification or correlation between subjects. The auditory area does not seem to give any consistent pattern, and certainly the inion does not. The vertex shows a large response but not of the type shown in the auditory area. It is possible that the location of the primary auditory cortex, relatively hidden in the sylvian fissure and with other active areas on either side of it, makes it difficult to find a suitable location for auditory electrodes that will provide a constant and stable auditory average evoked potential. It is even possible that it becomes contaminated with hippocampal responses, as well as parietal and temporal contributions.

Finally, figure 1–10, also from Gastaut et al. (1967), demonstrates that somatosensory and visual evoked responses (five overlapped averages of each) recorded over their respective zones for a 200-msec

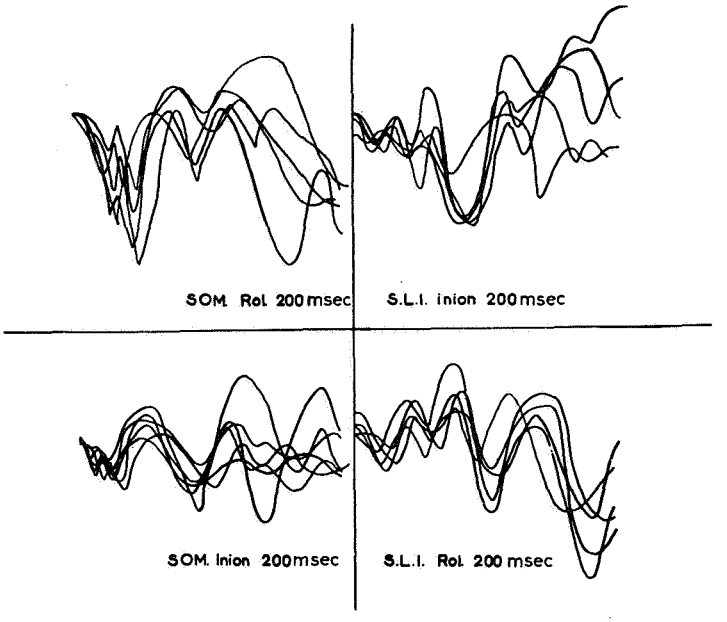

FIGURE 1–10.—Superimposition of five somatosensory (SOM) and five visual (S.L.I.) average evoked response traces recorded from rolandic and inion regions. Positivity downward; 200-msec epochs. (From Gastaut et al., 1967, in: "The Evoked Potentials." Amsterdam: Elsevier, 1967, by permission of author and publisher.)

epoch show a reasonable consistency of early and late components, whereas only late or nonspecific responses show some commonality over other regions. It is encouraging that regional visual and somatosensory average evoked responses provide reasonably clear and consistent early (primary and specific) and late (secondary and possibly nonspecific) components when recorded from scalp to contralateral ear reference. Whether further improvement in the reliability of such responses can be achieved remains to be seen. Bipolar and vertex referenced derivations do not seem to provide the answer, and, as Gastaut and colleagues suggest, a vertex reference may be contraindicated because the primary components are not clearly seen and the late components may be contaminated by other activities. Special computer strategies, as previously suggested, may help to separate further components and background interferences.

This important paper by Gastaut et al. (1967) serves as a significant point of departure for this conference because it touches on some of our most crucial problems concerned with where and how we record average evoked potentials (topography); how and where the most

definitive sensory evoked responses can be recorded so far as primary, secondary, and other nonspecific components are concerned; and with what consistency intra-individual and inter-individual responses can be obtained. Several other aspects of this study should be discernible as we proceed with our discussion.

NATURE AND SOURCES OF EVOKED POTENTIALS

I think it will be evident from what I have said earlier that in addition to standardizing our methodology and procedures for recording average evoked potentials in order to obtain consistent and definitive response patterns, a major problem is the theoretical and actual source of the potentials (generators) and the factors that modify and control them (modulators and regulators). Obviously the generators and some of the controlling mechanisms reside within the cortical layers, whereas synaptic drive imposed from specific thalamic relay nuclei and other rhythmic pacemakers presumably residing in non-specific thalamic nuclei furnish additional control and regulation. A very significant contribution along these lines is provided in a paper by Creutzfeldt and Kuhnt (1967). They have shown schematically (see fig. 1–11) a corticogram and an intracellular record, and, below these, the hypothetical intracortical potential distribution and mechanism presumed to account for the above schematized electrical records. This model is based on empirical data from Creutzfeldt et al. (1966 a, b). It attempts to explain the relationship between individual cellular activity and the evoked potential as shown in the corticogram. It does this by hypothesizing the sequential intracortical steps by means of which specific and nonspecific projections upon pyramidal cells change the distribution of potentials during the course of the evoked potential. The details of this model, which seem very plausible, are illustrated in the diagram and explained in the legend. The emphasis here, of course, is on the results of electrophysiological investigations carried on by Creutzfeldt and collaborators, with only the simplest neurohistological schemata hypothesized, including specific and nonspecific excitatory and recurrent collateral inhibitory synapses. The relationships are undoubtedly much more complex, as the work of Collonier (1966) and others, working with the electron microscope, attest. The type I and type II synaptic contacts, the number and distribution of the spines, the morphological and physiological columnar arrangements, and a host of other details, including some of Collonier's more recent differentiations of rounded and oval terminals and their differential distributions on pyramidal cells and their assumed differential inhibitory or excitatory functions, all serve to complicate this problem. Nevertheless, Creutzfeldt and his colleagues have made

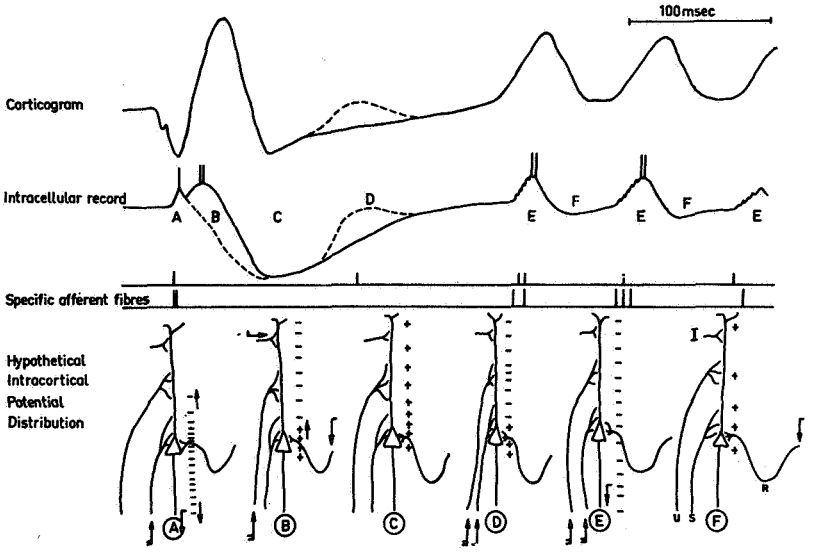

FIGURE 1–11.—Hypothetical transcortical potential distribution underlying an evoked potential recorded at the surface of the cortex. Top trace: Schematic evoked potential from sensorimotor cortex after electrical stimulation of specific thalamic projection nucleus VPL. Surface positivity downward. Second trace: Intracellular record from a pyramidal cell (EPSP upward, IPSP downward). Traces 3 and 4: Spike discharges in two afferent fibers. Bottom: Schematic drawings of a pyramidal cell with its specific (S), nonspecific or unspecific (U), intracortical (I) afferent, and recurrent collateral (R) from a neighboring cell, considered to be inhibitory, whereas other afferents are excitatory (all shown in F). At A, a synchronized afferent volley depolarizes cell, causing it to discharge an impulse via its axon, but the basal negativity gives rise to a surface positive wave in the corticogram; at B, the negativity spreads upward to the surface and gives rise to a large negative wave; at C, a return to positivity along the entire cell and its apical dendrite gives rise to positivity at the cortical surface (C)—because of IPSP; in D, an unspecific afferent discharge (arrow with two tails) impinging on apical dendrite interrupts polarization and causes surface negative wave; E, partially synchronized discharges in U and S afferents depolarize whole cell and cause efferent discharge of spike during the after-discharge and spontaneous spindle waves—recurrent negativity; F, a return to a resting polarized state. (From Creutzfeldt and Kuhnt, 1967, in: "The Evoked Potentials." Amsterdam: Elsevier, 1967, by permission of author and publisher.)

a very auspicious start in the analysis of the functional basis of the evoked potentials.

In these diagrams, they are trying to illustrate those particular features that they conceive in the matrix of the cortex as underlying the electrocortical activities that one can record from the surface of the scalp. I think this is a particularly important development for us. There have been difficulties in trying to correlate activities recorded by microelectrodes and gross surface recordings—we have sometimes thought that never the twain shall meet. Li and Jasper (1953) attempted to do this several years ago. However, much progress has been made, and there is more to come. Part of the difficulty is caused by the fact that the conditions under which we record one type of activity are not really the best conditions for recording the other. But there are many other reasons, as well. This is a problem that we must solve if we are going to understand better the nature of these average evoked potentials that we record from the outside of the scalp.

Creutzfeldt and Kuhnt recorded (Figure 1–12) from occipital, parietal, precentral, and temporal areas. They tried to indicate how one could determine where a certain wave began and ended. Using the characteristic six waves of Cigánek and the early primary positive wave (CD) of Cobb and Dawson, they plotted the positive and negative reversal points. Whereas Gastaut recorded from one electrode on the scalp and one on the contralateral ear, Creutzfeldt and Kuhnt recorded with a reference electrode on the chin. They found by this method of analysis that they can detect very reliably each of these component waves, except for No. 2, which seems to be less clear and definite than the others.

Many other attempts have been made to separate these wave components. If two or three things are happening in the same period of time, the electrical activities as recorded are bound to interfere or interact with one another. If some are going positive while others are going negative, it is like the electroretinogram, where the A and B waves antagonize one another. If you can remove the B wave by poisoning the retina, or by anoxia, the A wave will come into prominence. Similarly, if one could remove some of the underlying mechanisms that are generating particular components, then the pattern should change, and this may be one of the ways of analyzing records by lesion, by cooling, or cryogenic blockade. In this way, it may be possible to determine whether some components are part of another component, or whether they are quite independent, and whether they are operating in opposite directions.

Creutzfeldt and Kuhnt demonstrated another point I wanted to bring up. In studying the development of brain potentials—both the

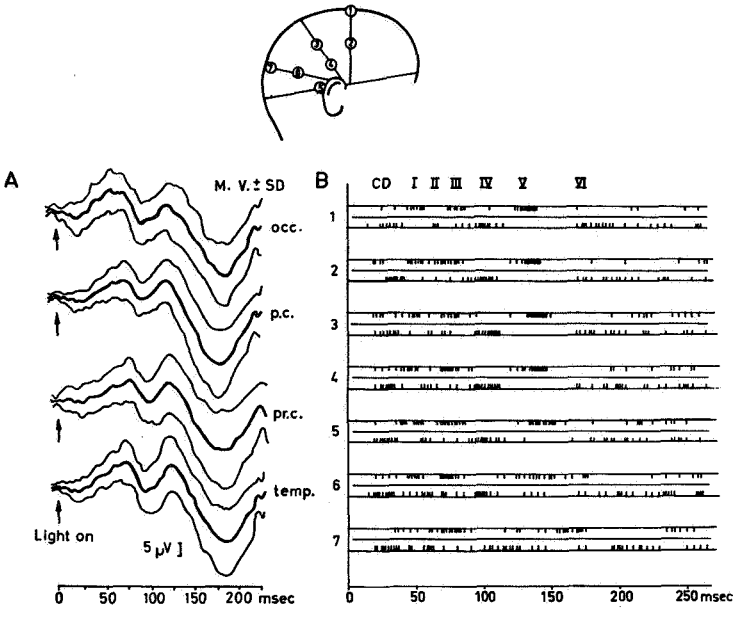

FIGURE 1–12.—(A) Mean of visual evoked potentials (VEP) from 20 individuals recorded over occipital, parietal, precentral, and temporal regions; (B) state of VEP, characterized as negative (down) or positive (up), at top CD equals Cobb-Dawson early positive wave, followed by Roman numerals designating Cigánek's classification of components—reversal of the small vertical lines corresponds in the main with waves classified by Cigánek, except for wave 2 and wave CD. This procedure aids in identifying the wave components of the evoked response. (From Creutzfeldt and Kuhnt, 1967, in: "The Evoked Potentials." Amsterdam: Elsevier, 1967, by permission of author and publisher.)

spontaneous activity and the evoked activity—I think we have a procedure for gaining some insight into the possible separation of components. I will show a little later, in the kitten, that a particular component will appear at certain stages, and not until later in development will another component appear. This is in part what Creutzfeldt and Kuhnt have shown (see fig. 1–13), where they have compared average evoked potentials at a few days of age with those of a couple of months, 3 to 9 months, 1 to 2 years, 2 to 4 years, and 5 to 14 years of age. Throughout there is a consistent negative wave that is of long latency and small at the start, but, as it grows in amplitude, it shortens in latency.

They state that it is not until 6 years of age that the principal pattern or maturity of the average evoked potential has been achieved. Before that time, they believe that it has not been well established although, generally speaking, most of us thought that it was.

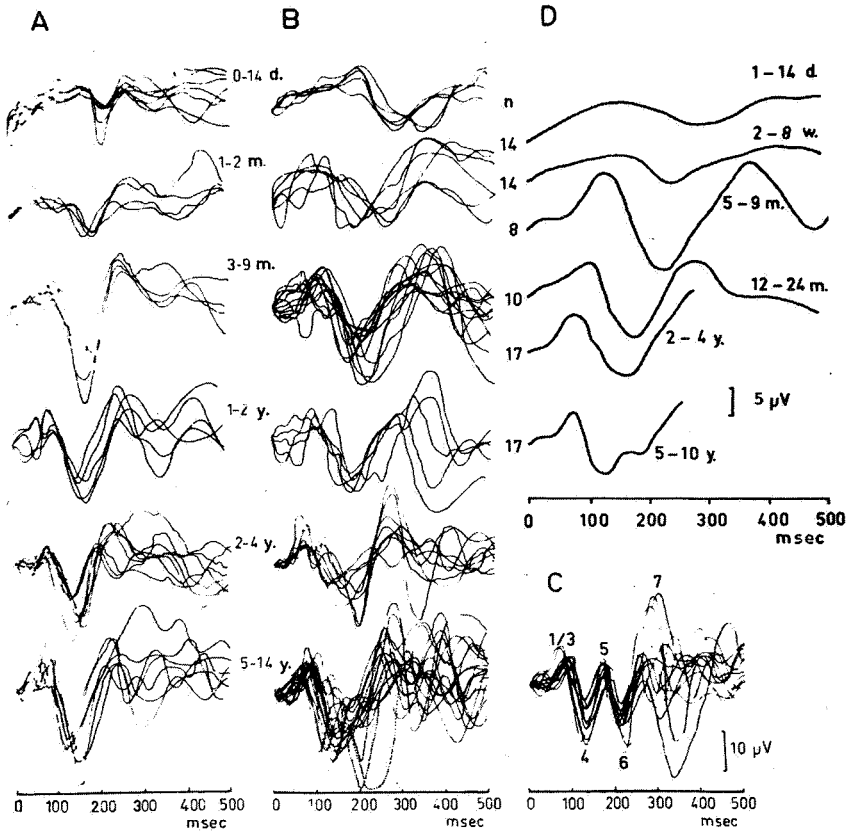

FIGURE 1–13.—Superimposed VEP of different individuals in different age groups shown as days, weeks, months, and years. (A), (B), and (C) Evoked potentials classified according to their shape; (D) mean of potential from small samples shown at left, age at right. At birth only a flat, broad biphasic negative-positive wave is seen with long latency; subsequently its latency shortens; it becomes compressed, and other components appear. Wave V of Cigánek doesn't appear until fifth year. Thus, age differentiation of VEP assists with classification and analysis. (From Creutzfeldt and Kuhnt, 1967, in: "The Evoked Potentials." Amsterdam: Elsevier, 1967, by permission of author and publisher.)

Another point made by Creutzfeldt and Kuhnt concerns the effect of the characteristics of the stimulus that produce changes in evoked potentials. Figure 1–14 shows how increasing the intensity of the light shortens the latency of a large, long-latency component; however, more than that, it adds another new, shorter latency component. It was demonstrated by Donchin et al. (1963) and by Wicke et al. (1964) that if one starts with a very bright light, there will be, as shown here, 80 and 160-msec peaks. As light intensity is decreased, the short-

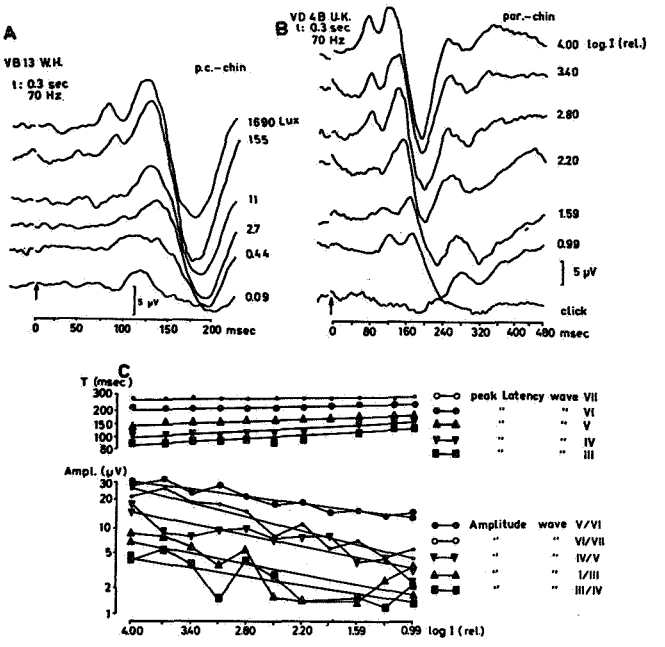

FIGURE 1–14.—(A) VEP elicited by flashes at different intensities: values in lux, (B), relative intensities of photoflash. Pattern and latency change with intensity. (C) Double log plots of intensity against latency. Both log and power functions fit the data. (From Creutzfeldt and Kuhnt, 1967, in: "The Evoked Potentials." Amsterdam: Elsevier, 1967, by permission of author and publisher.)

latency wave will diminish in amplitude and eventually drop out, leaving only the longer-latency component. Creutzfeldt and Kuhnt emphasize that the latency and amplitude relationships to stimulus intensity are identical in cats and humans, that the data could be expressed by logarithmic as well as power functions, and that the two were very similar.

SPATIO-TEMPORAL DISTRIBUTION OF POTENTIALS

Grey Walter (Walter and Shipton, 1951) was one of the first to use the toposcope to display distributions of potentials on the surface of the scalp. More recently, Rémond in Paris has used chronograms, topograms, and spatio-temporal maps extensively (Rémond and Lesèvre, 1967). One of the goals of this work, which relates to our present concern, is determining the relationships between background alpha rhythm and the response of the visual cortex to repetitive light flashes of independent and fixed-frequency or of a frequency-determined and triggered by an alpha source or sink. Their spatio-temporal maps, as

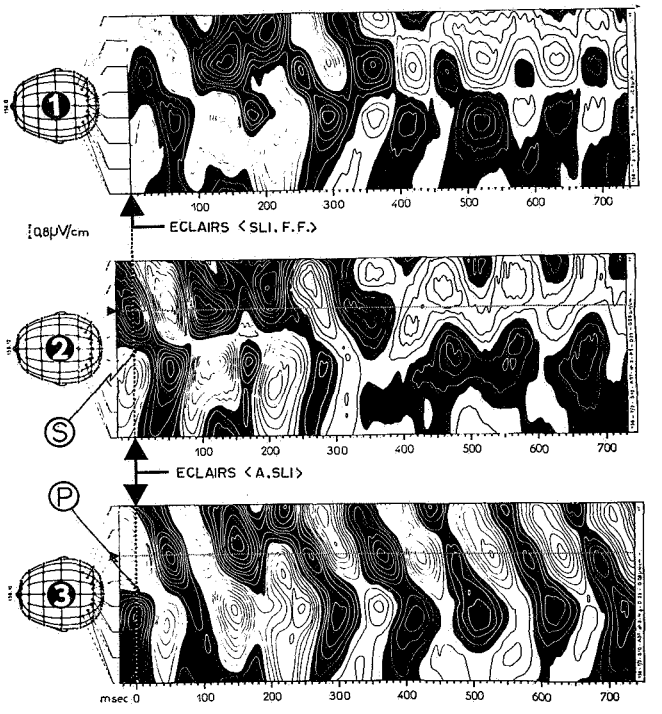

FIGURE 1–15.—Three spatiotemporal maps corresponding to the average visual response by a transverse montage, from the same subject with closed eyes: (1) repeated flashes at fixed frequency; (2) flashes at the time of a maximum alpha source; (3) flashes triggered at the time of a maximum alpha sink. Black: zone of negative gradient; white: zone of positive gradient. Zero time corresponds to onset of flashes. (From Rémond and Lesèvre, 1967, in: "The Evoked Potentials." Amsterdam: Elsevier, 1967, by permission of author and publisher.)

illustrated in figure 1–15, show the differences, especially in the nature of the after-discharge, when the light flashes are introduced under these three conditions: no relation to alpha, related to maximum alpha source shown by phase reversal, and related to maximum alpha sink. Their attempts to use these transverse montages in displaying the average alpha activity and the contrast to those with visual stimulation and visual evoked responses obtained by autostimulation form marked contrasts. The former shows regularity of alternation of negativity and positivity, whereas the visual stimulation shows the various components of the evoked response but no clearly differentiated after-discharge such as is shown if the visual stimulus is linked to the maximum alpha sink. This is a promising way to seek out the relationships

between spontaneous and evoked activity, and a variety of dynamic and unusual patterns result.

This reminds me of the work of John Lilly (1958) some years ago. With a high concentration of electrodes over a relatively small area of the cortex, he plotted topographically the distribution of these potentials during the course of stimulation. He could show that wave-like activity, not unlike the contour distributions of some of these patterns of Rémond and Lesèvre, could be demonstrated and photographed under a sort of tent-like arrangement showing a kind of geodetic distribution of potentials rising and falling dynamically as background and evoked activity interacted.

DeMott (1961, 1966) at the University of Rochester, did something similar. He implanted in the skull of a monkey a high concentration of electrodes—perhaps 160—with the intention of having 160 low-cost amplifiers because they were mainly going to amplify those frequencies above 50 Hz. He demonstrated to skeptical engineers that he could do this and demonstrated to me that the potentials generated under these points would illuminate little lights on a screen, which, when photographed, showed clearly that the pattern of flashing lights changed distinctly when a stimulus was administered. Even though we believed at the time that the higher-frequency components above 50 Hz were out of the field of interest of most of us, nevertheless, this young man demonstrated that whatever it was he was recording changed systematically with the stimulus. This is what we seem to be seeking in the average evoked potential. We seek some kind of systematic change that corresponds, or correlates, with change in the stimulus variables themselves—the duration, the intensity, the wavelength, etc., or the various states that we attempt to conjure up of a psychological nature such as a state of attention, or set, a probability situation, or one of expectancy, in which the subject's state of psychological anticipation is such as to produce a CNV or a negative dc shift.

AVERAGE EVOKED POTENTIAL AND ATTENTION

Because Cigánek is unable to be here and since we have referred to his system of wave or component classification, I would like to present one of his figures that illustrates, not only the components, but also the method that he uses to differentiate changes in the components under different psychological states or conditions. In an investigation of attention and distraction, he has used paired flashes (see fig. 1–16) and finds that the response to the second one often better reflects the amplitude changes in the late components where attention or distraction is involved. The six or seven components that he classifies in the whole average evoked potential are shown for the first flash and also

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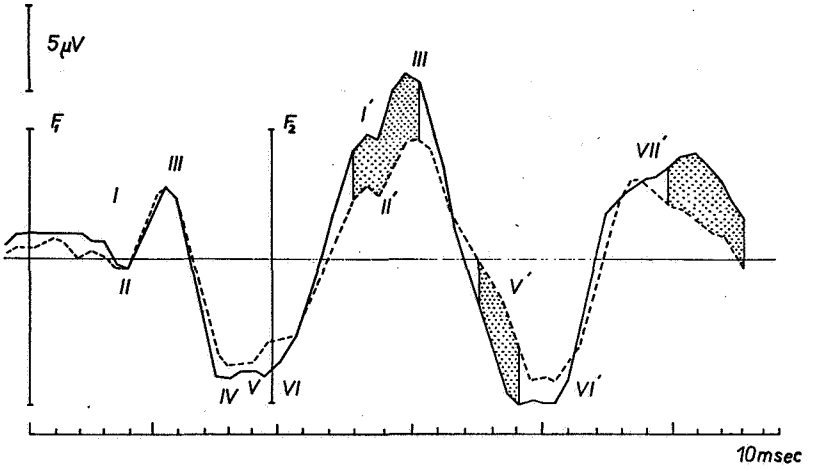

FIGURE 1–16.—Average EEG response evoked by paired flashes with an interval of 100 msec. Repetition rate of paired flashes, one per three seconds. Each average, 50 double stimuli. Flashes F_1 and F_2 marked by vertical lines. Leads O_z to P_z; negativity at O_z upward. Solid line: response with attention; dashed line: response with distraction. Statistically significant difference marked by dotted fields. Significant differences in waves I, II, III, V, and VII occur only after the second flash. (From Cigánek, 1967, in: "The Evoked Potentials." Amsterdam: Elsevier. 1967. by permission of author and publisher.)

for the second flash. The shaded area, in the case of the second stimulus, emphasizes the change (enhancement) in amplitude of certain components when the subject is attentive to the task (distinguishing whether there were two or three flashes) in contrast to the condition when he was distracted (simultaneously doing mental arithmetic). As illustrated here, these components are I, II, and III, plus a late component VII. Cigánek calls attention to a component during distraction which he identifies as a rudimentary wave V, which is not otherwise prominent.

There is, of course, considerable published work that emphasizes that some of the later components (probably corresponding to III to VI or VII, according to Cigánek's classification) are enhanced in amplitude during attentive tasks (Garcia-Austt et al., 1963, 1964; Haider et al., 1964; Spong et al., 1965; Davis, 1964; Chapman and Bragdon, 1964; Donchin and Lindsley, 1966; Satterfield, 1965). There are also some studies that have shown attention to be accompanied by a reduction in amplitude or no change (Callaway et al., 1965; Satterfield and Cheatum, 1964; Van Hof et al., 1962).

Nätäänen (1967), working in my laboratory, confirmed the finding of enhancement of late components with attention given to regularly

spaced stimuli, as were used in all of the previously described experiments; however, he did not find it when the stimuli were presented irregularly. This led him to question the role of selective attentiveness as the amplitude-enhancing factor and to attribute it to anticipatory and preparatory arousal and activation differentially preceding the relevant stimuli (stimuli to be attended to or responded to, in contrast to irrelevant stimuli to be ignored). This is indeed an interesting finding and one not to be overlooked or ignored; however, the question may be raised fairly whether it is possible to assume and maintain an attentive set toward given stimuli when it is impossible to organize and regularize one's internal neural systems of response because of irregularity of stimuli presentation. Certainly the task is made much more difficult; in general, it has been found that more difficult mental and physical tasks raise the level of arousal or activation, which, within limits, has its own excitability and amplitude-enhancing influences. In this connection, Spong and Lindsley (to be published) have found that in selective attention experiments where differential levels of alertness or task difficulty were involved, two factors were operating to produce amplitude enhancement of the later components in the case of the selectively attended-to stimulus. One of these was clearly the greater level of arousal or alertness required by having to make a discrimination relative to the selectively attend-to stimulus (i.e., to respond to the dimmer of two flashes, or weaker of two clicks or shocks). The second factor was one of selective attention to a given sense modality of the two or three alternately presented. Thus there may be a factor of selective attentiveness involved, as well as an underlying arousal or alertness level. The former emerges to a greater extent when task difficulty is reduced and when it is apparently unmasked by a more diffuse and powerful influence (general arousal level). It thus might appear that some degree of arousal or alertness was essential to selective attention and the enhancement in amplitude of late components; however, arousal pushed to greater limits may work at cross-purposes so far as performance efficiency and enhancement of evoked potentials are concerned, with the result that selective attentiveness may become impossible. This would seem to be the case where a heavy load of information processing is involved (e.g., multiple and rapidly occurring stimuli), where stimuli occur irregularly spaced and it is difficult to organize responses to them, and where the level of anxiety or emotionality exceeds motivating and reinforcing effects and leads to disorganization of behavior. One additional point from the Spong and Lindsley study is relevant to our consideration here, namely, that in the case of the much more distinct and reliable primary somatosensory responses, there seemed to be a clear indication

in the selective attentiveness experiments that although the late components were enhanced in amplitude with attention directed toward that mode (shock to median nerve), the early or primary components were affected in the reverse manner; they were reduced in amplitude. This led us to ponder the relative role of arousal, alertness, and attention upon specific (primary) and nonspecific (secondary) mechanisms.

SPECIFIC AND NONSPECIFIC SENSORY SYSTEMS

I was speaking earlier about a systems approach and the possibility of interfering with specific or nonspecific systems in such a way as to demonstrate that particular evoked potential components or responses might be accounted for by combinations of these activities of specific and nonspecific nature. It so happens that Rose and Lindsley (1965, 1968) were able to separate quite clearly two such systems in the developing kitten between birth and 30 days of age. At about 4 days of age, a long-latency negative wave was the sole response to a flash of light (see fig. 1–17). At 10 to 15 days of age, two responses were seen clearly separated in time—a short-latency positive-negative complex and the original long-latency negative wave. The former was found only over the visual area, whereas the latter was present over the visual area and over certain nonvisual areas (hence visually nonspecific).

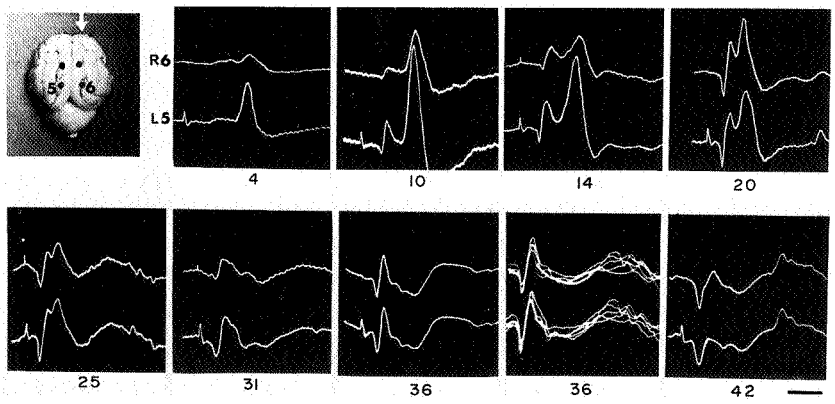

FIGURE 1–17.—Visually evoked potentials in same kitten from 4 to 42 days of age recorded under light pentobarbital anesthesia. Arrow before brain indicates eye stimulated. Light flash at initial pip on lower line. Superimposed tracings at day 36 show consistency of response (flash at onset of trace). Upward deflection negative at recording site. Calibration: 100 msec, 100 μv. Note only long-latency negative wave at day 4; short-latency positive-negative complex (specific) followed by long-latency negative (nonspecific) thereafter until latter coalesces with former at 31 days; thereafter evoked response similar to that of an adult cat. (From Rose and Lindsley, 1968, by permission of author and publisher.)

From 10 to 30 days of age, the latency of the long-latency negative wave was reduced greatly, and it coalesced with the negative component of the short-latency positive-negative complex to form the traditional evoked response of the more mature animal.

Thus there was evidence of two separate response systems very early in life that had a differential time of onset, different latencies, and differential topographical distribution. Furthermore, the assumption was made that the short-latency positive-negative complex, which was relatively invariant in latency, was a response of the specific or classical visual pathway to the visual cortex via the lateral geniculate body. It was hypothesized that the early-appearing, long-latency negative wave, which eventually coalesced with it and had both a visual and nonvisual cortical area distribution, was perhaps a secondary or nonspecific type of response that followed a caudally directed pathway from the optic tract via the brachium of the superior colliculus to the superior colliculus and pretectal area. We decided to make selective lesions of these two systems and investigate. A lesion of the superior colliculus and pretectal region in a 15-day-old kitten, when the responses were clearly separated in time, blocked the long-latency negative wave ipsilaterally but not the short-latency positive-negative wave. A lesion of the lateral geniculate had the reverse effect. A lesion of the brachium of the superior colliculus (see fig. 1–18) neatly removed the long-latency negative wave. These and other maneuvers seemed convincing that these were indeed two separate, but undoubtedly interacting systems—one a specific and direct projection to the visual cortex that evoked a short-latency positive-negative wave complex and the other a nonspecific or indirect system possibly operating via the reticular formation, the pulvinar, or other diffusely projecting systems from the thalamus. This response system was believed to affect some of the later components of the evoked response in the mature animal.

The reason for mentioning this now is that we are seeing evidence in our average evoked potentials of the differential influence of stimulus parameters or states of arousal and attentiveness and so forth upon the different component waves of the average evoked response. This experimental evidence from kittens studied in the course of their early development suggests that there may indeed be two or more sensory systems; specific, nonspecific, etc. Some of our evidence from the use of computer strategies in the study of background EEG and evoked potentials in humans are suggestive of this also. Thus I think we should be on the lookout for ways to bring out any possible differential effects that we can while studying average evoked potentials. This would suggest the action and interaction of two or more neural systems

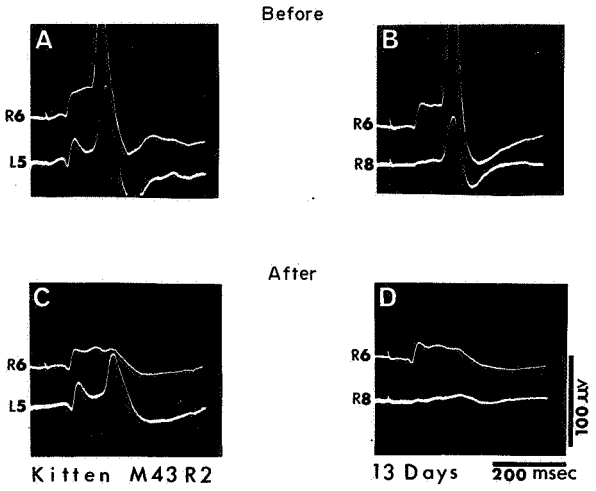

FIGURE 1–18.—Effect of lesion of right brachium of superior colliculus on nonspecific, long-latency, negative wave in 13-day-old kitten with both short- and long-latency response components well developed. Left eye stimulation. (A) and (B) Before lesion, show positive-negative complex (specific response) in R6 and L5 (right and left visual area—marginal gyrus) followed by high amplitude, long-latency negative wave (nonspecific response), but R8 (nonvisual, midectosylvian gyrus) shows only the nonspecific response. (C) and (D) After lesion, show only the short-latency positive-negative complex (specific response) on the side of the lesion (R6); nonspecific response also abolished in R8. Both responses are intact in L5 contralateral to lesion. Short-latency specific response was unaffected by lesion indicating mediation by direct geniculostriate pathway. When lateral geniculate destroyed, this response also disappeared. (From Rose and Lindsley, 1968, by permission of author and publisher.)

that may be contributing to the variations in these potentials. In this way, if we can separate systems by their evoked potentials, we will be able, possibly, to correlate and tie in our results with those rapidly developing in the more direct approaches utilized in animal studies in identifying the loci and conditions of the cortex and subcortical centers that contribute to and modify the electrocortical activity recorded from the cortex or human scalp.

Another indication of the role of nonspecific systems upon electrocortical activity, and especially those of the midline thalamus to which

we were originally introduced by Morison and Dempsey (1942, 1943) and Dempsey and Morison (1942a, b) when they demonstrated that 7 to 8 Hz stimulation there would cause recruiting responses over widespread areas of the cerebral mantle, has been followed up by many investigators. These studies have involved stimulation and lesion in the thalamus aimed at determining what pathway these influences took and where they might be blocked. Recent investigations by Velasco and Lindsley (1965), Skinner and Lindsley (1967), and Velasco et al. (1968) have shown that anterior thalamic lesions (ventralis anterior and reticular nucleus) block recruiting responses initiated more caudally in midline nuclei. Similarly, it was found that the only cortical ablations that block recruiting responses and spindle bursts created by a previous mesencephalic tegmental lesion are lesions of the orbitofrontal cortex. Skinner and Lindsley (1967) found a forebrain connecting pathway (ITP—inferior thalamic peduncle) from nonspecific midline thalamic nuclei to orbitofrontal cortex where local lesions, or local cooling with a cryogenic probe, would block spindle bursts and recruiting responses, but not augmenting responses initiated more laterally, and nearer to, specific thalamic nuclei. The blocking of these effects in an acute cat preparation by cryogenic cooling of ITP was reversible when the local region was brought back to normal temperature and spindles and recruiting responses returned. With cryogenic probes located bilaterally in the region of ITP in a chronic cat preparation, cooling to +10° C. not only blocked recruiting responses and failed to block augmenting responses, but also blocked synchronized electrocortical activity, enhanced evoked responses in the visual cortex elicited by optic tract stimulation, and blocked ongoing bar-pressing behavior previously learned (see fig. 1–19). Thus blocking of the midline thalamo-orbitofrontal cortex system had significant effects on nonspecific, diffuse electrocortical activity, upon specific visual cortical responses and upon learned and motivated behavior. It is quite probable that this is not the only thalamocortical system that is concerned with the control and regulation of electrocortical activity; however, it is one that has something to do with spontaneous rhythms as well as evoked potentials, and this is what should interest us in relation to average evoked potentials. Andersen and Andersson (1968) contend that synchronized after-waves can be created by sending an afferent volley into any specific sensory relay nucleus, as well as several nonspecific ones although the duration of the effect may be much less extensive. The upshot of all of this is that it is becoming increasingly clear that thalamic rhythmic regulators have much to do with the

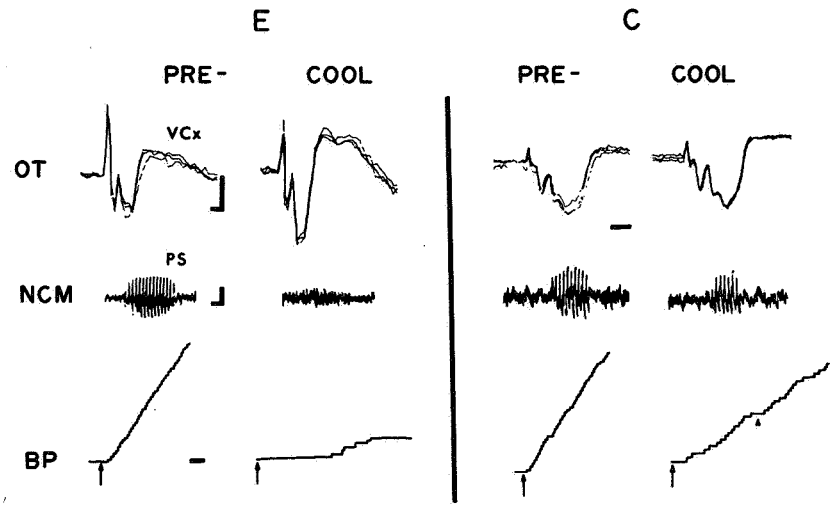

FIGURE 1–19.—Effects of cryogenic blockade of the inferior thalamic peduncle. Stimulation of the optic tract (OT) evoked responses in the visual cortex (VCx); each of three superimposed traces represents the mean of 30 averaged responses. Stimulation of n. centralis medialis (NCM) evoked recruiting responses on ipsilateral posterior sigmoid gyrus (PS). Cumulative response records of bar-pressing (BP) for milk reward; (E) chronic preparations with cryoprobes implanted bilaterally in critical region of ITP; (C) control preparations with cryoprobes implanted bilaterally close to, but not in, critical region of ITP. Left columns (PRE–) in (E) and (C) show responses before cooling of tip of cryoprobe; right columns (COOL) during cooling to 10° C. Calibrations: 100 μV for vertical amplitude markers; 0.5 sec for recruiting response, 5 msec for visual response, and 1 min for bar-press. Note that cooling blockage of ITP (thalamo-orbito-cortical pathway) enhanced evoked response of visual cortex, blocked recruiting response, and blocked or inhibited the bar-pressing response for milk. Similar cooling in a region slightly displaced from ITP did not have these effects. (From Skinner and Lindsley, 1967, by permission of author and publisher.)

nature of electrocortical activity of both spontaneous and evoked nature. Some of these changes seem to bear an important relation to the performance of learned behavior, possibly through their effect on neural systems that regulate or influence inhibitory mechanisms of the cortex. These in turn, when differentially affected, serve to regulate attention through selective action upon the evoked potentials of the various sense modes, or through differential action upon general and specific modulators of electrocortical activity.

SLOW POTENTIAL SHIFTS: THE CNV

Another aspect of human electrocortical activity has only recently come into our consideration through the work of Walter et al. (1964) and Walter (1964). This is in connection with the slow dc potential shifts associated with anticipation or expectancy, which Grey Walter refers to as the contingent negative variation (CNV). Thus we now have the possibility of recording not only spontaneous EEG activity such as alpha waves and other ongoing rhythms, but also by averaging we can bring out evoked potentials that otherwise are generally so small that they are lost in the background activities, and also the slow dc potential shifts.

If we return to the Cold Spring Harbor Symposium of 1936, we find that Bishop (1936) and Jasper (1936) presented papers there that hinted strongly at the possibility that the ongoing alpha activity bore a relationship to slow dc shifts of potential. Dc amplifiers of that day were either too unstable or insensitive to record such changes, but at that time laboratory-made R–C coupled amplifiers didn't have all of the restrictions of modern-day commercial models. That is, they had sufficiently long time constants to record some of the slow dc potential shifts. It was reported by these investigators that some of these slow potential shifts were accompanied by reduction or disappearance of the alpha rhythm and a return of it when recovery or a reverse shift occurred. So I think we must investigate the problem of the nature of the dc shift in relation to spontaneous activity, as well as to evoked activity. We are doing this in my laboratory, and I am sure that others have or will in the future.

At about the time Walter et al. (1964) and Walter (1964) first reported on the CNV, we were also concerned with an effect that we did not recognize at that time as being dependent on the dc shift. Whereas Walter and collaborators used a warning or anticipatory stimulus to be followed by flashing lights to be turned off by the subject, thus permitting a period of buildup of the dc potential by the expectancy of the flashes or some other imperative stimulus to response, we used a different paradigm. Our subjects were told that they would see three light flashes about 0.5 second apart and that they were to press a key on the appearance of the third one. Two patterns were practiced with the same instruction, i.e., press on the third flash. One pattern (flash-flash-flash) consisted of three flashes in a series separated by 0.5 second; the other (flash-flash—flash) consisted of three flashes, but with the second and third flashes separated by 1 second. Thus the subject was faced with a probability decision when the two patterns were intermixed. Would he find the third flash at the third (regular series) or fourth (delayed series) position? If he decided it would be the

regular series and the third flash was delayed so that there was no stimulus in the third position, we found, nevertheless, that there appeared to be a response, as if triggered internally. We soon discovered after the report of the Walter group that our R–C coupled amplifiers were not responding to the slow dc negative buildup between the first and third flashes but were responding to the marked and more rapid shift that occurred upon termination of the expectancy and the dc buildup. Soon we began to record with dc amplifiers as well as the others. The R–C coupled amplifier shows the average evoked response to each of the three flashes just as the dc amplifier does, but no dc buildup; the dc amplifier shows nicely the gradual negative dc shift and its termination when expectancy was confirmed or disaffirmed and a response made.

We have come to believe that there are some indications, based on latency of responses and other characteristics, that the subject's anticipation, expectancy, or readiness prepares an internal response that may trigger a change when no external stimulus occurs in the regular expected series. There are indications that something like an "Aha!" occurs when the subject's expectancy or decision in this rapidly moving sequence of events is upset. This internal program or schemata built up through practice and expectancy then seems to release a response that causes the dc potential to display a delayed notch or shoulder before subsiding to the baseline. If the third flash occurs in the third position rather than the expected fourth, there will be a similar delayed response following the one elicited by the third flash. Although these clues are only suggestive and not strictly confirmed, we believe that they hold some promise for further investigation and possible value of evoked potentials in the investigation of cognitive processes, imagination, thinking, and so forth.

CENTRAL AND PERIPHERAL FACTORS IN AEP

Finally, I want to draw your attention to a problem that can be of concern in the interpretation of average evoked potentials; namely, what is caused by central factors and what is caused by peripheral factors? This problem was brought home to us in a study that used monkeys in a visual masking situation, comparable to visual perceptual masking that we have used in human subjects (Donchin and Lindsley, 1964, 1965). Monkeys were trained to discriminate between a square and a triangle, and gradually the time for the presentation of this informational discrimination flash was reduced to 10 msec. The monkeys learned to perform this task with 95 to 100 percent proficiency after which a brief, bright masking flash was introduced following the informational flash. It was found (Adkins et al., 1969), as in humans,

that when the interflash interval was about 35 msec, the monkeys were still performing at near 100 percent; however, at lower values, their perceptual discrimination was impaired, and by 18 to 20 msec, their performance was at chance level. That is, their perception of the informational content of the first flash was masked by the second.

At first it was thought that the interference was occurring centrally and that the arrival of the volley of impulses to the second or masking flash at the cortex interacted and interfered with the consolidation and elaboration of the responses generated by the first or informational flash since some of the primary and all of the secondary response components were overlapped by the responses to the second flash. However, by recording simultaneously at the visual cortex, in the lateral geniculate body and the optic tract, it was discovered that all recording stations showed the same kind of effect (Fehmi et al., 1969). The response to the second flash, as the interflash interval (IFI) became smaller, began to overlap the response to the information flash and, to our amazement, could essentially displace most of it without interfering with the animal's ability to make the discrimination and perform at near 100 percent proficiency (30-msec IFI); however, at a 15-msec IFI, performance was at a chance level (complete masking), and the response to the second flash had completely displaced that of the first (see fig. 1–20). Since this occurred in the optic tract fibers whose cell bodies are the ganglion cells of the retina, as well as in the lateral geniculate body and cortex, it was obvious that the interference was occurring in the retina. Thus much of the masking (although apparently not all) effect was caused by lateral inhibition or other interactions in the retina. To prove that there was no residual response to the informational flash at any of the three recording levels when the masking flash followed by 15 msec or less, we subtracted the average potential to the masking flash alone from that to the combined informational-plus-masking flash. The result was that there was no residual; on the other hand, at a 30-msec IFI when performance was near 100 percent, a similar subtraction showed that there was a residual response to the first flash at all levels (see fig. 1–21). These studies confirm the conclusion that we made from our studies of average evoked potential correlates of masking in humans (Donchin and Lindsley, 1965).

In relation to our problems with average evoked responses in humans, it should be noted that the cortical response in these monkeys to the first flash had secondary or late components, but these could be overlapped and interfered with by the evoked responses to the masking flash without causing any change in the animal's perceptual discrimination performance. Thus whatever functions the late potentials

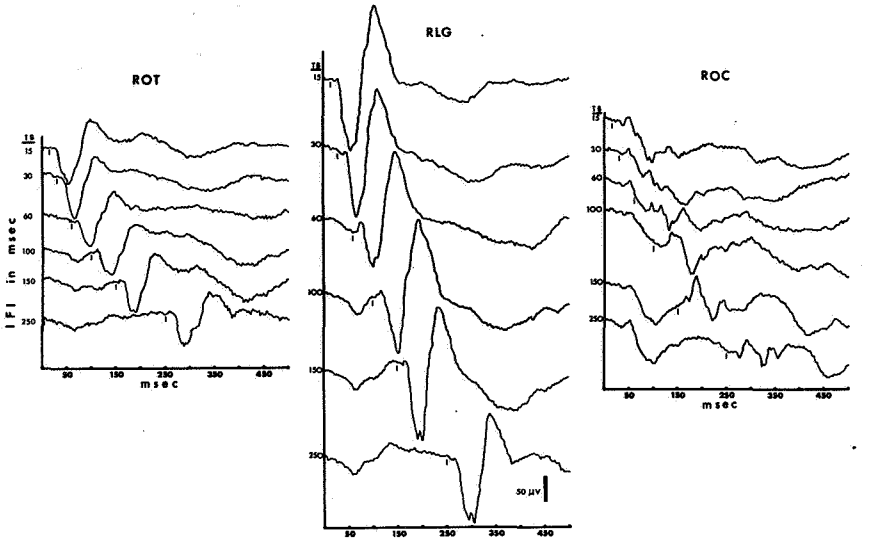

FIGURE 1–20.—Computer-averaged evoked potentials recorded from right optic tract (ROT), right lateral geniculate (RLG), and right occipital cortex (ROC) of monkey, while attempting visual discrimination of square from triangle in test flash (T) followed by masking or blanking flash (B) at interflash intervals indicated on ordinate. Visual discrimination performance was at chance level at TB 15, and nearly 100 percent correct from TB 30 to TB 250. T occurs at zero time; B occurs at small vertical mark. Responses are clearly separated at TB 250, but response to B progressively overlaps response to T as the interflash interval diminishes and finally at TB 15 completely displaces it. Note that only a very small portion of the T response is present at TB 30 when monkey's performance was nearly 100 percent correct; this was true at each recording site. None of T response is evident at TB 15 where performance was no better than chance level. All traces an average of 66 stimulation trials. Negativity at recording site, relative to a diffuse reference, gives upward deflection. (From Fehmi, Adkins, and Lindsley, 1969, by permission of author and publisher.)

serve, they did not in this case appear to be essential to the discrimination process, or at least that process was not interfered with by the simultaneous occurrence of two sets of response in the same visual cortical area.

I have brought up this last problem to emphasize the need to attempt to confirm in animals some of the functions we study by means of evoked potentials in humans, and to go back as far as possible toward the receptor side of the system in search of interacting and interfering factors. The point is that in the interpretation of average evoked responses with respect to stimulus parameters, we must be sure that the changes observed at the cortical level are not caused by interactions

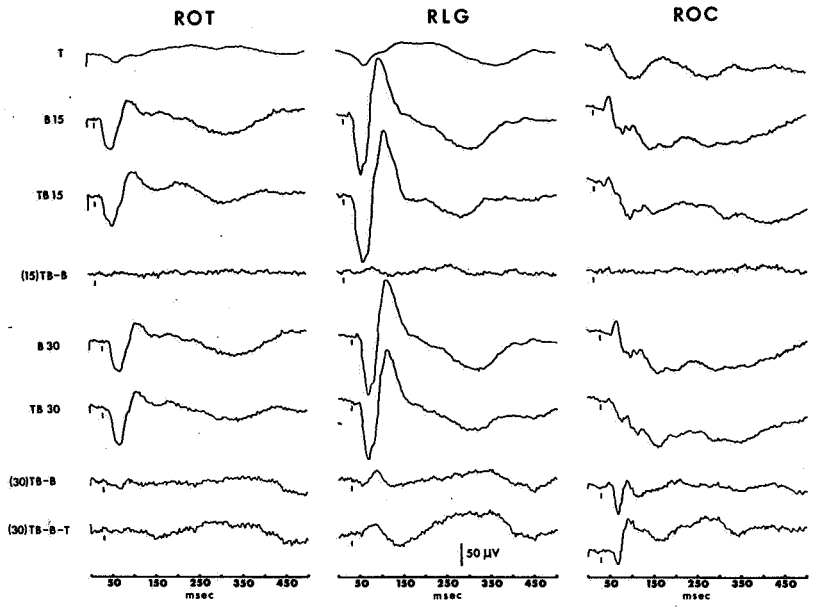

FIGURE 1–21.—Computer-averaged evoked potentials from right optic tract (ROT), right lateral geniculate (RLG), and right occipital cortex (ROC) of monkey during critical IFI for masking (TB 15) and nonmasking (TB 30). Blanking flash alone averages (B) were subtracted from TB averages to demonstrate absence of T response residual in trace (15) TB–B when performance at chance level, and presence of T residual in trace (30) TB–B when discrimination performance was correct. Test flash alone averages (T) are for comparison with T residuals. (From Fehmi, Adkins, and Lindsley, 1969, by permission of author and publisher.)

at the receptor level (e.g., retina) and therefore are only reflected at the cortical level, but do not originate there.

These are only some of the problems and concerns of which we must be cognizant. I am sure that this conference will bring out many more and perhaps supply answers for some of the problems I have mentioned.

CHAPTER 2

The Relationship of Brain Activity to Scalp Recordings of Event-Related Potentials[1]

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THE TECHNIQUE of response-averaging has made it possible to relate directly components of the electroencephalogram (EEG) to specific psychological variables. Although averaging was introduced primarily as a means of enhancing the signal-to-noise ratio of evoked potentials relative to the random background EEG, the procedure has broader implications for the statistical treatment of neuroelectric data and the formulation of a strategy for investigating brain-behavior relationships. The requirement that signals be related constantly to a specific time reference brings the analysis of electrophysiological events into direct conformity with the behavioral analysis of stimulus-response sequences. A stimulus initiates a sequence of physiological events underlying its perception as well as processes leading to an overt behavioral response, so that the analysis of electrical activity occurring between stimulus and response can provide clues concerning the timing and anatomical location of physiological events which have direct psychological correlates. Since cognitive and motivational variables as well as stimulus and response (SR) may be readily manipulated within the framework of reaction-time experiments, the SR paradigm provides a potent and flexible approach to behavioral physiology. Subjective experience may also be amenable to physiological correlation since perceptual and cognitive processes have a temporal course which may be defined rather precisely.

Although an SR approach figured prominently in early psychological (Donders, 1868) and physiological (Sherrington, 1906) ap-

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proaches to the analysis of brain-behavior relations, both disciplines did not fully realize its potential, largely because of technological limitations which existed until quite recently. Random variations of neural responses in the unanesthetized experimental animal, as well as the difficulty of differentiating relevant neural signals from spontaneous background activity and artifacts introduced by gross body movements, placed severe limitations on the physiological analysis of behavior. These problems led to the use of anesthetized preparations.

The interesting initial observations of Caton (1875) and Beck (1890) were lost in the ensuing flood of experimental data from anesthetized animals. Although anesthesia succeeded in reducing background rhythms and response variability, thereby permitting the recording of highly reliable evoked responses from all levels of the central nervous system, it delayed for half a century significant attempts to relate directly brain physiology to behavior. The discovery of the human EEG led to several attempts to introduce the reaction time (RT) technique to the analysis of sensory information processing in man (Cruikshank, 1937; Durup and Fessard, 1936; Bernhard, 1940; Monnier, 1949); the variability of the electrophysiological measure and the difficulty in detecting components specifically related to stimulation or to voluntary movement (Bates, 1951) again defeated a general application of the method to behavioral physiology.

The advent of convenient methods for EEG-averaging permitted an experimental fulfillment of the ideas advanced by Donders and his successors over a century ago. I suggested that, by suitable application of the averaging procedure, it should be possible to detect and analyze separately the sensory and motor components of sensorimotor sequences and to approach directly the problem of the central correlates of human perceptual and cognitive processes (Vaughan, 1962). This presumption has received substantial empirical support (e.g., Vaughan and Costa, 1964; Vaughan et al., 1965; Vaughan et al, 1966; Gilden et al., 1966; Vaughan et al., 1968). Since cerebral processes may be related to voluntary movement and to relatively stimulus-independent psychological processes (e.g., Sutton et al., 1967; Ritter et al., 1968), the term "evoked potentials" is no longer sufficiently general to apply to all EEG phenomena related to sensorimotor processes. Moreover, sufficiently prominent or distinctive physiological events may serve as time references for averaging, in addition to stimuli and motor responses. The term "event-related potentials" (ERP) is proposed to designate the general class of potentials that display stable time relationships to a definable reference event.

EVENT-RELATED POTENTIALS

The electrophysiological phenomena to be considered here comprise five classes of average ERP: (I) the sensory (evoked) potentials, (II) the motor potentials, (III) long-latency potentials related to complex psychological variables, (IV) the steady potential shifts, and (V) extracranial potentials. In many experimental situations, more than one class of potential is present concurrently. The investigator is faced, therefore, with the task of distinguishing the classes in analyzing the electrophysiological correlates of specific psychological variables. Characterization of specific ERP is assisted by the temporal, spatial, and morphological features related to experimental manipulations of psychological variables. As yet, neither the effects of psychological manipulations nor the descriptive features of the ERP are completely known; therefore, our treatment will be necessarily tentative. It is clear, however, that rational approaches to classification and description of these highly complex phenomena are required. I shall, in the succeeding portions of this review advance preliminary definitions of the five ERP classes and delineate some approaches to defining the underlying brain processes and their psychological concomitants.

Class I: The Sensory (Evoked) Potentials

These potentials are the most familiar and extensively studied of the cerebral events disclosed by averaging. Stimulus-evoked potentials of noncerebral origin, such as the ERG (Class V), are arbitrarily excluded from this category, as are potentials which are associated with motor responses (Class II) or are elicited only when the stimulus carries information of significance to the organism (Class III). The sensory potential is an obligatory brain response to a specific stimulus, the properties of which depend upon the stimulus parameters and the state of the brain at the time of stimulation.

Evoked responses in man have been elicited by auditory, somatosensory, visual, and olfactory stimuli, as well as by electrical stimulation of afferent pathways. Some information on the morphology and cranial distribution of these responses has been reported, although no definitive studies are yet available. The fragmentary basic information on evoked potentials and attempts to study the effects of various complex, and frequently poorly defined, psychological variables have produced an increasing volume of uninterpretable data. The need for careful parametric analysis of stimulus variables and the need for normative spatial data comprise the single most important task of investigators seeking to use evoked response measures as electrophysiological indices of behavior.

The morphology of the evoked responses has been described extensively and variously. The waveforms depicted in figure 2–1 are typical

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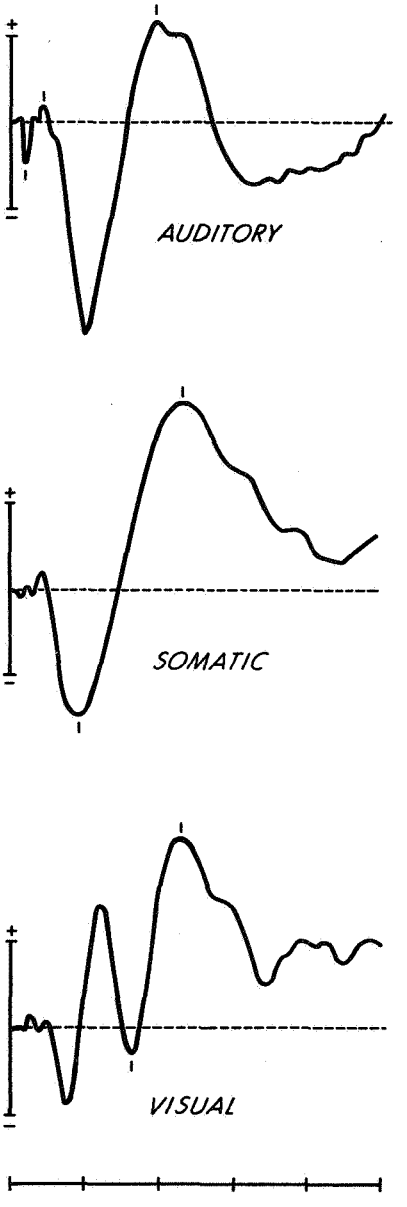

FIGURE 2-1.—Averaged evoked responses obtained from eight adult subjects. Each tracing is the computer average of 4800 individual responses. Calibration 10 μV, 100 msec/division (negative down).

of referential (monopolar) recordings of auditory, somatosensory, and visual evoked responses obtained from alert adults. These responses, composites of the evoked potentials obtained under standard stimulus conditions from eight normal subjects, illustrate the typical waveforms obtained at moderate levels of stimulus intensity. The amplitude and

peak delays of the various components vary as a function of stimulus parameters and arousal level of the subject. When stimulus and state variables are carefully controlled, and the number of samples taken is sufficient to reduce the level of background EEG adequately, waveform stability within subjects is quite high. In contrast, individual differences in the absolute and relative amplitudes of the various components are prominent. Peak delays tend to be substantially more reliable, so that for given stimulus conditions, a "standard" evoked response waveform can generally be defined. Discrepancies which appear in the literature may be attributed to the joint effects of variations in electrode placements and stimulus parameters, as well as variability contributed by background EEG activity and fluctuations in arousal level.

The substantial variations in amplitude, peak delay, and even the presence of evoked response components found under different experimental conditions demand a more flexible and informative nomenclature than the mere enumeration of peaks heretofore employed. A standard format [2] which would accomplish these ends and eliminate the present confusion concerning identity of components comprises an abbreviated designation of (1) electrode placement, (2) component polarity, (3) component peak delay, and (4) component amplitude in microvolts measured from baseline (optional). Thus the auditory evoked response depicted in figure 2–1 may be denoted as

Cz/Ch: N(18,3.3); P(42,1.3); N(104,18); P(196,8.8),

the chin reference being abbreviated "Ch."

Class II: Motor Potentials (MP)

These potentials are obtained by averaging with reference to the beginning of an electromyographically monitored muscle contraction. The MP comprise a series of deflections anteceding and accompanying all voluntary movements, including phonation and ocular movement. Typical waveforms recorded from scalp overlying the cerebral point of maximum amplitude are depicted in figure 2–2. Systematic differences in waveform associated with contraction of different muscles have not been observed although the amplitude of the MP varies with vigor and speed of contraction, and the lag between the fast antecedent components of the MP and the EMG burst increases as the distance from the brain increases.

Since it is difficult to ensure that the individual muscle contractions which contribute to the averaged MP are identical, systematic exploration of the relevant parameters of force, velocity, and mass of

[2] A formal proposal to implement this suggested system of designation will be presented separately.

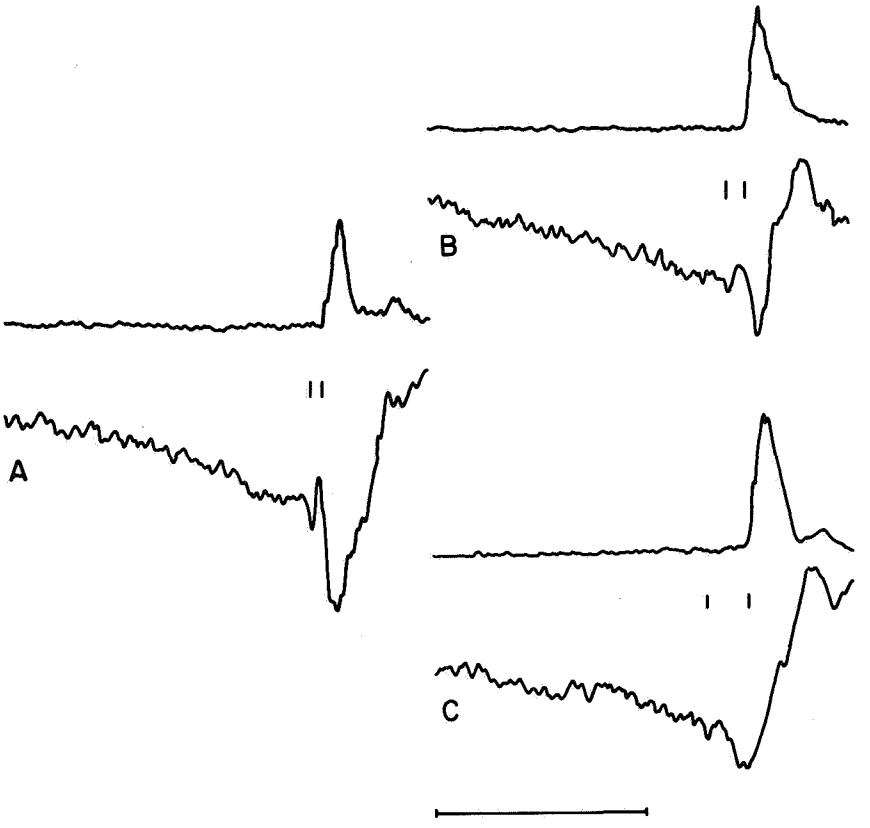

FIGURE 2–2.—Motor potentials (lower trace of each pair) and associated absolute EMG for (A) unilateral contraction of lower facial muscles, (B) clinching of fist, and (C) foot dorsiflexion. Time line 1 sec (negative down).

active muscle tissue is a challenging task. Furthermore, the MP are intrinsically compound in nature since the muscle contraction generates kinesthetic feedback which presumably contributes to the MP waveform. Further experimental analysis of the MPs should provide important insights into the timing and location of central processes underlying motor control.

The occurrence of MP must be anticipated in all experimental situations in which overt or covert muscle contractions in response to stimuli are present. It must be recognized, however, that the MP will not usually be time-locked to the stimuli, but to the motor activity, so that their contribution will not be proportional to the number of EEG samples taken. However, if their contribution is not assessed by averaging with reference to the response, misinterpretation of the complex of cerebral activity may occur.

Class III: Long-Latency Potentials

These potentials, long-latency (300 to 500 msec) positive components of evoked responses, are elicited in experimental situations which suggest a direct relation to the subjective response to the stimulus. The phenomenon, originally reported and studied in detail by Sutton and coworkers (Sutton et al., 1965a,b; Tueting, 1968) has been shown in more recent investigations (Ritter et al., 1968) to be closely related to the orienting response. It is observed in all situations involving evaluation of the perceptual significance of a stimulus, whether demanded by an unexpected change in stimulus characteristics or by a task variable such as discrimination of different stimuli. Sutton has also shown that this activity may be elicited by the absence of an expected stimulus. The delay of the major positive peak following a stimulus varies, depending upon the nature and the amount of stimulus change. In tasks involving a motor response, these P300–500 components occur concurrently with the large positive component of the MP so that these phenomena must be differentiated by appropriate experimental controls.

Class IV: Steady Potential Shifts (SPS)

The most widely celebrated of these phenomena, whose physiological origin remains obscure, is the "CNV" or "expectancy wave" (Walter et al., 1964c) recorded during the foreperiod in simple reaction time tasks. Antedating the more recent observations, the careful work of Köhler and associates (1952) demonstrated steady potential shifts during prolonged auditory and visual stimuli in recordings from the scalp of human subjects and the cortex of experimental animals. These phenomena have been studied in a variety of experimental situations in animals (Rowland, 1968), which indicates that SPS may accompany a variety of sensory, motor, and motivational processes. In man, SPS occurrence with voluntary movement was demonstrated by Kornhuber and Deecke (1965) and by Gilden et al. (1966). In view of the varied behavioral correlates of SP in man and experimental animals and the difficulties encountered in excluding the contribution by extracranial sources (notably the EOG), it is clear that investigators of human SPS have not yet come to grips with the complexity of their behavioral and physiological correlates.

Class V: Extracranial Potentials

Several physiological potentials originating from extracranial sources may be recorded from the scalp electrodes used to detect the EEG and the time-locked cerebral potentials it contains. Some of these are of considerable behavioral and physiological interest, providing measures of receptor activity (ERG) or muscular responses

(EMG). To the extent that their size and distribution confound the activity of cerebral origin, they present a major problem for the investigator of human brain-behavior relations. Undoubtedly, the most serious difficulty is presented by the corneoretinal potential (which generates the electrooculogram or EOG) since its large size in comparison to cerebral potentials permits it to contaminate significantly recordings taken from points as distant as the vertex. Its propensity for time-locking to stimuli, particularly in tasks requiring visual fixation, has led to the serious errors committed in the early work on the CNV. The ERG is a lesser problem since its amplitude decreases sharply as light intensity decreases and is quite small in the light-adapted eye. The EMG activity, celebrated by the caveat advanced by Bickford (1964), proves significant in situations in which stimulus intensity is high, muscular tension is maintained, and electrode placements overlie the cranial musculature. It is important to recognize that intracranial activity as well as extracranial muscle potentials may be affected by the maneuvers commonly employed to elicit the myogenic components of evoked responses; thus, this test does not establish unequivocally the extracranial origin of all potentials enhanced by muscle contraction.

The EKG seldom disturbs EEG recordings unless a non-cephalic reference is used, or the scalp-electrode interfaces are grossly unequal in impedance. If averaging is locked to the QRS complex, however, the EKG will appear large in scalp recordings. Furthermore, changes in impedance associated with cerebral and cranial blood flow changes may alter response recorded from scalp electrodes. Therefore, neuronal changes related to the cardiac cycle may be reflected inaccurately in scalp recordings. The GSR and respiratory effects are usually neglected, as is the cardiac cycle, in cerebral ERP studies. Such neglect is justified only when their time relation to the phenomena under study is random and the ratio of variance attributable to their action to that of the cerebral potentials is sufficiently small. Although in most instances this is probably the case, the paucity of data on this question suggests the need for some caution, particularly under experimental conditions in which intrinsic mechanisms of cyclic control might contribute to the timing of behavioral events. The tendency for ocular movements and respiratory activity to become coupled with voluntary movements of the extremities demands particular care in experimental monitoring and control.

THE PHYSIOLOGICAL BASIS OF ERP

The ultimate significance of the ERP recorded from scalp electrodes will be determined by the extent to which they may be related

quantitatively on the one hand to psychological variables, and on the other hand to the basic brain processes which underlie experience and behavior. Even under the best of circumstances, detailed observations of neural activity within the brain, using microelectrode techniques, provide a limited and biased sample of cellular behavior, and a number of practical considerations further limit analysis of neural interactions within the CNS of the higher organisms. The activity of individual neurones is even more difficult to analyze in sufficient detail in the behaving organism, despite the tantalizing glimpses provided by recent investigations (Evarts; 1966, 1968). Neither can studies of unit activities contribute directly to the analysis of human experience and behavior.

For these reasons, studies of reliable physiological indices of psychological variables provided by the ERP recorded from human subjects and experimental animals must share a substantial role in elucidating the biological basis of behavior. Although neurophysiologists have long been skeptical of the usefulness of the EEG in this quest, it must be recognized that earlier failures of the EEG as a tool in behavioral physiology arose from the lack of satisfactory behavioral correlations rather than from intrinsic difficulties in physiological interpretation of the EEG waveforms.

F. Morrell (1967) has asserted, "Given what is now known of the biophysical properties of cortical pyramidal cells and the differential localization on the membrane surface of inhibitory and excitatory synapses from specific, unspecific and intracortical terminals, as well as the careful analysis of intracortical potential fields by Spencer, Brookhart, and Calvet, et al., it is now possible to explain in detail the mechanisms that generate most of the wave shapes contributing to the EEG." Although Morrell overestimated the current understanding of intracortical synaptic mechanisms and field characteristics, it is nevertheless clear that the problem is not whether it is possible to relate intracortical processes to EEG recordings, but whether it is worthwhile to try. Such efforts are indeed worthwhile—indeed essential—respecting the ERP that comprise physiological correlates of time-delimited psychological processes.

There are three requirements of such an analysis: (1) differentiation of intracranial potentials from those of extracranial origin, (2) definition of the anatomical location of the intracranial generators, and (3) determination of lawful relationships between variations in the ERP waveforms and activity of their sources. This section considers some basic issues confronting solutions to the third problem. Approaches to the first two questions will be described later.

Consider the relationships among the electrophysiological phenomena that signal the functioning of brain mechanisms and their

parallel and largely unknown relationship with experience and behavior:

		Experience-Behavior		
ERP ↔ (Scalp)	ERP (Cortical and intracerebral)	↔ Local extracellular slow potentials	↔ PSP	↔ action unit potentials

This diagram forces an explicit recognition of the chain of neurophysiological and biophysical variables separating scalp-recorded ERP from the firing patterns of individual neurones. To the extent that each of the four transformations in the pathway may be evaluated quantitatively, the relations between the end variables may be specified. Usually, interest centers on the question of predicting unit firing pattern from scalp or cortical ERP. The reason for this particular concern is the general belief that the "codes" underlying the organization of experience and behavior are to be found in the firing patterns of cerebral neurones. Although it may be granted that all observable motor behavior is fully defined by the firing pattern of motorneurones, it is by no means clear that all of the critical information concerning the physiological determinants of perception, cognition, motivation, and memory is contained in the firing patterns of cerebral neurones. This question should be viewed at present as unanswered, so that attempts to discount the importance of graded potentials as critical measures of brain function are unacceptable on the basis of present evidence. On a more pragmatic plane, evidence on most of the transformations is insufficient to permit more than some inspired guesses on the likelihood of establishing generally useful rules for relating gross ERP recordings to cellular behavior. It is useful, nevertheless, to identify the variables which must be defined in order to establish such rules.

Four basic presumptions underlie any analysis of relations between graded potentials and unit activity: (1) firing is determined statistically by a specific threshold level of membrane depolarization in the region of the initial axon segment, (2) membrane potential in this region is defined by the spatio-temporal pattern of postsynaptic potentials (PSPs) over the neuronal surface, (3) the PSPs are conducted electrotonically and (4) over 90 percent of the average neuronal surface area is dendritic. These presumptions (which may not be entirely factual) imply that graded potentials near the axon hillock (i.e., axosomatic PSPs) are prepotent in determining cell firing, and that dendritic synapses should be substantially less efficient in this respect. To the degree that axodendritic endings represent highly redundant inputs, the electrotonic propagation of their effects could provide an important modulation of cellular excitability. The prominence of

axodendritic projections of the nonspecific thalamocortical system, in contrast to the more proximal endings of the specific thalamic projections upon cortical pyramidal cells, may represent an example of such a relationship. The geometry of synaptic distribution indicates that the absolute magnitude of PSP activity must be overwhelmingly dendritic. At first glance, this fact would suggest that extracellular potential fields generated by PSP also would be determined primarily by dendritic activation. If this were true, it would be rather easy to see that cell firing and extracellular potential changes are likely to be very loosely coupled, so that any physiological situation in which axosomatic and axodendritic synaptic activity were poorly correlated would result in a similarly low correlation between firing pattern and extracellular potentials. Unfortunately, theoretical analysis of the extracellular current flow patterns which might occur following synaptic activation of neurones has not been attempted at more than a primitive level (e.g., Rall, 1962). The popular explanations of extracellular potentials seem to be based largely on speculation, supported neither by detailed empirical data nor the quantitative analysis of field distribution of distributed current sources required to substantiate investigation of this problem.

In the absence of such data, what hope exists for relating neuronal events to the ERP? Any hope that presently exists arises from studies that surmount the no-man's-land of intracortical electrodynamics and compare the firing patterns of cortical neurones directly with extracellular potentials recorded either locally (i.e., somewhere near the neurone) or at the cortical surface. The report by Fox and O'Brien (1965) is a widely celebrated example of this approach. In this study, a virtual duplication of the poststimulus histogram (PSH) of unit firing was achieved by recording the average evoked response waveform through the same microelectrode following mechanical destruction of the neurone from which the action potentials had been recorded. These results suggest that an extracellular potential field generated by PSP in neighboring neurones either reflects or modulates the membrane potential changes that determine cell firing. The data would be consistent either with a synaptically determined synchronization of neural populations, with ephaptic influences, or both. The requirement for averaging an extremely large number of responses to obtain the observed fit of PSH and evoked potential indicates that the coupling of unit firing and slow potentials is probabilistic. The illustrative data reported by these workers (Fox and O'Brien) provided no information on the incidence of such relationships or their spatial extent within cortex. John and Morgades (1968) have reported similar results in recordings taken from the diencephalon of cats trained to perform

visual and auditory discrimination tasks. These data pose some intriguing problems of interpretation and seemingly provide a basis for expecting better correlation between ERP and unit activity than might be expected. John's data raise the virtually incredible possibility of rather extensive extracellular fields closely linked to the probability of the firing of all neurones within such a domain. These data demand careful attention to the biophysical possibilities for neuronal coupling by other than classical synaptic mechanisms. Regardless of the mechanism underlying these relationships between extracellular potentials and unit activity, there is an inescapable implication that the linkage between unit firing and local slow potentials depends critically upon the state of the organism and the specific behavioral operation being performed.

It is clear that use of anesthetic agents alters not only the behavioral capacity of the organism, but also the relationship between unit activity and slow potentials (e.g., Li and Jasper, 1953). Even the use of unanesthetized, paralyzed animals is not likely to escape this problem, since uncontrollable shifts in arousal level and attention occur in such preparations. Because of the differential projections of nonspecific and specific afferents upon cortical neurones, fluctuations in behavioral state may modify the relationship between unit firing and extracellular slow potentials. It is quite essential that these problems be given substantially greater attention by workers in behavioral physiology since a substantial amount of basic empirical data remains to be obtained on the critical relationships among behavioral state, slow potentials, and unit activity.

A further removed step is relations between surface cortical evoked responses and intracortical unit activity. The studies by Calvet et al. (1964); Creutzfeldt et al. (1966a,b); and Spencer and Brookhart (1961a,b) indicate that definite patterns of individual cellular behavior are related to certain spontaneous and evoked surface-recorded potentials. Even the few types of cortical potentials that have been studied do not relate to unit activity in a manner that can be predicted from the appearance alone of the surface potential. Knowledge of the intracortical potential distribution is required to differentiate potentials of the same surface polarity, but possessing different relations to the probability of unit discharge. It is important to recognize that these ambiguities, which appear to preclude any useful inferences concerning neural activity from the surface potential record, do not actually imply such indeterminacy if, as in the case of the previously studied potentials, there are for a given type of potential known and consistent relations between the two phenomena. In order to define such relationships it will be necessary to extend the observations to the ERP in

behaving animals by concurrently recording surface potentials, unit PSH, and laminar patterns of intracortical slow potentials.

Our observations from the striate cortex of monkeys adumbrate the complexities to be expected in resolving the problem of relations between surface-recorded evoked responses and the firing pattern of subjacent cortical neurones. Several PSH patterns are found in figure 2–3. In many neurones, there is a close relation between the peaks of the evoked potential and the firing maxima and minima. The sense of this relation can be in either direction although the relations of surface posi-

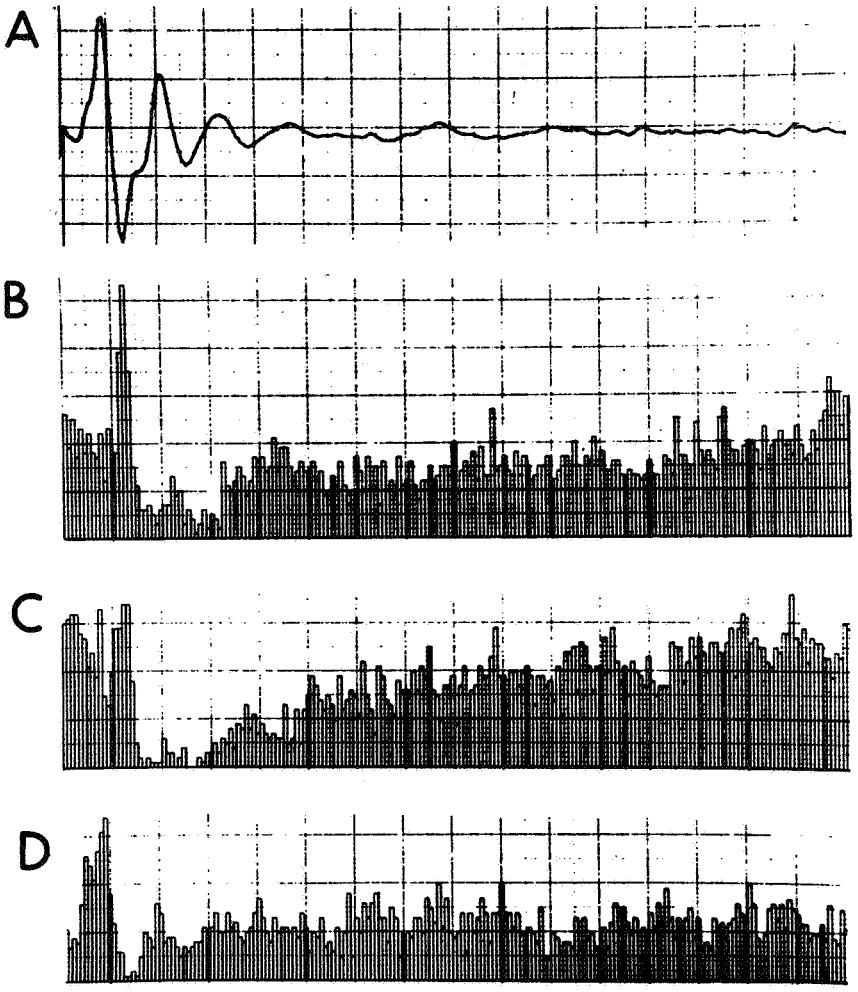

FIGURE 2–3.—(A) Evoked response to light flash from striate cortex of unanesthetized monkey. Voltage 50 μV/box. (B,C) Poststimulus time histograms from the same unit taken 1 hour apart. (D) PSH from an adjacent neuron. Sweep duration 1 sec (negative up).

tivity to increased firing and surface negativity to decreased firing seem more common. If, as is usually assumed, the surface potentials primarily reflect activity in the perpendicularly oriented pyramidal neurones, and the relatively large size of these cells favors their sampling by microelectrode recording, one might presume that the evoked potential and most of PSH selectively reflect the behavior of cortical pyramidal cells. This correspondence of PSH and surface cortical evoked response extends the observation of close correlations between local fields and unit activity noted by Fox and O'Brien and by John to a site relatively distant from the neuronal site whose membrane potential is presumed to determine its firing. Furthermore, the reciprocal linkage of increased and decreased firing rate with evoked potential polarity strongly suggests that the occurrence of excitatory (depolarizing) and inhibitory (hyperpolarizing) PSP is reflected rather accurately at the cortical surface. It is possible that the various demonstrations of dissociation between surface slow potentials and unit activity (Purpura, 1967) are quite irrelevant to the normal state of affairs in the cerebral cortex. This remains to be seen.

It is commonly noted that the initial biphasic deflection of the evoked potential most faithfully depicts the firing pattern and that, by increasing the number of samples making up the PSH, the correspondence for later portions of the response tends to be improved. Recordings taken over long periods of time from the same neurone demonstrate a substantial stability of firing pattern although, as seen in figure 2–3 (B) and (C), the unit activity may undergo changes in absolute magnitude of firing while retaining the same pattern of excitation and inhibition of discharge. The PSH patterns follow accurately changes in evoked response produced by alteration in stimulus parameters.

Another feature of cellular behavior seen in figure 2–3, is the prolonged suppression of firing after the initial transient response, frequently occurring with intense stroboscopic stimulation. In this record, no surface potential correlate of the unit depression is seen. This failure of correspondence is of instrumental origin, because of the short amplifier time constant used in this study. Fully adequate assessment of surface responses and unit activity requires dc or long time constant, capacitively coupled amplifiers. In addition to the PSH patterns that relate closely to the evoked response waveform, several less common types are seen. One shows a decrease in firing during the entire evoked response, some follow only one of the deflections, and others are shifted in phase with the evoked potential so that they appear to be related more closely to its slope. Neurones of the latter type have been reported by Dill et al. (1968) in a lateral geniculate body and by Freeman (1968a,b) in prepyriform cortex.

Although a detailed analysis of the relations between cellular

behavior and slow activity at the surface will be an arduous undertaking, it is a task of greatest importance to behavioral physiology. Since the detailed analysis of neuronal interaction within the brain requires intracellular recording in anatomically favorable structures, using simple afferent activation (e.g., Kandel et al., 1961), there is little likelihood that the patterns of brain activity associated with normal behavior may be analyzed directly by these techniques. Chronic microelectrode recordings, although feasible in behaving animals, are laborious and provide a limited view of brain activity within a circumscribed region. Recording of gross potentials, in contrast, may be taken concurrently from chronically implanted electrodes in many sites. When the inferences concerning unit activity that may be drawn from gross potential recordings are defined more clearly, we may anticipate the development of a behavioral physiology that can explore readily the patterns of brain function within all relevant neural systems, rather than in the limited areas that heretofore have been scrutinized in a single experimental study. If, as we shall show in the succeeding section, scalp recordings of ERP may be related to specific sites of intracranial activation, an investigative chain of behavioral physiology will have been forged, ranging from quantitative correlations of human experience and behavior, with scalp-recorded ERP at one end and the mechanisms of cellular behavior at the other. It will remain for the creative ingenuity of psychobiologists to assure that information begins to flow freely in both directions along this chain.

ANALYSES OF THE SOURCES OF ERP

The literature provides little encouragement concerning the possibility of defining quantitative relationships between activity of intracranial sources and their reflection in scalp recordings. Most of the empirical studies of intracerebral and scalp recordings have concerned the spontaneous EEG (e.g., Abraham and Ajmone-Marsan, 1958; Cobb, 1957; Cooper et al., 1965; DeLucci et al., 1962). This work suffers from the virtual impossibility of defining the geometry and strength of the actual sources of the EEG. For this reason, it has not been possible to apply the principles of volume conduction to compute expected intracranial and extracranial field distributions. Although some attempts to do this have been reported (Shaw and Roth, 1955), the lack of reasonable hypotheses concerning the intracranial sources of the EEG has thwarted application of a powerful technique for predicting the distribution of scalp-recorded potentials. The lack of a suitable quantitative model of cranial volume conduction has left unchallenged the impression from the empirical data that volume conduction ordinarily has a small role in defining the EEG at points more than a small distance away from a generator.

These conclusions concerning the insignificance of volume conduction possess some validity when the spatial and temporal relationships among the generators are complex and loosely correlated, as is probably the case with spontaneous EEG activity. The situation is quite different when a small number of generators are present and their geometrical features and timing permit them to be viewed as specifically definable current sources. Unfortunately, the conclusions concerning the "insignificance" of volume conduction for the spontaneous EEG have been accepted uncritically by investigators of evoked potentials despite the presence of strong evidence for intracranial volume conduction of evoked potentials. A study particularly relevant to the volume conduction of ERP in man (Kelly et al., 1965) demonstrated by means of transcortical recordings of somatosensory evoked responses in locally anesthetized human patients that the SER was generated in a localized region conforming to the primary projection area defined by cortical stimulation. The widespread potentials recorded by monopolar techniques were caused by volume conduction from the primary areas, shown by their absence in transcortical recordings taken outside of these areas. These important data not only emphasize the importance of volume conduction in interpreting recordings of evoked potentials taken at a distance from their sources, but also suggest that the generators of evoked cortical responses may be circumscribed much more than might be expected from the rather extensive distribution of these responses in scalp recordings. We have demonstrated the somatotopic representation of the motor potentials (MP) and SER in recordings taken from the human scalp (Vaughan et al., 1968) and have presented evidence confirming the contention of Goldring and his colleagues that the SER was generated solely in the primary somatosensory projection area. The results of this study prompted us to reconsider the feasibility of predicting the scalp distribution of ERP generated by intracranial sources from a model conforming to the configuration and impedance characteristics of the human brain and its coverings.

The quantitative analysis of volume conduction within the body has been developed extensively by students of electrocardiography, and interest has begun to develop in applying these methods to the analysis of cranial current flows. The computations required to evaluate a model of sufficient complexity to portray accurately even a simplified physiological system are quite formidable but are well within the capability of modern digital computers.[3] We have approached the problem of identifying the intracranial sources of ERP by comparing

[3] A quantitative treatment of the model will not be presented here. This study has been done in collaboration with Mr. James Siagus and Dr. Herbert Schimmel and will be published separately.

the potential distributions obtained from scalp recordings with the field computed from the model, assuming generator configurations suggested by known anatomical and physiological features of the brain. Although an intracranial source configuration cannot be predicted unambiguously from the epicranial field distribution, in practice, the limited number of reasonable hypotheses concerning location and configuration usually permits the selection of one alternative.

Mapping studies have been completed for several representatives of each class of ERP. The general procedure followed in these studies has been reported in detail (Vaughan et al., 1968). After preliminary studies defining the morphological features and general distribution of the potential under consideration, electrode arrays were placed so as to be centered upon the point of maximum amplitude, with spacing and orientation appropriate for definition of the spatial gradients. In all instances, a reference was chosen (chin or nose) that showed no significant activity when referred to a noncephalic reference. Care was taken to note the presence of muscular and eye movement artifacts in preliminary runs for each subject and to eliminate these by appropriate instructions and positioning. These precautions proved essential for obtaining reliable ERP maps. For each ERP study, the data were displayed for each subject in montages, thereby greatly facilitating the assessment of the complex waveforms over the entire spatial array. The information provided by visual inspection served as the basis for selecting specific points of the ERP for measurement to provide the quantitative mapping data. This step proved absolutely critical since the validity of the entire procedure rests upon the correct identification of ERP "components" generated from a single, stationary intracranial source. Although visual inspection is subject to interpretive error when it constitutes the sole basis for conclusions, there is not as yet a practical alternative possessing its power and flexibility in detecting regularities in complex configural data. Our experience with computer analysis of evoked-response waveform indicates that careful visual scrutiny of the raw data cannot be replaced without serious hazard, by formal and seemingly more precise data reduction techniques.

A number of general points concerning ERP measurement should be noted. Since most prior investigations of these phenomena have been concerned with the morphology of the potential when recorded from electrode placements yielding maximal amplitudes, the importance of assessing the level of residual background activity has not been fully appreciated. The relation of background EEG activity to the potential of interest becomes of substantial importance in those portions of the recording array where the time-locked activity has decayed to a fraction of its maximum value. Consider, for example, a

subject whose mean peak-to-peak EEG amplitude is 25 μV and whose auditory evoked response is 10 μV at its maximum point. Averaging responses to 100 stimuli will produce a signal-to-noise ratio of about 4:1 ($100\times10:10\times25$). At a point where the AER has decayed to one-fourth of its maximum amplitude, the signal-to-noise ratio will be only 1:1, and substantial measurement errors will be unavoidable. For this reason, a routine estimate of background amplitude to facilitate selection of an appropriate sample size, as by the $\pm$ method of Schimmel (1967), and several estimates of the mean ERP at each recording point are necessary to assure reliable results. In general, ERP components less than 5 μV in maximum amplitude have proven difficult to map with precision except in subjects selected for low-amplitude-background EEG activity. Even larger components may be resolved inadequately in subjects with large and widespread alpha rhythms during sleep, or in patients with abnormally high-voltage slow activity. This should be considered in any study involving routine application of standard experimental conditions to groups of subjects since individual differences in background EEG may render the data from some subjects unsuitable for quantitative analysis.

The studies reviewed here used a minimum of six subjects to provide the field distribution data. In several instances, the studies have been replicated with changes in stimulus parameters and reference electrode position to confirm the generality of the results. We shall consider first the ERP of Classes I, II, and III, which comprise the discrete time-locked potentials of cerebral origin.

Class I: Visual, Auditory and Somatosensory Evoked Responses

When recorded to stimuli of moderate intensity, these ER comprise a complex series of low-amplitude deflections that peak earlier than 100 msec. A more prominent biphasic negative-positive sequence follows (peaks indicated in figure 2–1). Over a group of Ss, the late negative and positive deflections show comparable changes in amplitude over the head so that for purposes of amplitude mapping, they may be considered as a unit. This peak-to-peak measurement is more accurate than measurements from a prestimulus baseline because of its greater size. It also eliminates the occasional "negative" values of a positive wave that prevents the amplitude scaling required to standardize measurements across Ss. The maps shown here are based upon the average scaled peak-to-peak measure of the "late" components of ER in each modality. The conclusions derived from these maps relate to some of the shorter latency components, which are, however, significantly more difficult to map accurately because of their small amplitude. Errors in interpretation may occur if it is not recognized that the smaller components may be confounded both with background

EEG activity and with myogenic responses, unless special measures are taken to identify and eliminate these contaminants.

Somatosensory responses.—Evoked-response maps obtained from electrodes placed over the left hemisphere during electrical stimulation of the right median nerve and right superficial peroneal nerve are depicted in figure 2–4. The zones of maximum amplitude overlie the estimated location of the Rolandic cortex, with the response to lower-extremity stimulation located just laterally to the vertex and the

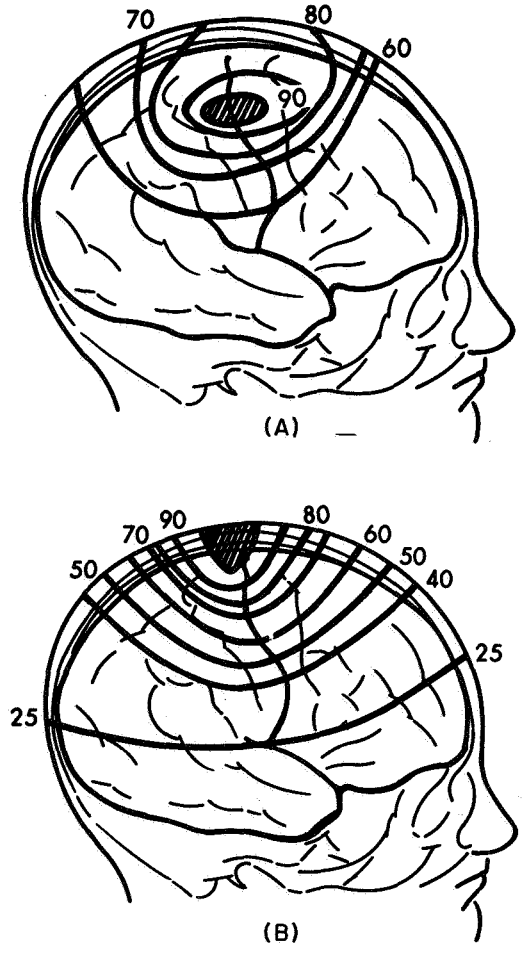

FIGURE 2–4.—Isopotential maps of P200 component of somatosensory evoked response. (A) Shock to right median nerve and (B) shock to right peroneal nerve. Chin reference.

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response to upper extremity stimulation about 4 cm laterally to the midline. The distributions of both responses conform to the field of dipole layer of the size and depth of the appropriate sensorimotor cortical area.

Auditory responses.—The map of auditory responses to binaural 1000-Hz tones at a 60-db sensation level is shown in figure 2–5. Responses are absent along a circle defined by the plane of the Sylvian fissure as it transects the surface of the head. Above this line, the evoked response is opposite in polarity to those recorded below it. Both the coronal field distribution (fig. 2–6) and the sagittal distribution conform to dipole layers in the position of Heschl's gyri. The dipole orientation is parallel to the surface of the scalp, so that a null potential is recorded in the plane of the layer and opposing polarities above and below it.

Visual responses.—The recorded evoked responses to a circular 10-msec light flash subtending 5° of visual angle with luminance of about 0.5 log mL showed a more complex configuration and distribution than either the somatosensory or auditory responses. A map of the deflections comparable in latency to the responses in the other modalities is presented in figure 2–7. Although both the early and late components of the VER show a maximum overlying the occiput, the later wave possesses a secondary peak in the central region. Inspection of the individual data indicates that these late components, although similar in appearance, are not identical in that the central component in some subjects peaks at a different latency than the posterior component, and the relative amplitudes of central and occipital components differ

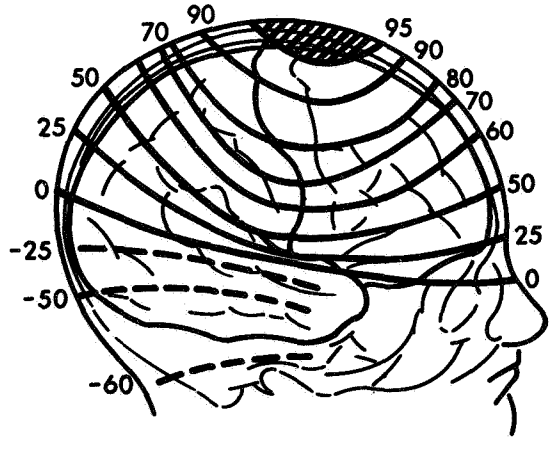

FIGURE 2–5.—Isopotential map of auditory evoked response (P200). Chin reference.

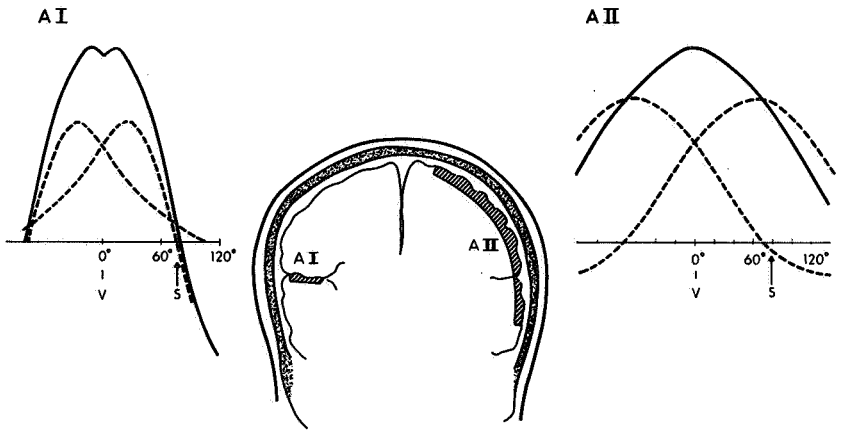

FIGURE 2–6.—Left: Solid line: Coronal amplitude distribution of P200 component of AER (AI). Dashed line: Theoretical distribution of components of AER generated by sources located in primary auditory cortex (center left). The sum of these components matches the observed distribution. Right: Similar plot for the P300 wave. (AII) This field corresponds to the sum of two fields, each generated by sources in parietal association cortex.

markedly from subject to subject. These data suggest that the late components of the VER result from two distinct generators rather than from volume conduction of the occipital response.

Since the geometrical arrangement of the visual cortex is substantially more complex than either the somatosensory or auditory, the dipole model is not as simple. Nevertheless, the very complexity of striate cortical geometry provides a test of the assumptions underlying the field analysis. The projections of the central retina are located at the occipital pole, and the peripheral projections are at the mesial occipital cortex. Furthermore, the upper hemiretina (receiving input from the inferior visual field) projects to the superior bank of the calcarine fissure and the lower half of the inferior bank. Similarly, the right homonymous field of vision projects to the left striate cortex and vice versa. Taking into consideration the retinocortical projections and the field distribution for an appropriate configuration of dipole layers, a number of predictions can be made. Foveal and immediately parafoveal stimuli will activate cortex on the surface of the occipital pole, representing a dipole layer with axes perpendicular to the surface. As field size is increased so that the mesial occipital cortex is activated, very little change in the evoked response is expected because of the symmetry of opposing dipole layers of mesial occipital cortex. This fact has been repeatedly confirmed (cf. DeVoe et al., 1968) although it usually has been attributed erroneously to a lack of surface

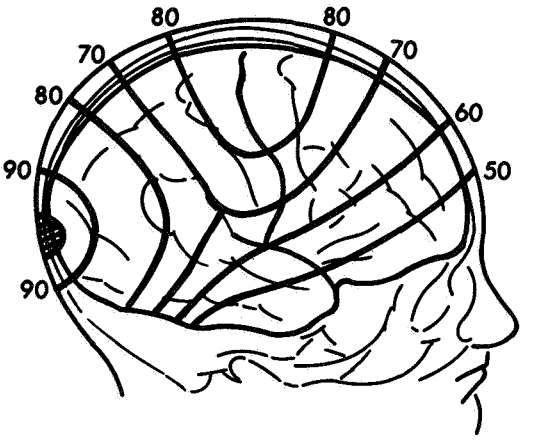

FIGURE 2–7.—Isopotential map for P200 components of VER. Note the complexity of the field with a secondary zone of increased amplitude at the central region.

reflection of activation of the peripheral retina. As has been shown (Eason and White, 1967), punctate stimuli presented to the peripheral retina can generate sizable evoked responses. As first suggested by van Balen and Henkes (1962), these have a different scalp distribution from foveal responses, as predicted by the model. If care is taken to exclude the prominent effects on the visual evoked response of stray light striking the fovea (Vaughn and Silverstein, 1968), the features of the focal distribution to peripheral stimuli may be defined accurately. The technique is as follows: First, the position of the calcarine fissure must be established by plotting the field of foveal stimulation. This is essential because of individual variations in the geometry of the occipital lobe. Arrays of electrodes are then placed around the posterior portion of the head, passing through the point of maximum foveal response. Selective stimulation of the peripheral retina is then carried out, using stimuli within the scotopic range of luminance (i.e., below cone threshold) or using a suitable adapting field for photopic stimuli. As expected by the geometry, the field of peripheral stimulation conforms to a dipole layer with the axes parallel to the surface of the scalp at the occipital pole. A number of specific features of scalp distribution remain to be analyzed in detail, particularly the specific contributions of rod and cone mechanisms in the periphery. The most easily interpretable results will be derived from selective stimulation either of the fovea or an asymmetrical peripheral locus. The data now at hand permit an appreciation of the

spatial variables which must be taken into account in future studies of the human VER.

Class II: Motor Potentials

Both the negative component of the MPs preceding muscle contraction and the positive wave that accompanies the movement show the somatotopic distribution over central cortex depicted in figure 2–8. The generators for hand and foot MP are smaller than for the somatosensory responses and are therefore almost certainly limited to the precentral gyrus. The somatosensory responses to electrical stim-

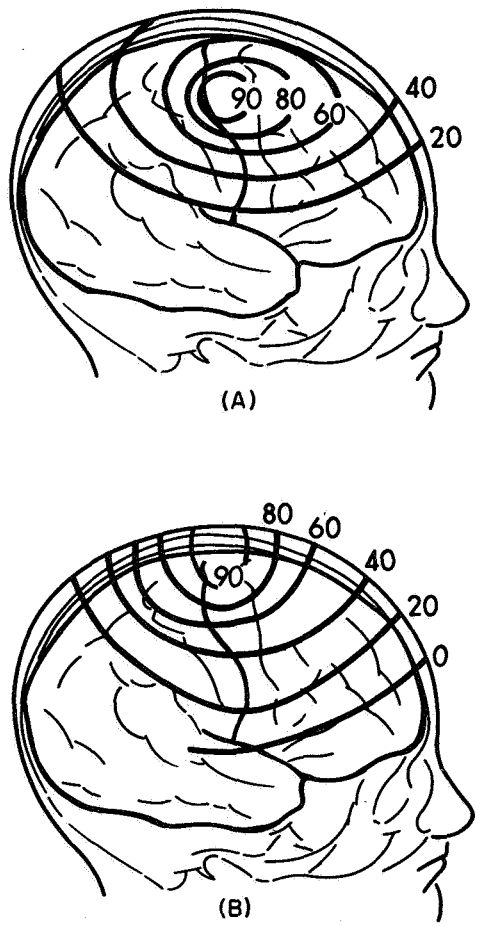

FIGURE 2–8.—Isopotential maps for the motor potential. (A) Hand movement and (B) foot dorsiflexion.

ulation probably arise from both precentral and postcentral gyri, because of the activation of muscular afferents that project to the precentral motor cortex as well as the cutaneous afferents that have a strictly postcentral projection (Albe-Fessard and Liebeskind, 1966). Such subtle distinctions in distribution inferred from scalp-recorded data are quite unexpected and emphasize the importance of precise mapping carried out under carefully standardized experimental conditions.

The MPs associated with tongue movements and articulated speech arise from generators near the lower end of the Rolandic fissure that are larger in extent than those associated with hand and foot movements. They are bilateral, in contrast to the predominantly contralateral generators for hand and foot movements. As yet, there is no evidence for lateralization of MPs associated with verbal utterances, as might be anticipated from the hemispheral specialization of speech mechanisms. This question merits further investigation.

Eye movements also are associated with antecedent cortical potentials. Their distribution is not as yet well-defined because of the extraordinary difficulty of conclusively excluding small eye movements (and consequent contamination by the EOG during ocular fixation). Present evidence indicates that antecedent potentials are present both over the posterior frontal (premotor) cortex and in the inferior parietal-posterior temporal region. Following each eye movement, an evoked potential (lambda wave) appears in the occipital area, conforming to the distribution described for the flash evoked responses (Remond and Lesèvre, 1965).

Class III: Long-Latency Potentials

The large P300–500 waves are found in several previously described experimental situations involving stimuli of any sensory modality. We have mapped their distribution during visual and auditory stimulation in one of the experimental arrangements which elicit these waves. The maps shown in figure 2–9 were obtained by stimuli, presented at infrequent intervals, which elicited orienting responses. Although the distributions of the waves elicited by visual and auditory stimuli are not identical, they extensively overlap and center upon the midparietal region. Distributions with this extent cannot be attributed conclusively to one specific source, as was possible with the more localized distributions previously described. They could be caused either by a large cortical area of activation, roughly corresponding with the extent of parietal association cortex (fig. 2–6), by a deeper source (posterior thalamus), or by both. A generator subtending a large angle with the surface produces fields that decay less sharply as a function of depth than those of smaller generators, so that large,

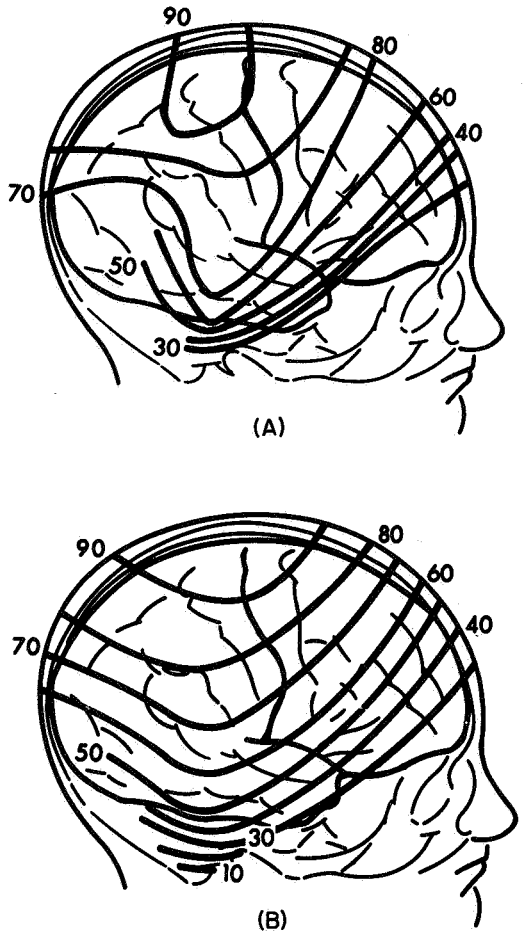

FIGURE 2-9.—Isopotential maps for P300 component. (A) Auditory stimuli, and (B) visual stimuli.

deep sources could be reflected at the surface of the scalp if they possess a suitable geometry. It should be noted, however, that the cellular anatomy of most subcortical nuclei suggests that they would be poor external field generators because of unsystematic cellular orientation or closed configuration (e.g., lateral geniculate). Empirical studies have shown the field of subcortical structures to be quite complex (e.g., Freeman and Patel, 1968), so that accurate predictions are not possible without detailed anatomical and physiological knowledge of each structure.

Class IV: Steady Potential Shifts (SPS)

The cranial distribution of SPS can be mapped in a manner similar to the other classes of ERP. These potentials present difficulties not encountered in mapping the transient responses because of the almost ubiquitous contamination by the EOG. We first encountered this difficulty in mapping the initial slow component of the MP and the SPS seen in reaction time tasks ("CNV"). According to the data reported by Low et al. (1966a,b), the latter potentials were most prominent over the frontal lobe as had been asserted by Walter et al. (1964). Upon monitoring eye movements with an orbital lead, we found that the more anterior SPSs were associated with vertical eye movements that occur before a motor response or in anticipation of a tachistoscopic visual stimulus. When these ocular movements were attenuated or eliminated, the maximum SPSs were found at, or near, the vertex. In the case of extremity movements, either selfpaced or in response to a signal, a somatotopic central distribution of the SPSs was found, comparable to that of the later positive component of the MP. In tasks requiring a sensory discrimination, SPSs were found to center upon the scalp projection of the sensory-evoked responses. Thus, in visual discriminations, an occipital negative SPS was recorded, distinct from the central SPS associated with preparation for a motor response. In choice reaction time tasks requiring a different motor response to each stimulus, the central SPS was small or absent during the interval between warning and presentation of the response signal; when a response was required to only one of the signals, the central SPS reappeared contralateral to the extremity responding to the positive signal. This shift was always smaller than in the simple reaction time task. These observations suggest that SPSs may be developed specifically in relation to sensory and motor preparatory sets and reflect some process that antecedes an anticipated activation of the specific sensory or motor cortical area. This interpretation is consonant with the observations by Shvets (1958) on the SPSs which appeared over the sensory and motor cortex of rabbits during the elaboration of a conditioned response.

Class V: Extracranial Potentials

The ubiquitous presence of the EOG has already been noted. A typical distribution is depicted in figure 2–10. These potentials are particularly troublesome in tasks requiring visual fixation or motor response, or when intense, unexpected stimuli are presented. Since these conditions are frequently present in behavioral experiments, constant attention must be directed to this problem. Although an instrumental method for reducing the effects of the EOG has been suggested (McCallum and Walter, 1968), it cannot be relied on for a general solu-

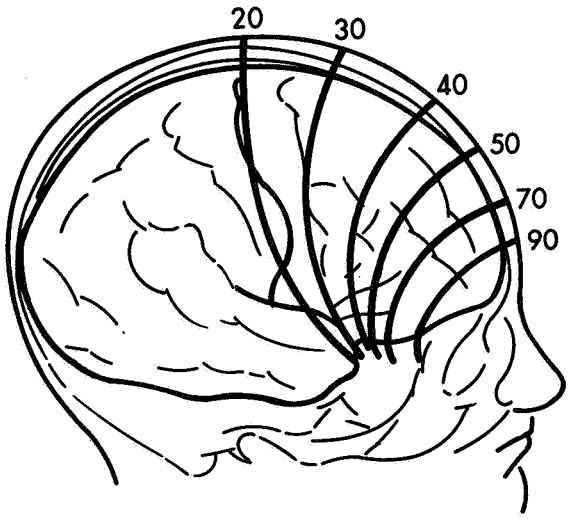

FIGURE 2–10.—Isopotential map of EOG for vertical eye movement.

tion since the distribution of EOG potentials differs from subject to subject and for movements that differ in direction. The only fully satisfactory method is the elimination of all trials on which eye movements are detected. Optical methods, although more difficult than electrical monitoring, are most satisfactory. This problem seriously affects recordings of ERP in clinical populations and must be taken into consideration whenever voluntary ocular fixation cannot be assured.

Muscle potentials (EMG) present the second major challenge to valid extracranial ERP recording. Their distribution has not been resolved in detail except for the postauricular potential, originally described by Jacobson et al. (1964). In mapping this response to high-intensity clicks, we found that it was sharply circumscribed to the immediate vicinity of the muscle, as predicted by the volume conduction model. It appears, therefore, that extracranial muscle potentials may be eliminated from ERP recordings by avoiding electrode placements that directly overlie the superficial cranial musculature (i.e., mastoid, inion, temporal region). When records are required from these regions, scrupulous attention to relaxation of the underlying muscles and use of moderate stimulus intensities can succeed in eliminating myogenic potentials from the ERP records.

To sum up our data on the distribution of the ERP, we have found that:

(1) The distribution of the late biphasic deflection of auditory,

somatosensory, and visual-evoked responses is consistent with localized sources located within their respective primary projection areas.

(2) An additional central field is noted for visual responses over the central region. This may reflect the direct polysensory projection to motor cortex. The extent of the somatosensory field also suggests precentral activation. There is no evidence for a similar additional projection of auditory responses.

(3) The motor potentials for extremity movements and for movements of facial and tongue muscles possess fields pointing to generators in precentral motor cortex according to its known somatotopic organization.

(4) The long latency (P300–500) potentials associated with orienting responses and discrimination tasks have similar distributions for both auditory and visual stimulation overlying parieto-temporal association cortex. A deeper generator cannot be ruled out conclusively but appears less likely because of anatomical considerations.

(5) Steady potential shifts are present over the areas from which the sensory responses and the motor potentials are recorded under conditions that imply a state of preparation or expectancy. The distribution of these potentials is quite different from that suggested by early studies of the "CNV".

(6) Extracranial potentials, notably the EOG and EMG, frequently present in scalp recordings, may be distinguished by their cranial distribution. Their presence must always be suspected, and efforts made to eliminate them or to differentiate them from the intracranial ERPs.

Several general comments upon the results and their limitations should be made at this point. The data are surprising, and the conclusions drawn therefrom conflict with long-established beliefs concerning the localization and presumptive origin of the long-latency components designated "vertex waves." The results reported here leave little doubt that the major source of these waves is the specific cortical projection areas. The possibility of a second central generator (possibly because of polysensory projections to motor cortex), strongly suggested by the visual-evoked response data, leaves some vestige of the classical vertex potential. Recent evidence obtained by Williamson, et al. (1968) indicating that all components of the somatosensory-evoked response are eliminated ipsilateral to lesions involving the lemniscal system also is inconsistent with a "nonspecific" origin of the late components. This evidence reemphasizes the importance of the primary sensorimotor cortical regions and shows the necessity for elucidating the mechanisms producing their prolonged activity following the arrival of an afferent volley. These mechanisms undoubtedly involve subcortical as well as cortical structures, providing an oppor-

tunity for the intermodal interference effects noted for the late component of evoked responses (Allison, 1962).

Further analysis of the shorter-latency components of evoked responses is required. This is difficult in scalp recordings, and as reported by Goff (this conference) and ourselves, the distribution of these components shows considerable variation across subjects, seemingly because of contamination by evoked myographic activity. Broughton (1967 and this conference) has obtained useful data on somatosensory responses from cortical recordings in man. Whenever available, this type of recording can provide invaluable aid in clarifying the small early components and assisting in defining their origin. In these studies, however, careful quantitative application of field theory is essential for properly planning and interpreting the observations.

ERP AND BEHAVIORAL NEUROPHYSIOLOGY

I have sketched the lines along which research on brain electrophysiology may provide data linking the cellular mechanisms underlying experience and behavior with gross electrical phenomena (ERPs) which may be observed directly during appropriate psychological experimentation. There are many who question the value of research which records macropotentials from the scalp of man or the brain of experimental animals. There is a current vogue for microphysiology which discounts the importance of the grosser neurophysiological phenomena. Nevertheless, there is a large gap to be traversed between the behavior of individual neurones in striate cortex and the perception of form. Large areas of brain, most of which remain unexplored by the microelectrode, must function in concert to produce the simplest visual experience. Where are these areas? When within the span of perception should we seek the relevant neural events? Some answers to these questions already emerge from the study of the ERP in man. In the visual modality, the VER has permitted us to define cortical events specifically related to geniculocalcarine input to striate cortex (Vaughan and Katzman, 1964; Vaughan and Gross, 1966); to brightness perception (Vaughan and Hull, 1965; Vaughan, 1966); to spectral sensitivity and other aspects of foveal vision (DeVoe et al., 1968); to the suppression of pattern vision during saccadic eye movements (Gross et al., 1967); to metacontrast suppression (Vaughan and Silverstein, 1968); and to motor responses to photic stimulation (Vaughan et al., 1965a, b). None of the direct quantitative correlations that have been possible in the human subject have been obtained, to my knowledge, with microelectrode recordings in experimental animals. Although feasible in principle, concurrent behavioral and physiological studies in animals are substantially more difficult than com-

parable studies in man. Human subjects may readily modify their behavior in response to instructions and may be studied repeatedly and extensively under a wide variety of conditions. Although animals may be trained to a wide variety of specific tasks, they possess neither the flexibility of the human subject nor his unique cognitive abilities. The latter, in addition to providing convenient means of experimental manipulation, offer the greatest challenge to an understanding of brain mechanisms. Although beyond our present experimental ken, the linguistic abilities of man must not be dismissed arbitrarily from the realm of behavioral neurophysiology. Similarly, the phenomena of consciousness, long banished from psychology, cannot be ignored in any attempt to comprehend the physiological basis of perception, cognition, and effect. The myth that only externally observable motor behavior can accurately reflect psychological processes has been demolished by observations of brain responses directly correlated with subjective perceptual variables.

There remains an enormous task. The neurophysiologist must provide a substantially more detailed indication of intracortical processes. The mechanisms underlying the striking linkage between neuronal firing pattern and extracellular potential field observed in some conditions and not in others, the biophysical determinants of current flow and associated intracortical fields, the effects of glial modulation (Grossman and Hampton, 1968) and macromolecular binding (Adey, 1967) upon these processes, and other problems await resolution by the neurobiologist. In the last analysis, however, none of these details of cerebral physiology will provide us with an understanding of human experience and behavior. Only direct demonstrations of concomitant variation of psychological and physiological variables will suffice. This task falls to the investigation of ERP in man and behaving experimental animals. Consideration of the history of human "evoked-potential" investigation over the past few years suggests that a reconsideration of the requirements for effective implementation of the powerful technique of averaging is required.

Unfortunately, the wide availability of the EEG averaging procedure has permitted a "magical" approach to human psychophysiology. There has been a widespread tendency to view the evoked response as just another psychophysiological measure such as the GSR. Thus, we find numerous attempts to correlate evoked responses with a host of complex psychological variables ranging from I.Q. to psychiatric diagnosis. Although it is possible that such exercises may accidentally stumble upon some stable and comprehensible relation, the possibilities at present seem to be rather dim (none of the widely publicized correlations appear as yet to have survived the test of cross-validation). It is necessary for investigators of human

ERPs to deal explicitly with the anatomical, biophysical, neurophysiological, statistical and psychological variables which define their system of inquiry. To neglect any one of these factors may render an otherwise well conceived study just an accidental case whose relevance to the puzzle of behavioral neurophysiology may long remain obscure. If one adopts an approach to ERP analysis that recognizes the anatomy of the human brain, the physical properties of its coverings, and the necessity for comparing psychological and physiological measures directly, the power of ERP analysis is no more limited than that of any presently available method of neurophysiological or psychological investigation. The problem may be stated rather simply. The neurophysiologist must recognize the specific impact of behavioral variables upon the validity of his observations; the psychologist must accept the necessity for dealing with the intimate details of brain function in his quest for the mechanisms of behavior. There is no easy path. Neither the facile analogies so glibly adopted by neurophysiologists nor the mindless correlations fashionable among psychologists provide more than an illusion of understanding. The biophysical and neurophysiological anlagen of experience and behavior will be disclosed only by a laborious quantitive analysis of each step along the long path from molecular biology to psychology.

DISCUSSION

DR. KNOTT: My remarks are based upon the problems as they have existed for many years in electroencephalography, where we have been trying to determine the exact geometrical relation between the electrical activity recorded on the scalp and the electrical activity in the cortex. In electroencephalography, the problem of relating cortex and scalp activity has existed for some 35 years. We are pleased that there are now other investigators who are also interested in the problem.

While one presumes from simple schemata of an electrical field that an electrical event at the cortex at point A would be proportionally represented on the overlying scalp at point A′, investigation was not adequately provided until 1958 (Karl Abraham and Cosimo Ajmone-Marsan, 1958). These investigators simply plotted the relative amplitude of cortical spikes and the same spikes at the scalp. While there was a seemingly reasonable correspondence, it was by no means perfect. The ratio of the voltages at the cortex and the scalp may change with time for the same cortex versus scalp leads. A ratio of 50 to 1 may increase rather strangely to a ratio of 90 to 1 or more, or may become infinite, which means that the spike is not apparent on the scalp, although it still is apparent at the electrodes on the cortex. When the position of a reference electrode was shifted, it became apparent that the position of the electrode pair in relation to the field was

an extremely important factor. While this is obvious, especially following Brazier's classical analysis of fields (1949), perhaps it is a point that needs to be reemphasized from time to time.

A study by DeLucci, Garoutte, and Aird (1962) revealed rather interesting data. Electrodes were implanted on the pia mater of the cat, while other electrodes recorded from scalp surface directly above; the degree of correspondence between the two ongoing electroencephalograms (pial and scalp) was determined. The electrodes in the cortex were very small and scattered over a comparatively small area. The EEG derived from a single electrode on the cortex, under a scalp electrode, did not show tremendously good correspondence with that from the scalp. When a number of cortical points were recorded together, the correspondence with the scalp was extremely good, showing that the area of electrically active brain is important when one wishes to correlate scalp EEG with cortical events.

Cooper et al. (1965) have addressed themselves to the same problem with human subjects, using visual-evoked responses as a measure of cortical and scalp electrical activity. It is extremely interesting that a "ringing" response could be recorded from scalp more clearly than from the cortex just beneath the scalp electrode. Again, brain area is probably very crucial in this matter. They also noted the variability in the relationship of the voltages and reported ratios of cortical-to-scalp voltage as low as 2 to 1 on some occasions, with maximum ratios of about 5000 to 1. In general, they concluded that these ratios become larger if the brain areas involved are smaller.

An experiment by Morrell and Morrell (1965) presented to the American EEG Society a computer analysis of these problems. By using scalp electrodes and electrodes lying over the dura mater in man, they were able to construct contour maps that enabled them to distinguish the components of an evoked response that were primarily deep midline in origin and those which were predominantly propagated over the cortical surface. What appears on scalp, therefore, may have rather varying origins and cannot be arbitrarily assigned to immediately underlying cortex.

Bickford and his associates have been engaged in some exciting contour mapping. He and Harris have been able to program a computer to give the probable contour over a fairly large area by using a relatively small number of electrodes (see fig. 6–16). If experimental verification of this can be extended, some tremendously important leads may be provided with respect to the correspondence of surface activity to underlying events.

Goff, Rosner, and Allison (1962) studied evoked responses from a number of points on the scalp, using both chin and nose as a reference (generally getting off the scalp and off the ear—hence "off the head"—

so that the plotted evoked potential (EP) field would be contaminated minimally by activity at the reference point). They observed a great variability in the EP depending upon the active scalp point. It is interesting that their data can be interpreted as showing either a very broad projection to scalp, for somatosensory EPs, or a very broad spread of the field.

The reason for the apparently broad spread can be easily understood. A scalp electrode is, in reality, far from the skull. When the thickness of the skull is added, plus the distance from inner table to actual cortex, the pickup lead is found to be some distance from the presumably active cortical tissue. If one studies visual-evoked potentials, he must remember that most of the calcarine cortex (area 17) is not at the convexity. Still more remote from convexity is the auditory cortex. Perhaps we should recall the classical study by Marshall, Woolsey, and Bard (1937), which showed very small responding areas of somatosensory cortex. Considering these data with those showing that area of cortex is important in relating direct brain events and scalp events, the magnitude of the problem can be appreciated.

This is not to state that these problems cannot be solved. It is only that we need to generate a degree of caution, and perhaps a little modesty now and then, and to steer a course which will keep us from beginning to believe ourselves when the accuracy of some basic assumptions may be in question.

DR. VAUGHAN: I would like to emphasize that the problems encountered in the application of volume-conduction theory to EEG data derive from two important aspects of earlier approaches. First, studies of spontaneous EEG activity, either normal or pathological, suffer from the fact that it is difficult to define accurately the location and orientation of the generators. It is axiomatic that the characteristics of dipole generators within a spherical volume conductor cannot be defined uniquely by the fields measured at its surface. This limitation becomes considerably less forbidding when the generators can be assumed to be very simple in their configuration and limited in number. Then, the constraints are such that it is necessary to test only a few anatomatically reasonable hypothetical generator configurations against the observed field distributions. This is what we have succeeded in doing for the ERPs.

The second problem concerns the relationship between generator size and field penetration. It is well established (e.g., Abraham and Ajmone-Marsan, 1958) that EEG activity that is synchronous over a substantial cortical area is well represented at the scalp, while activity such as epileptic spikes, although of large amplitude at the cortex, may be generated within a circumscribed area and fail to be seen in scalp records. The reason for this is illustrated in figure 2–10(A). For

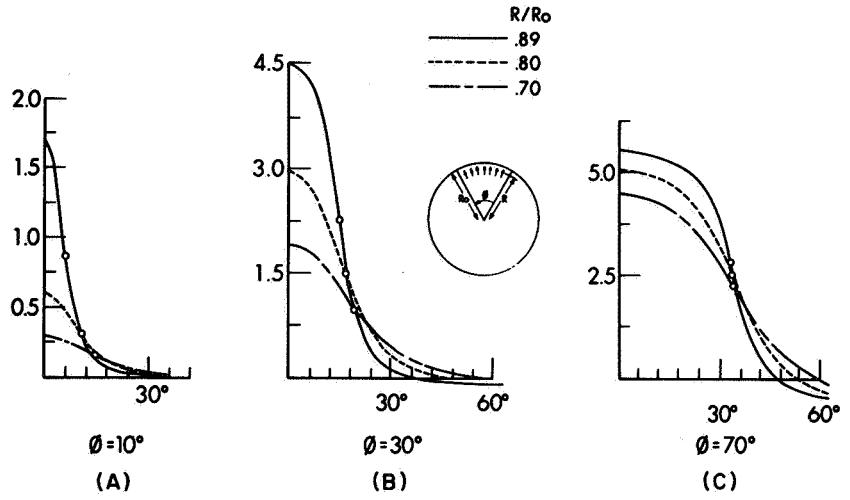

FIGURE 2–10A

simplicity, a uniform conducting sphere is depicted here; however, the principles for a multiple shell, which more accurately represents the brain and its coverings, are the same. The maximum potential generated at the surface by a dipole layer subtending a solid angle of 10° and located 89 percent of the distance from the center is only one-third as great as the maximum generated by a similarly situated layer subtending 30°. As the generator is moved further from the surface, or alternatively as layers possessing different conductance are interposed, the disparity between small and large sources becomes increasingly great. While the field of a 70° generator suffers relatively little attenuation, the potentials produced by a small generator become extremely small. The common assertion that the scalp is a "spatial averager" is not a correct description of the mechanism underlying the observations. These follow directly from the properties of a volume conductor and are just as true for potentials recorded within the brain as for those recorded from the scalp. It is also important to note that the "smearing" of fields, which has been described frequently (e.g., Geisler and Gerstein, 1961) is more apparent than real. If the half-amplitude point on each curve is taken as a measure of dispersion, this point moves out very much only for the small generator as the distance of the generator from the surface increases.

It must be emphasized that the conclusions presented in my paper are derived from averaged data from several normal subjects. Individual variations in field distribution are seen which are to be expected, considering the variation in thickness of the layers covering the brain and differences in gross morphology of the brain. Thus, the

very detailed spatiotemporal displays obtained by Rémond and Lesevre (1965) for individual subjects will tend to emphasize these differences, rather than common features of distribution that permit the gross but quite unequivocal localizations we have inferred from our data.

DR. BROUGHTON: For the past 4 years at the Montreal Neurological Institute, we have studied the somatosensory-evoked potential (SEP) of epileptic patients undergoing lobectomy, under local anesthesia, for temporal lobe seizures. The cortex in the region of the central sulcus was essentially normal. We have been able to compare pre-operative scalp recordings referred to an earlobe electrode with direct cortical recordings referred either to an earlobe or to the bone. This has given data suggesting the possibility of dividing the early portions of the SEP into a sequence of current generators with different spatial orientations as the basis of different components. It has also helped to clarify the important problem of cortex-to-scalp transfer.

The most striking and constant feature of the cortical SEP is the inversion of polarity of early components 1 and 2 across the central sulcus. Figure 2–11 shows a recording at parallel locations on the precentral and postcentral gyri, the latter being at the point where direct cortical stimulation produced sensation referred to the contralateral index finger. Stimuli in all the studies consisted of a percutaneous depolarizing shock over the contralateral median nerve at the wrist sufficient to produce a just-visible thumb twitch.

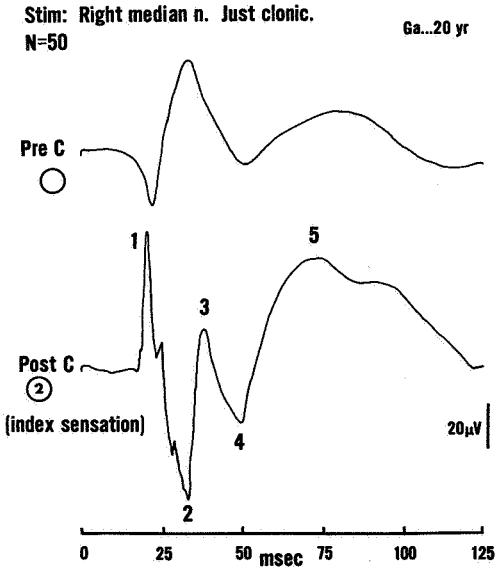

FIGURE 2–11.—Distribution of the cortical SEP at the central sulcus (positive down). Note apparent inversion of postcentral gyrus components 1 and 2 over the precentral gyrus. Brief spike-like potentials are only recorded on the postcentral gyrus. Component 3 appears to be present only on the postcentral gyrus. Component 5 is synchronous over both the precentral and postcentral gyri, and component 0 is absent.

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The SEP components 1–5 are well developed on the postcentral gyrus. The precentral gyrus shows a potential whose polarity is inverse to that of postcentral negative component 1 and positive component 2. Brief spike-like potentials ride on component 1 over the postcentral gyrus, a phenomenon present in about one-half of the cases. Whether these are somatic or not, I do not know. But they have been seen by other workers (Kelly et al., 1965) and are never recorded over the precentral gyrus.

Figure 2–12 shows the polarity inversion of components 1 and 2 in four additional patients, the last (Ab) also demonstrating spike-like potentials. Negative component 3 is usually present only on the postcentral gyrus or on a precentral and postcentral gyri synchronously. Positive component 4, on the other hand, shows a very different spatial distribution, being of higher amplitude and more widespread distribution in the posterior parietal region.

These distinctive field distributions also are observed on the scalp. Figure 2–13 presents records of the scalp SEP of a normal subject showing the same polarity inversion of postcentral components 1 and 2 between the parietal and central electrodes. This inversion is obvious in about 30 percent of scalp recordings. In the others, the more wide-

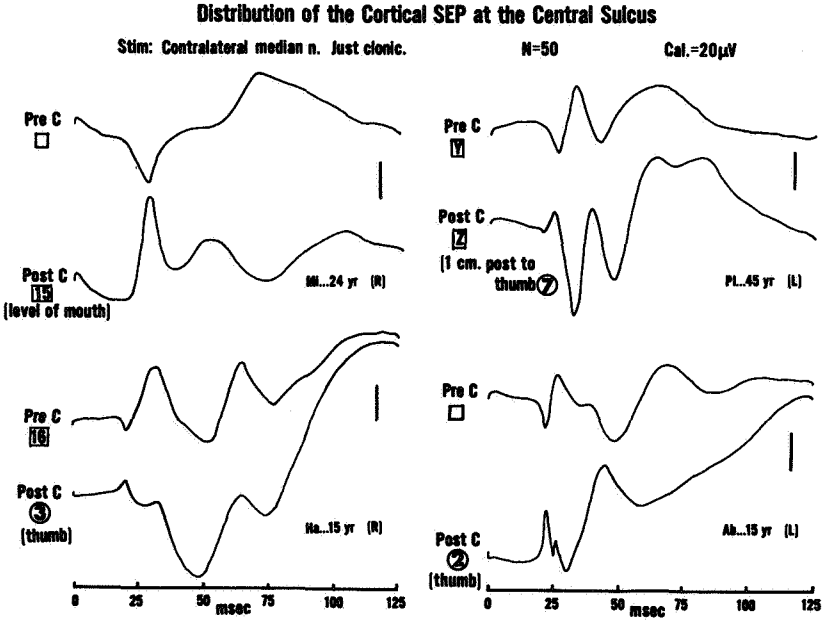

FIGURE 2–12.—The cortical SEP at the central sulcus in four subjects (positive down). All four patients show polarity inversion of postcentral component 1 and, usually, component 2 on the precentral gyrus. This is sufficient alone to locate the central sulcus.

spread postcentral potential appears to obliterate the relatively localized inverted precentral potential. Positive component 0 at 15 to 16 msec is widespread over the scalp, but is generally not apparent on the cortex. Component 4, on the other hand, has a more posterior location, being maximal in the parietal region.

In the early part of SEP, therefore, positive component 0 is present diffusely in scalp recordings and absent on cortex-to-bone recordings; components 1 and 2 show constant polarity inversion on the cortex in the region of the central sulcus, and this is sometimes visible on the scalp. Component 4 on both cortex and scalp is maximum in the parietal region. These findings suggest different origins or generators for the different phenomena.

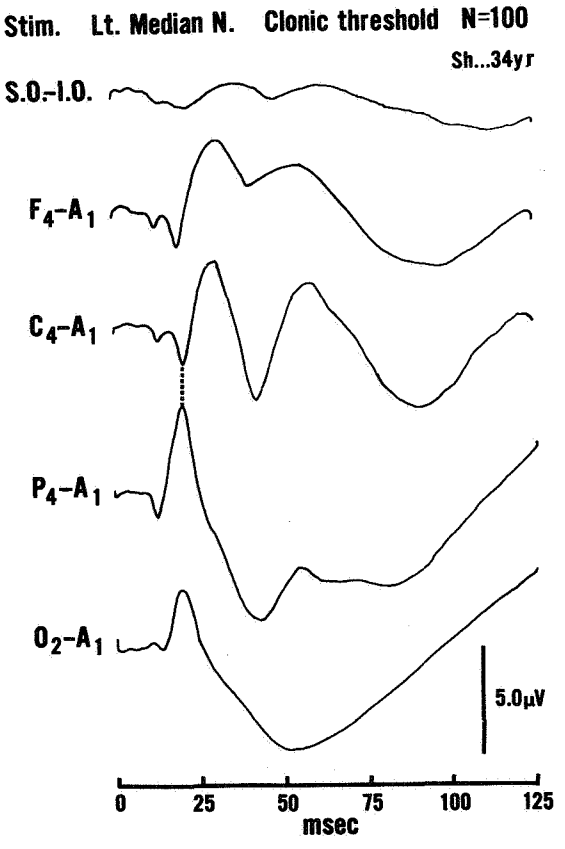

FIGURE 2-13.—Topographical distribution of the scalp SEP (positive down). The polarity inversion of early components over the central region is apparent in this scalp recording.

Component 0 can be explained as reflecting a potential of subcortical origin that is equipotential for cortex and bone. The ascending thalamo-cortical radiation volley or a ventro-basal thalamic potential is a likely candidate. Recordings in the thalamus have shown latencies of this order (Mathews et al., 1968).

Components 1 and 2 are best interpreted as arising from a horizontally oriented "dipole" generator, probably the primary somatosensory cortex folded into the posterior wall of the central sulcus. With this orientation, the precentral electrodes would "look" at the top of the dipole, whereas electrodes over the central sulcus "look" at its bottom. In the latter situation, the usual positive-negative polarity is inverted to a negative-positive sequence. Component 4 appears to represent yet another independent posterior projection to the parietal cortex, perhaps from thalamic association nuclei or secondarily from the primary somatosensory cortex. Additional generators can be hypothesized for later components 5–6 and 6–7, even if they require transmission in the primary cortex, as Williamson et al. (1968) important data suggest.

The problem of cortex-scalp transfer is of equal importance in our analysis of evoked potentials. Figure 2–14 shows the SEP of a patient at corresponding scalp (solid line) and cortical (dotted line) positions before and during surgery. Note that the scalp reflects the cortical potential accurately, although it is attenuated considerably in amplitude. Contributions from scalp, muscle, or eye movements are therefore improbable.

Such combined scalp and cortex studies can also clarify other principles of cortex-scalp transfer. The next two figures demonstrate two of these. In the figure 2–15, scalp electrodes C–4 and C–6, in solid lines, show a wide positivity peaking at about 40 msec whereas the underlying cortical points, in dotted lines, show a briefer positivity of earlier peak latency. Moreover, the scalp electrode at C–4 shows a small notch riding on negative component 1 at 20 msec, which is synchronous with a spike-like potential on the underlying cortex. Figure 2–16 helps to explain both these features. The upper right insert shows the cortical electrode positions. The scalp electrode C–4 was over the half-moon position in the parietal region. It now becomes evident that the briefer positivity peaking at about 28 msec in the cortex directly below C–4 is being averaged with a larger and later positivity present more anteriorly, together producing a single large positivity (fused components 2–4). The later components on the cortex always tend to be of greater latency than on the scalp, apparently because of cortical cooling. In this patient, spike-like potentials, which usually are very localized on the cortex, were recorded on the scalp only because of their widespread distribution. The scalp electrodes therefore perform a

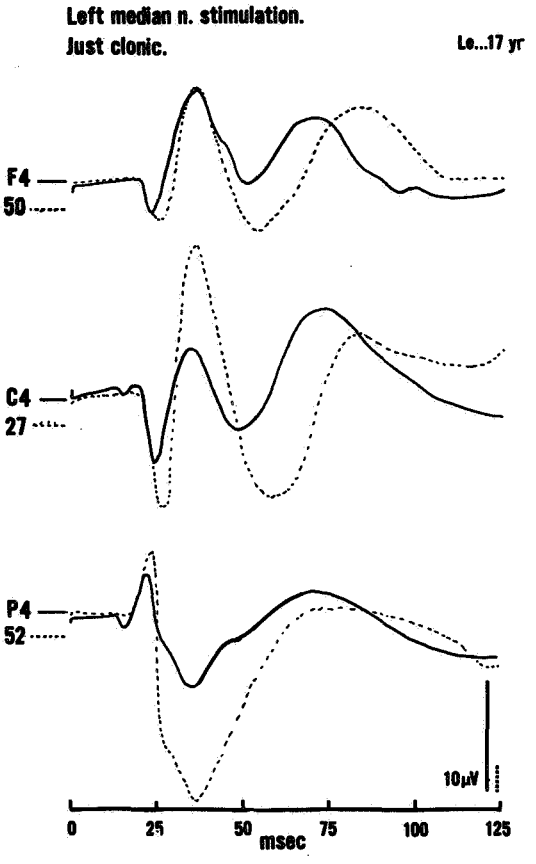

FIGURE 2-14.—Comparison of scalp and cortical SEP in the same patient (positive down). The scalp and subjacent cortical recordings have been superimposed for those electrodes where close topographical relationships were possible and show good correspondence. The cortical SEP (dotted line), however, shows somewhat increased latencies of all components by about 2 msec, believed to be caused by cooling of the exposed normal somatosensory cortex. Component 0 (positive, 16 msec) is not present in cortical responses.

temporal-spatial average of subjacent cortical activity; widespread potentials are conducted preferentially, even when of lower amplitude or containing high frequency components.

Cortical recordings, therefore, help in the analysis of the scalp-evoked potential both in terms of underlying generators and in terms

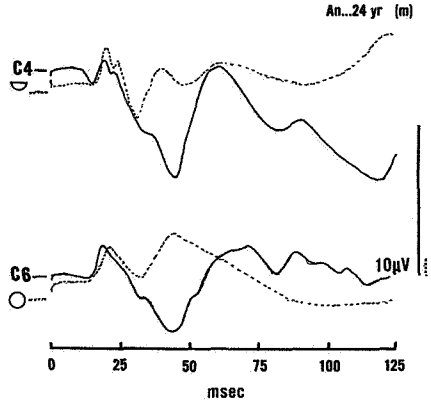

FIGURE 2–15.—Comparison of scalp and cortical SEP (positive down). The C4 electrode shows component 1 with a brief spike-like potential synchronous to that of the subjacent cortical electrode. The curves are also identical for the beginning slope of positive component 2. But on the scalp, there is a virtually fused component 2–4, whereas the underlying cortical point shows a well developed component 3 (negativity at 40 msec) and a lower voltage component 4. Similar findings are observed at electrode C6.

of certain principles of cortex-scalp transfer. Thus looking at a scalp-evoked potential, one can surmise the underlying cortical activity, when noncerebral potentials have been excluded.

DR. STORM VAN LEEUWEN: I wonder whether the classification that has been presented by Dr. Vaughan will serve as a model which we will use in coming days. If so, I think we are very fortunate to have such a classification. However, the meaning of the various items is not completely clear to me. For instance, the category III seems somewhat vague. I am also not certain that the extracranial potentials (category V) belong in this classification. It might be better to have a dichotomy between noncerebral and cerebral potentials and then classify the cerebral potentials in four categories. May I also ask how Dr. Vaughan would classify the lambda wave?

DR. VAUGHAN: There is, of course, a certain arbitrary nature to my classification, which is in large measure dictated by the practical inaccessibility of most brain structures to the recording probe of the behavioral physiologist. In the history of psychology, measurement of the relationship between stimulus and response has appeared to provide a means for inferring some of the properties of the intervening mechanism. These "transfer functions" have in some circles become substitutes for a direct analysis of brain mechanisms. In using electrophysiological data readily accessible in the intact human, we are limited to certain phenomena such as the ERGs which are generated early in the SR sequence, to electromyographic indices of behavioral response, and to those intervening cerebral events that manage to reach our recording electrodes through the skull and scalp. I believe, nevertheless, that the five classes possess, for the time being, heuristic value, whether one is disposed to consider the extracranial events of category V as artifactual nuisances or as valuable indices of peripheral components of the sensorimotor chain of events.

Dr. Storm van Leeuwen has raised an interesting question, namely, the status of the "lambda wave." This phenomenon may be considered a true evoked potential, elicited by the burst of afferent activity which occurs at the onset of the fixational pause following each saccadic eye movement. These potentials are absent in the dark and show characteristic changes in amplitude and latency with variations in luminance of the field of view. We have demonstrated physiologically (Gross et al., 1967) the phenomenon of "saccadic suppression" of the VER, which predominantly affects the input of information concerning form. The lambda wave presumably represents the disinhibition that occurs at the termination of the eye movement. It is noteworthy that the lambda wave, like saccadic suppression, is related primarily to pattern vision. Thus, the lambda wave provides an important example (which I had inadvertently neglected and am indebted to Dr. van Leeuwen for calling to my attention) of an ERP of category I not elicited by a discrete external stimulus, but by a change in excitability of the nervous system time-locked to an observable behavioral event, i.e., saccadic eye move-

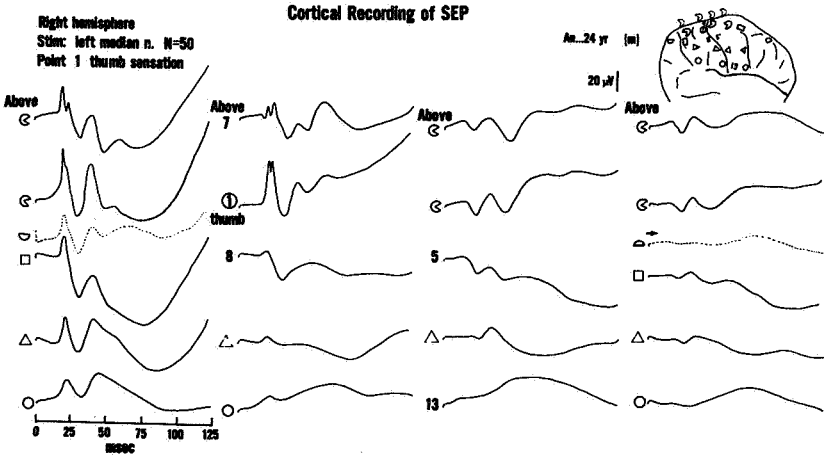

FIGURE 2–16.—Distribution of the cortical SEP (same subject as figure 2–15). A sketch of the exposed cortex in the position of the electrodes relative to the gyri and sulci is seen in the upper right-hand corner. The circled location 1 on the postcentral gyrus is the point where direct cortical stimulation produced sensation referred to the contralateral thumb. Some of the recordings were performed above the upper bone margin at the level of the dotted notched circles.

This figure, along with figure 2–15, indicates that the spike-like potential in the scalp recording in this case probably reflected cortical activity. And the apparent fused component 2–4 on the scalp is caused by spatial averaging over a wide area of cortical activity.

ments. It is necessary to recognize the distinction between the motor potentials associated with voluntary eye movements and the evoked lambda activity. These have distinctive spatial and temporal properties, with the lambda waves localized to the occipital distribution characteristic of visual-evoked responses, and the antecedent motor potentials preponderant over the inferior parietal region. Frontal activity is also present, but this is very difficult to differentiate conclusively from the oculogram and does not begin before the onset of the eye movement. In the latter regard, the frontal activity conforms to the unit recordings by Bizzi from the frontal eye fields which contrast with observations from motor cortex (Evarts, 1966). No units began firing before the onset of voluntary saccades. Since the timing relations between cortical MP from motor cortex and the unit data are in good agreement, there is reason to believe that the command signals for eye movements may arise from the posterior eye fields rather than from the frontal region.

Dr. Lifshitz: Would it not be appropriate to include among the event-related phenomena, in category V, those changes which are not phase-locked to the stimulus? It would seem appropriate that any event which is related to the stimulus must also be considered part of the event-related response, even if it is not phase-locked. Thus spectral distribution changes, coherence changes, etc., although they do not show up in the average, should be considered part of the response.

Dr. Clynes: A review of developments that have occurred in this field in the last 6 or 7 years suggests that we have been looking at sensory inputs in too much of a "single-channel" manner. For example, our working concept of the visual-evoked potential system seems largely an attempt to regard vision as a single stimulus modality rather than as a many-channel experience.

Stimuli vary in quality as well as in quantity. In a particular response waveform, there are various components. The results we have obtained in our own experiments suggest that these components do not bear a simple relation to stimulus parameters. A flash may be a simple thing from the physicist's point of view, but as the physiologist sees it, it is quite complicated. This is caused in part by the interaction of different fields within portions of the retina. Even a flash will cause a relative inhibition of retinal area, so that the evoked potential caused by a flash is by no means a simple function of the intensity of the stimulus, even when we consider only the sensory end of the communication channel.

Figure 2–17 shows flash AEP to the flash generated by a Grass stimulator, as well as AEPs elicited by a "solid" color and an assembly of random dots of much reduced intensity (10 000 times). The latter AEP is a much larger response than the flash AEP. This figure also

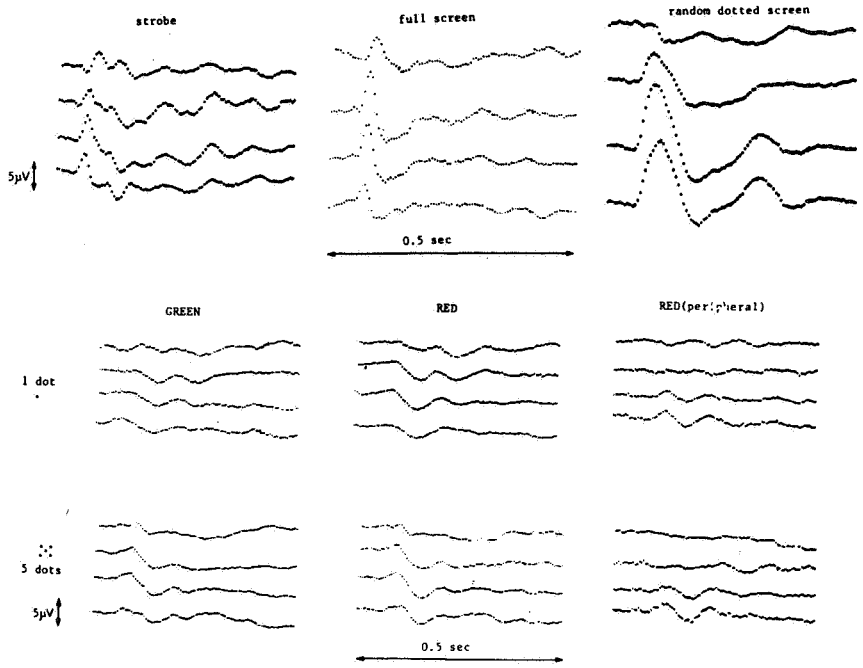

FIGURE 2–17.—Potentials evoked by a bright flash of a Grass stimulator (top left); by reflected light from a screen of 8100 cm² area illuminated with red light from a 500W projector (top middle), many small random dots of total area 500 cm² (upper right), are responses to single dots and to a configuration of five dots, as illustrated. Note the simplicity of the responses to dots and the large amplitude obtained from the random dots. Modes of visual field structures are more important than energy of illumination in determining character and amplitude of the response. Little color differentiation is seen in the central field. The peripheral green response, however, is very small (not shown). Note the straightening of the wave and appearance of the initial peak in comparing the 5-dot response with that for single dots. Note also the dc shift seen for single dots in trace 3. This dc shift occurs at a latency of about 80 msec and is present at very low intensities of stimulation (negative down).

illustrates how an assembly of dots will inhibit portions of the responses to single dots. A single-dot AEP has a certain response shape, whereas two-, three-, five-dot stimuli will accentuate certain AEP components and inhibit others. The very large response caused by dots is an indication of how this system is sensitive to the visual structure, edge and unit, rather than just intensity.

Figure 2–18 shows in the left corner an AEP to a green stimulus as opposed to the previous black stimulus. The four traces are from a rosette configuration. We see that different components appear at dif-

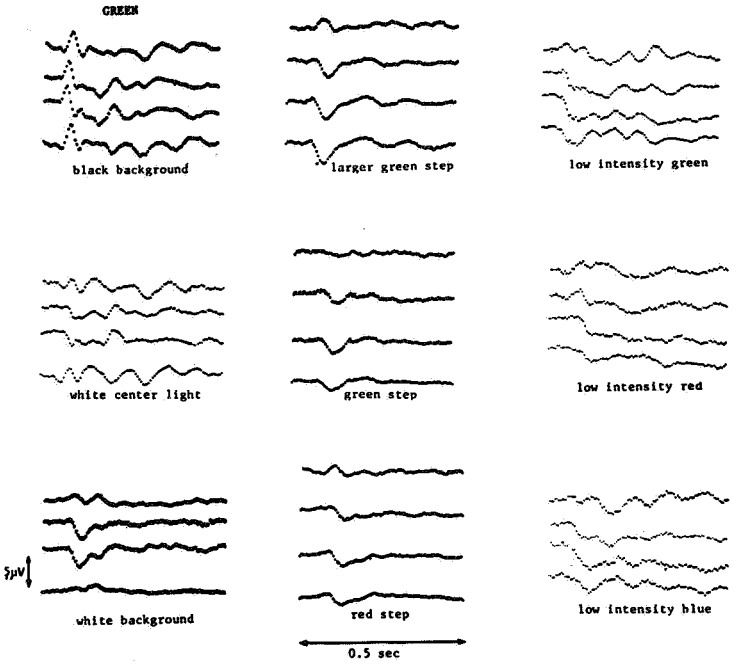

FIGURE 2–18.—The left side of this figure shows how the response to green from black (top) is changed by the presence of a small steady white center light diffused over a 10-cm circle (middle). Note that the initial peak disappears in traces 2 and 3, and is altered in traces 1 and 4, while all other components appear unchanged. With steady white light over the entire screen, the response to green is shown. This eliminates all but two major components, those on secondary and tertiary latency. The central group shows responses to different size intensity steps of green and red. These are rather similar to those on the bottom left but have different spatial orientation. The white "background," of course, contains red and green. Note also the absence of color discrimination. The response shapes are largely independent of the size of the step and the range of intensity from which the step is taken, provided that the initial level is high enough, paralleling the perception of color saturation beyond a certain intensity. On the right are shown low intensity responses emphasizing the different sensitivities of various components to intensity. The dc shift of traces 2 and 3 in the lower group of records is present for quite low intensities and seems, from most indications, to be a rod phenomenon. Increasing the intensity by a factor of 100 does not increase this component (top left). Instead, the initial peaks are emphasized (negative down).

ferent angles. The next lower trace shows how one of these components can be controlled visually through a simple change in the form of the stimulus, leaving the other components unchanged. Thus, there is an individual control of components that appears to have no relation to

influences other than the actual visual configuration. With a white background, one may control other components, making the response simpler. This figure shows also that if colored stimuli are changed by a step of intensity, without a change in hue (thus stimulating the same set of cones), they elicit a very simple type of AEP. For very low intensity, the dc shift still appears in the second and third traces, representing the 90° angle in all three colors. There are precise processes that cause very different types of shapes depending on the stimulus qualities.

Figure 2–19 shows how response components and shapes relate to the stimulus shape. Dots and line coordinates were used; if these stimuli are defocused, the response amplitude is reduced although the total amount of light in the stimulus is not changed. Changes in the structure of the visual stimulus are clearly reflected by corresponding changes in the patterns. Note on the top right of the figure the appearance of a number of different components which look different; the orientation of these components can be obtained by the examination of the angles at which they are maximal or minimal.

To show how well changes in structure are reflected in the evoked-potential shape, Table I shows how a computer can recognize both size and shape of a line stimulus: circles and squares drawn in different sizes. Table I shows recognition of simple line circles and squares (white on black) of size 6 and 12 inches. The maximum correlation identifies both shape and size, the next highest being the same shape of different size. The computer thus is able to recognize the family of shapes and the particular size.

Each correlation figure in this table is the result of adding the sum of four correlation coefficients corresponding to the respective four leads of the master and test patterns. Leads of corresponding angles are correlated against each other, and the four correlation coefficients added. Maximum correlation means identification of the test with the master pattern. (See also: Clynes, M., Kohn, M., Gradijan, J., Computer Recognition of the Brain's Visual Perception Through Learning the Brain's Physiologic Language. IEEE International Convention Record. Part 9, pp. 125–142. 1967.)

Figure 2–20 shows the inhibition produced by steady white lines on a solid black background. The solid background here is thousands of times more intense than the few concentric lines in the lower set. Inversion and inhibition of the particular component at about 80 milliseconds occurs—a very radical change in evoked potential caused by the continuous presence of lines.

I am discussing these properties now, before we get into the question of classifying the various AEP shapes, so that we become aware that these AEP shapes are related to stimulus qualities, and not to a single

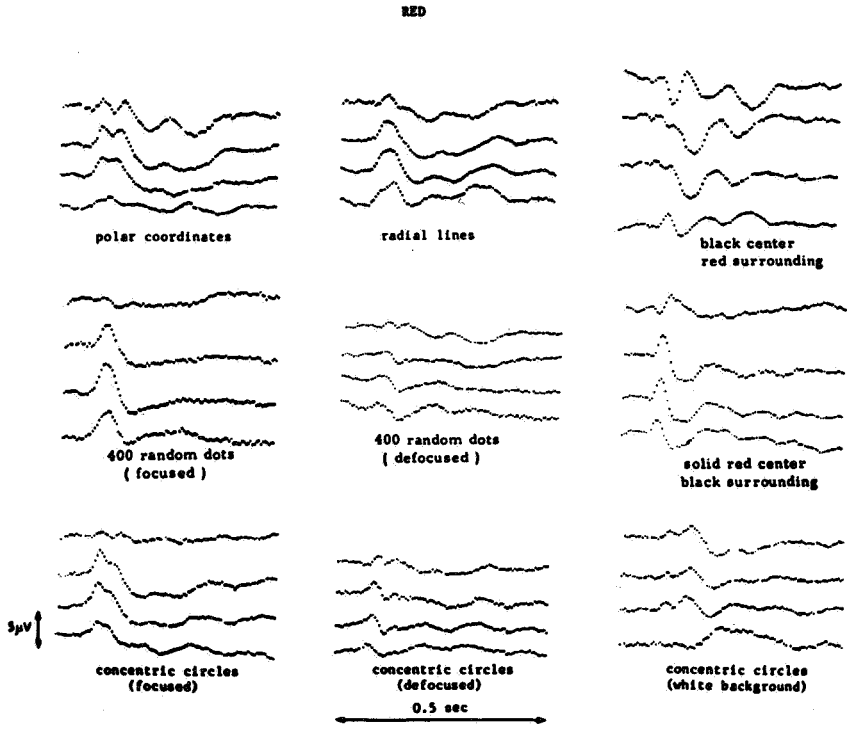

FIGURE 2–19.—Examples of varieties of shape obtained from various visual field structures of lines and shapes. Lines are projected on black background except at bottom right. Amplitude of responses drops sharply when images are defocused. Color differentiation is marked for the defocused images and is relatively masked by the edge sensitive responses to the focused images. Top right is a response to a black central circular field 12-inch diameter surrounded by red. Below it is a red central field of similar size surrounded by black. With these response shapes, component analysis reveals the existence of four main independent spatial components of different latency; this is also largely evident from visual inspection. Responses to radial lines and circles appear to be basic. The bottom right response pattern illustrates that the response to lines is greatly sensitive to the color and intensity of the surrounding field. This important aspect is analogous in space to the color sensitivity shown when changing from one color to another at constant intensity. Peaks of random dot responses occur later than the initial peaks for solid red and green (see Figure 2–1). Two initial peaks close together tend to coalesce, resulting in a single broad peak, for some of the responses to dots and lines.

quality. There are a number of qualities in each sense, and we should determine the number and nature of these qualities. We must determine whether and how qualities are related to the spatio-dynamic nature of the specific components, each of which is rather simple when

TABLE I.—*Identification of Circles and Squares and Their Sizes*

Master	Test 1 (small circle)	Test 2 (large circle)	Test 3 (small square)	Test 4 (large square)
Small circle	2. 785	1. 948	1. 039	1. 849
Large circle	2. 181	2. 474	1. 011	1. 782
Small square	1. 389	. 912	2. 860	2. 254
Large square	2. 092	1. 375	2. 061	2. 669

compared with the entire complex shape of the evoked potential. In the visual sense these different channels are related to hue brightness, saturation, and the visual field structure. In auditory and somatic types of experiments, there would be others—loudness, pitch, etc.—which I will not discuss. I think we ought to bear stimulus qualities in mind as inherent in the data processing channels of our nervous system.

DR. SHIPLEY: I would like to second this point, but with another sense modality in mind. Too often, in the literature on the "somaesthetic" sense, one is unable to find an exact specification of the nature of the stimuli that were used. Shock stimulation on the finger, for example, is a fundamentally different event from touch or temperature stimulation, though they are all too often casually grouped under the terms "somaesthetic" or "somatosensory." I would like to emphasize that all research papers in the field of evoked responses, and particularly those in the somaesthetic modalities, should specify quite exactly the nature of the stimulation used. We have done some work in our own laboratory trying to compare shock-evoked responses to touch or to temperature-evoked responses, and these can be very different; however, one says, "well, they are all somaesthetic." I would emphasize very strongly that the peripheral neurology is different for these sensory qualities, as the peripheral neurology of the retina is different for shapes and for colors, so that the stimulus parameters used should be specified very carefully. This stricture, in the long run, is quite as important as that upon electrode configuration.

DR. DONCHIN: Dr. Vaughan has commented on the large variability sometimes observed in evoked-response data. His comment implied that such variability is often excessive and that one should try to reduce the variability. This, of course, is a commendable sentiment. However, it brings up an interesting point. If you consider the published evoked-response studies you immediately note that there are two major types of studies. There are some studies in which there is very little variability and others in which there is as much variability

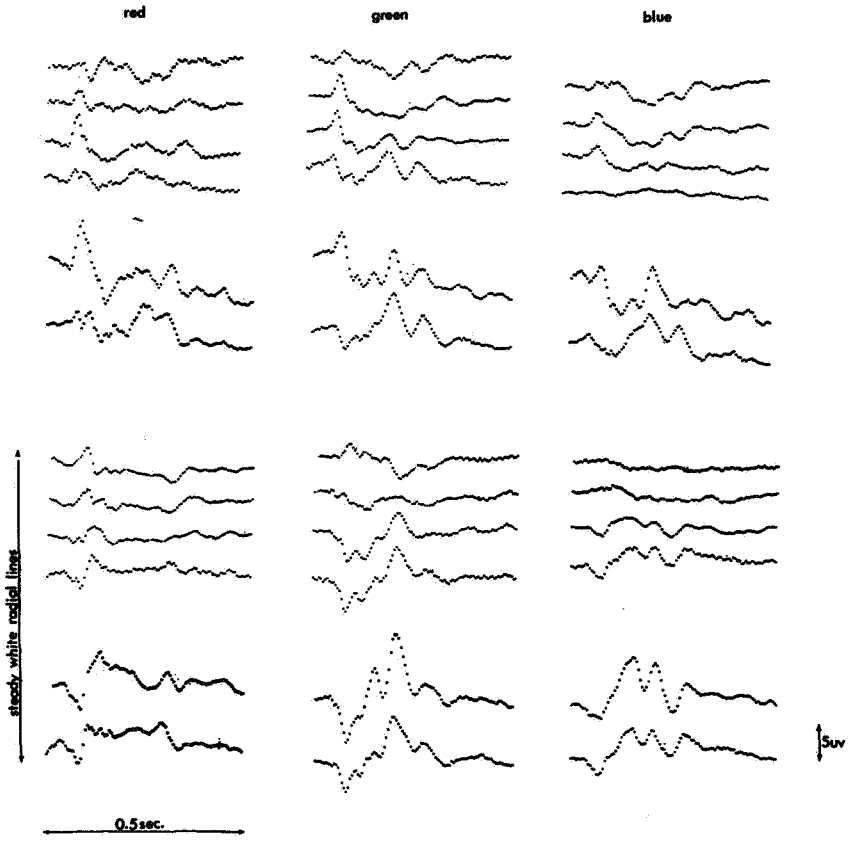

FIGURE 2–20.—Effect of continuous presence of thin white radial lines on responses to whole-screen color illumination. Marked changes occur in components 1 and 3 of red response. DC shifts are also affected. Astonishingly large effect of this steady presence of four thin radial lines of low intensity shows how important field structure and inhibition are in determining evoked potential shape. Groups of four traces from electrode rosette are supplemented by two additional traces representing sagittal pairs of electrodes, occipital to vortex, and vortex to frontal, respectively. In each case there is an inversion of component 1. In green, there is remarkable accentuation of characteristic component (latency 150 msec), noted previously. Comparison of lower groups of traces with upper group shows striking changes that result in perhaps even greater color differentiation.

as there was in the data commented on by Dr. Vaughan. The first types of studies are usually those in which the investigator uses two or three subjects and studies them very intensively over a long period of time. Commonly, the authors themselves participate as subjects as well as some trusted laboratory technicians. In this case, the inter-

subject variability is quite small. In the second group of studies, a large number of subjects, usually from the undergraduate pool at the university or from a hospital population, are employed. Naturally, these subjects cannot be used for an extended period, and most of the data are collected in one or two sessions. Under these circumstances, one discovers an immense amount of intersubject variability. A possible factor working to increase the variability in these experiments is the intrusion of effects related to Vaughan's third category. When you have a large number of subjects, each entering the session with a different set of prejudices, worries, and attitudes, you might expect to find a greater amount of intersubject variability. Another possibility that might be considered is that the variability results from the fact that electrodes that are placed according to skull landmarks are in fact placed in different locations with respect to the brain in different subjects. I wonder if those who have recorded evoked responses directly on the cortical surface have observed a larger or a smaller degree of intersubject variability than that which is observed on the scalp.

DR. RUHM: Our experience with cortical recordings has suggested that evoked responses exhibit as much variability at the cortex of man as at the scalp. Therefore, we cannot attribute such variance to electrode placement or to the distances between neural material and the electrodes (Ruhm, Walker, and Flanigin; 1967).

DR. SHAGASS: We have worked with large numbers of subjects, and the variability, of course, from subject to subject is enormous. There is much intrasubject consistency. We studied the same subjects over and over, particularly in an attempt to see what changes were brought about by treatments in psychiatric patients. We were very discouraged by the fact that treatments that would change the patient considerably did not seem to do much to the evoked response, and that there was a great deal of consistency apart from that.

We have also had the opportunity to examine the evoked responses in animals with implanted electrodes for a period of approximately 1½ years; here again the variability is enormous in recordings taken directly from the cortex. In fact, amplitude changes range from 100 to 75 μv in the same animal, with the same configuration, from one week to the next.

DR. GOFF: Grey Walter (1969, in press) has examined restricted areas of frontal cortex with depth electrodes and found each area to have its own individual responses to sensory input.

DR. SHEVRIN: I have been doing studies with twins, using in one study somatosensory stimulation (a touch stimulus of the index finger) and in another using visual stimuli. It is quite striking how similar the evoked responses to somatosensory stimulation are in twins. The similarity between the AEP is not as great when the stimuli are visual.

DR. RODIN: We are supposed to be raising provocative questions at this symposium, so I hope you don't mind if I do raise what I regard as a provocative question with regard to basic assumptions of our averaging techniques. One is the assumption that, as we continue averaging, we cancel the background and enhance the signal; therefore, the next assumption is that whenever we get a curve, all aspects of this curve are indeed a response to the signal. Now I don't know whether this assumption is really justified or not. As a matter of fact, it seems to me that we may not cancel the background entirely, and that part of the background could slip into the curve, and we can get a conglomeration of true response and some background activity. This may also introduce considerable variability in the appearance of the evoked response.

DR. COHEN: I think maybe we are all to be congratulated that finally as physiologists we have found responses that are individually different in humans. We should not be surprised that we have variability when we are dealing with behavior. Thank goodness we are now seeing in the neurological substrata some individual variability that is consistent, and which perhaps relates to an individual's experiences and life patterns. We have reached a level where we can look at individual differences. I think this is probably one great reason for looking at human behavior, in addition to animal behavior.

DR. LIFSHITZ: I wonder whether it is appropriate to think of a signal in a background of noise. Thinking that we are averaging out the information and being concerned about whether we are cancelling the background may lead to conceptual errors. All of the brain's electrical activity is probably affected by any perceptual input. Our perception of a repetitively presented stimulus varies from moment to moment even though the stimulus remains constant. The sum of all previous experience affects any new input, and any new input probably affects, in a diffuse sense, all ongoing activity. When we use averaging, we are left with a representation of some small part of the response which tends to occur repetitively, and it is very difficult, if not impossible, to know how good a representation of activity uniquely related to a stimulus this is.

CHAPTER 3

Cross-Modality Comparisons of Averaged Evoked Potentials[1]

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THERE is extensive literature documenting the characteristics of human averaged evoked potentials (AEP). However, differences in emphasis, procedure, recording techniques, and other technicalities have obscured systematic intermodality comparisons. About 3 years ago, we decided to extend our analysis of the averaged somatic evoked response (SER) to other sensory systems because we believed that an examination of commonalities and differences among them would advance understanding of a modality. We especially hoped that we could identify homologous components among modalities and differentiate modality specific components from nonspecific components. Secondly, we contemplated similar studies in chronically implanted, unanesthetized monkeys and hoped that cross-species, cross-modality comparisons would indicate similar kinds of homologies.

We decided to begin with an examination of the form and distribution of auditory, visual, and somatic AEP recorded in the same subjects under identical experimental conditions from an array of electrodes large enough to give a reasonable representation of cranial topography. In view of recent reports of time-locked potentials generated by extracerebral sources in all three modalities, it was appropriate to include in our array electrodes that would permit analysis of the distribution, and therefore the degree, of "contamination" of cerebral responses by these extracerebral generators.

[1] Supported by U.S. Public Health Service Grant MH–05286, National Science Foundation Grant GB–5782, and the Veterans Administration.

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Neither the idea of a large-scale topographical analysis nor of cross-modality comparisons was original with us. For example, Rémond (1964) and Rémond and Lesèvre (1965) have published spatio-temporal maps of visual evoked responses (VER) from a montage of as many as 57 electrodes. Grey Walter (1964a) recorded visual, auditory, and tactile AEP from scalp and intracerebral electrodes; Gastaut et al. (1967) compared the three types of responses from six electrodes; and Ciganek (1967a) used a P_z–O_z bipolar derivation. However, a large scale, cross-modality topographic analysis has not been reported.

This was our first cross-modality study, and it generated many problems. Since the purpose of this conference is to discuss problems occurring in the conduct of AEP experiments, we think it appropriate to present the problems we encountered that seem to be of general importance for cross-modality studies.

Our study required an electrode array that included the scalp electrode locations of the 10–20 system and O_z, an electrode on the outer canthus of the right eye, electrodes on the right and left mastoid processes, and one over the neck muscles near the second cervical vertebra—a total of 24 electrode locations. For each subject, we obtained 8 averages of 64 responses per electrode per modality—576 averages or 36 864 responses per subject. Twelve subjects participated in the main experiment. Our LINC computer is set up to sample four data channels simultaneously. Even if additional data channels were available, considerations of time and the subject's comfort would not permit the application of the entire array in one session. We therefore sampled electrode locations in a constrained, random order using six electrodes per session and sampling each electrode twice within a session. It required 16 sessions to sample each electrode 8 times. The LINC controlled the entire experiment; it presented the stimuli in the three modalities also in a constrained, random order and summed the responses according to the modality stimulated.

Having chosen our electrode locations, we had to choose between bipolar and monopolar (or referential) recording. In many excellent articles, we have found that it was essentially impossible to compare the results to our own work, or that of others, because of differences in reference electrode location. There is an astounding lack of consistency, and inadequate concern, in the choice of a reference location.

Consider the literature on VER as we did in the course of preliminary work for the cross-modality study. Ebe et al. (1962), Nagata and Jacobson (1966), and Schwartz and Shagass (1964) compared waveforms from monopolar and bipolar records and noted more complex or variable waveforms in bipolar records. Vaughan (1966) compared

the two methods and called most of the bipolar components artifactual. On the other hand, Bergamini and Bergamasco (1967) emphasized the similarities between monopolar and bipolar data. In despair, we investigated this problem for ourselves using Maxwellian-view stimulation of the right eye. P_z–O_z is a commonly used bipolar derivation for VER. We recorded from both locations against the left (contralateral to the stimulus) earlobe. Experiments, which we will discuss later, showed this reference to be essentially indifferent for the VER. We also made bipolar recordings between these locations.

Figure 3–1 compares the monopolar and the bipolar records at three levels of flash intensity. The dashed line is the monopolar record from the P_z location, and the dotted line is the monopolar O_z record; the solid line is the bipolar P_z–O_z record. First, it is apparent that stimulus intensity has a marked effect upon the waveform of the VER. That is, components that are quite well differentiated at low to moderate intensities, such as components P4a and P5a, tend to fuse at the higher intensities. It is also apparent that bipolar derivation introduces distortions into the evoked response, which in the absence of reference to monopolar records from the two recording locations, can be very misleading. For example, one of the most consistent features of the

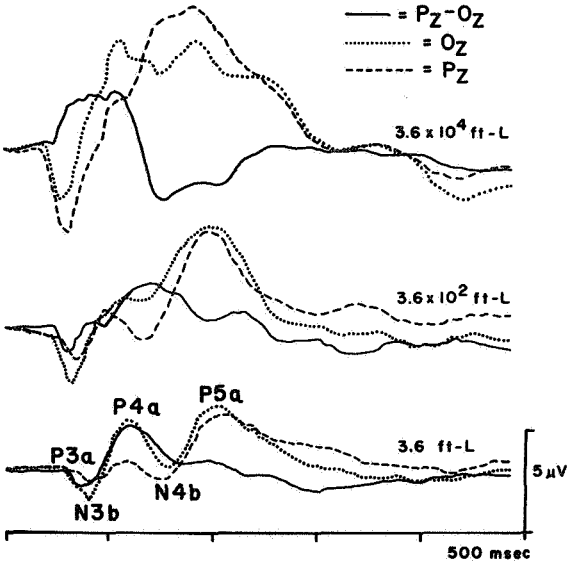

FIGURE 3–1.—Comparison of bipolar and monopolar records from P_z and O_z at three intensities of light flash to the right eye. Monopolar: reference is left earlobe; positivity up at scalp electrode. Bipolar: negative down at O_z (from Matsumiya et al., in preparation).

monopolarly recorded VER is the so-called "vertex potential," a negative-positive wave with a latency to the peaks of approximately 140 and 190 msec, respectively. These are labelled N4b and P5a in figure 3–1. In bipolar recordings at moderate intensities, this potential is almost obliterated, and at higher intensities, the bipolar potential in this latency range becomes negative. Reference to the monopolar records shows that the vertex potential is of approximately equal amplitude at P_z and O_z at moderate intensities. Thus the algebraic difference between them in bipolar recording is negligible. At higher intensities, the P_z amplitude somewhat exceeds that of O_z. Thus O_z is negative with regard to P_z, and the bipolar record shows a negative potential. Thus we conclude, as did Vaughan (1966), that bipolar recording methods introduce uninterpretable distortions into evoked response records. The distortions are more serious in cross-modality comparison. The differences in the distribution of the components (as described later) may cause (with a given reference electrode) some records to be effectively monopolar (i.e., the reference electrode will be on a relatively inactive area), while others would be effectively bipolar (i.e., both electrodes will be on active areas).

If we are convinced that bipolar recording concatenates confusion, the practical alternative is monopolar recording. Unfortunately, there is no such thing as monopolar recording. The term is used when the second electrode is located in an area which, in the ideal case, is isoelectric with regard to the evoked potentials we seek to record, but is equipotential to other leads with regard to other electrical activity such as muscle potentials, 60–Hz interference, etc. It is impossible to demonstrate that such an area exists because even when no potential difference is recorded between two locations, this may mean either that neither electrode is picking up evoked activity or that they are both picking it up identically.

If bipolar recording can distort evoked potential records and create spurious response components, and monopolar recording is impossible to establish, what can we do? We must settle for a reference-point location that can be demonstrated to be relatively indifferent with regard to the evoked signals. We can estimate the probability that a location would be indifferent by comparing a selected location with several other locations that are not likely to have identical voltage-time functions. If little or no consistent time-locked activity is found at these locations, even at maximal stimulus intensities and in all modalities, we have found a common reference location that is unlikely to distort evoked response waveform.

In preliminary experiments, we tested in this way several possible reference locations such as the earlobes, mastoid processes, nose, nasion, and chin. We found that the earlobe contralateral to the stimulus was

the best common reference point for all three modalities. Figure 3–2 shows records from various nonscalp electrodes using the left ear as a reference. Responses recorded at the same time from C_z are also shown to compare cerebral potentials. The stimulus intensities were 80 to 95 db above absolute threshold for the auditory, 3 ma above the thumb twitch threshold for the somatic, and 32 000 ft–L for the flash stimulus.

Records from the right eye show that the source of most of the potentials seen in the nonscalp locations used arise from the eye region. The component peaking at approximately 100 msec is recorded bilaterally from anterior scalp locations such as F_{p1} and F_{p2}. This component is also seen in bipolar records across the eye. It is apparently a reflex of the musculature in the eye region. It is curious that the potential in the eye region is far larger to somatic and auditory than to visual stimulation. In most subjects, this potential is also seen at the nose, and, in some cases, a temporally similar potential appears at the chin. Myoelectric activity usually present at the chin obscures the record and also eliminates the chin as a reference location in many

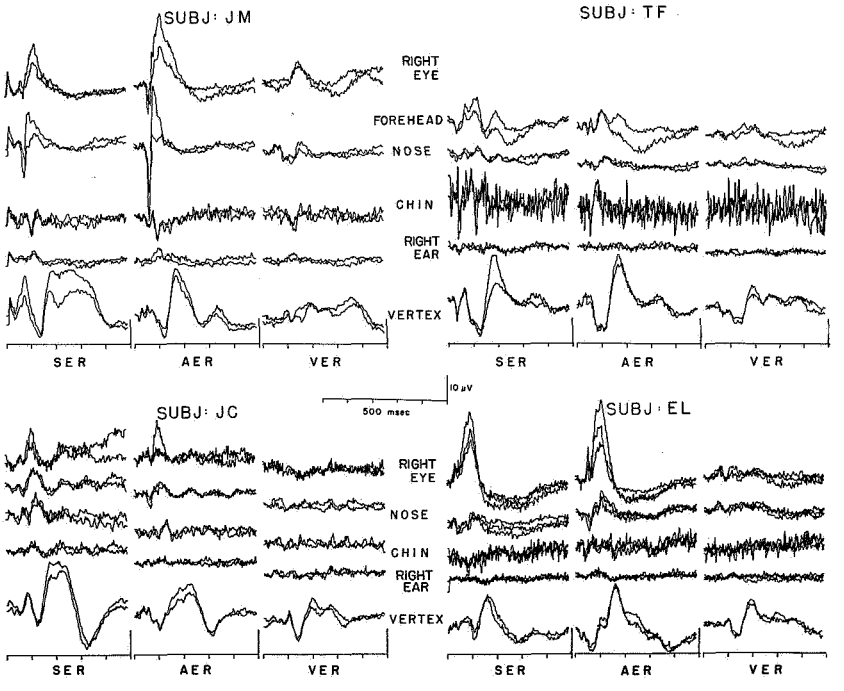

FIGURE 3–2.—SER, AER, and VER from the outer canthus of the right eye, the midline forehead, the bridge of the nose, the point of the chin, the right earlobe, and the vertex (C_z). In this and all subsequent figures, negative is down with reference to the left earlobe.

subjects (e.g., subjects T.F. and E.L.). It is worth noting that this experiment was a part of our initial screening when naive subjects are maximally apprehensive and jumpy; thus the possibility of picking up these potentials was maximized. Even under these "worst-case" conditions, recording between the earlobes yields a relatively "silent" record. As we have said, this could mean that the earlobes are isoelectric with regard to the cerebral potentials shown at C_z, or that they are equally and simultaneously active. The latter seems unlikely. Futhermore, any potential arising from the left ear should appear in common to some degree at all electrodes shown; it does not. We have examined these records on a fast time base, and the results are the same. Some potential difference does arise in some subjects between the earlobes. Our experiments indicate that the source is the earlobe ipsilateral to the stimulus. This indicates that for unilateral stimulation, the contralateral earlobe is preferable to the linked earlobes.

While absolute proof of "indifference" is impossible, we believe that these data show that the contralateral earlobe is a reasonable reference for AEP recording in all modalities.

In summary of this discussion of recording techniques, we suggest that for general use in evoked potential studies, bipolar recording—that is, recording the algebraic difference between two electrodes placed on known neuroelectrically active areas of the scalp—is disadvantageous. It may be useful for specific purposes, such as improving the resolution of very small potentials or precisely localizing the source of an AEP component by the phase reversal technique. Even for this latter purpose, we believe that monopolar analysis of distributions shows quite adequately the focus of cerebral potentials. In any event, interpretation of bipolar records should always be made with reference to simultaneous monopolar records. We believe that it will facilitate progress greatly in evoked potential research if we can establish a standard reference location that is adequate for all modalities. Only then can we integrate results of experiments performed in different laboratories.

Having established our recording method, how would we stimulate? After consideration of possible visual stimulating systems, we chose the Maxwellian-view system because it provides measurable intensities of light while eliminating intensity variations caused by pupillary constriction (Riggs, 1965) and has been reported to give the most reliable VER results (Shipley et al., 1966). We were immediately in trouble because the Maxwellian-view requires a fixed head position, and this is best achieved by means of a biting board. But in most subjects, the myoelectric activity associated with biting is incompatible with evoked response recording. We substituted a chin rest, head holder, and fixation light which enabled the subject to maintain adequate

fixation and minimized the myogram. The auditory stimulus was a 1-msec click via an earphone; the somatic stimulus was a 0.5-msec, constant-current median nerve shock using a system which we had designed (Allison et al., 1967).

The next problem was the choice of stimulus intensity. High intensities increase the possibility of evoking myogenic potentials, especially in the auditory system. Furthermore, as we have seen in figure 3–1, response components that are differentiable at moderate intensities may fuse at higher intensities. Finally, since the amplitude of response is a function of stimulus intensity, the extent of the distributions could be affected by stimulus intensity because of passive spread. On the other hand, if intensity is too low, smaller components may not be resolved. We chose to use moderate intensity levels and decided that it would be of interest to compare the amplitudes of responses in the different modalities when the subjective intensities were equated. Therefore, in a preliminary psychophysical experiment, we obtained subjectively equal stimulus intensity values using a cross-modality matching technique. We chose a light intensity of 3600 ft–L and, using it as a standard, obtained matched click and shock intensity values using a method of limits.

From past experience with naive subjects' apprehension about being shocked, we were afraid that our inexperienced subjects might give us exceptionally low shock values as a match for the less emotional visual and auditory stimuli. The values that we obtained are shown in table I. The shock values are quite consistent despite considerable differences in experience ranging from 10 years for the top subject to none for the last. The auditory values were also reasonably consistent. The psychophysically matched stimuli were used on the first six subjects. Two problems arose with this group which caused us to change our procedure for the second six subjects. For all subjects in the psychophysically matched group, the equated shock values were higher than was needed to evoke a well differentiated SER. It has been our experience that the more intense the stimulus the more trouble one is apt to have with shock artifact. The second problem concerns the first group, in which we were unable to resolve certain early VER components reported by others (Brazier, 1958; Cobb and Dawson, 1960; Gastaut et al., 1967). Therefore, in the second group, we dropped the psychophysical matching and used stimulus intensity values that we considered optimal for the particular modality. These were 3 ma above thumb twitch threshold for shock, 85-db sensation level for click, and the visual stimulus was raised to 18 000 ft–L in an attempt to resolve early VER components.

On balance, we do not believe that there is much to be gained from using psychophysically equated stimuli in cross-modality comparisons.

TABLE I.—*Psychophysical Matches to 10-msec, 3600 ft–L Light Flash*

Subject	Shock (ma)	Click (db S.L.)
W.G.	6. 4	95
T.A.	4. 6	74
G.G.	4. 9	82
Y.M.	5. 1	97
G.H.	10. 1	90
E.D.	4. 1	82

It is probably better to determine intensity values on the basis of the technical considerations of the particular modality and purpose of the experiment. It was relevant to use subjectively equal intensities in this study because it allowed us to compare the amplitudes and distributions of the vertex potentials which are said to be modality nonspecific.[2] An analysis of variance revealed that the SER and AER vertex potentials were significantly larger ($p < .05$) than the comparable VER component. The amplitude distribution of the positive phase of the VER vertex potential distributes more posteriorly than the other two; there was also some difference in the latency distributions. Thus, the vertex potential has characteristics that are differentiable in terms of the evoking modality.

Stimulus repetition rate is an important variable in cross-modality comparisons because while recovery time within modalities has been examined by many laboratories (e.g., Allison, 1962; Schwartz and Shagass, 1964; Ciganek, 1964; Bergamasco, 1966; Davis et al., 1966), a systematic study of cross-modality recovery functions has not been done. From the available evidence (Allison, 1962), we can infer that interactions between modalities probably have a shorter time course than within modalities. If we are interested in examining the total evoked response, we must set the stimulus repetition at a rate which the within-modality recovery studies indicate is slow enough so that the latest components are not seriously suppressed. The suppressive effects of stimulating at high rates are all too frequently ignored in AEP experiments. However, when large numbers of stimuli are used, even a second added to the interstimulus interval significantly prolongs the experiment and increases the possibility of alterations in

[2] The term "modality nonspecific" is ambiguously used in evoked potential research. Most authors apparently mean simply a wave that is grossly similar in appearance and is evoked by different modalities. However, it is easy to move from this meaning into physiological connotations and construe "modality nonspecific" to mean generated by a population of neural units of the type which Buser and Imbert (1961) called "polysensory." This may well be the case, but it has not been demonstrated.

attention and of drowsiness, which we know affect AEP components markedly. Thus, we chose a rate of 1 per 4 seconds as a compromise between these two considerations.

These then are some of the problems which will be encountered in the data acquisition phase of cross-modality experiments. With the exception of the electrode placement problem, about which we'll have more to say in the context of our distribution results, they are the less complex problems. Much more complex problems are encountered in the data analysis phase of a cross-modality experiment:

(1) Establishing a nomenclature that is informative and applicable across modalities.

(2) Establishing a meaningful system of measurement of response components.

(3) Presentation of data in such a way that communalities and differences across modalities will be maximally apparent.

(4) The differentiation of all extracerebrally generated potentials so as to avoid confusing cerebral potentials in one modality with extracerebral potentials in another.

Obviously, these problems, especially nomenclature and measurement, are not unique to cross-modality comparisons. However, any approach to them should consider the goal of such comparisons. As we see it, this goal is to discover homologous components between modalities in man and to derive homologies between human cerebral components and evoked response components in animals so that hypotheses about the neural systems generating the components can be explored fully by basic neurophysiological techniques. We think it parsimonious to assume that the somatic, visual, and auditory systems process sensory information in analogous ways. If this is the case, the resultant summation of this neural activity should produce components that are functionally homologous.

The first step in finding such homologs is to select components of similar appearance across modalities and then compare them for other characteristics. Such comparisons would be facilitated greatly by a common nomenclature, that is, consistency in the way we label the complex sequence of peaks, valleys, and inflections that comprise human AEPs. It seems especially appropriate to discuss the problem here since it is seldom mentioned formally in the literature. There are a number of labeling systems now in use, and it is often difficult even for those doing research in this area to determine whether X laboratory's wave 3, for example, is or is not the same as Y laboratory's P_2. Consider the nonspecialist trying to make sense of this literature. If one is optimistic, as we are, that the evoked response technique will spread from the basic research laboratory and become accepted procedure in the larger world of clinical neurology, then it is clear that

eventually we will need some standardized way of characterizing evoked responses.

A good labeling system would include the following properties. It should be descriptive in two senses—first in providing information about the response, and second in avoiding any implicit assumptions about the nature of the potential being named. The system should be sufficiently flexible so that if waves need to be added or deleted from the original description, the whole system will not be jeopardized. From the point of view of cross-modality comparisons, the system should be constructed in such a manner that if homologies across modalities are established, the same label will probably apply to the response of any modality.

With these considerations in mind, let's examine three typical systems presented in figure 3–3. The upper trace shows Ciganek's terminology for the VER in which the waves are numbered sequentially. A preferable system, because it denotes component polarity, is illustrated by the middle trace. The disadvantages of both these methods are:

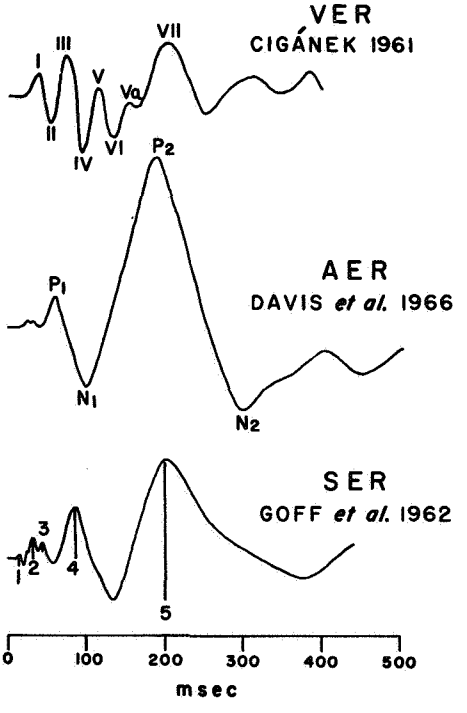

FIGURE 3–3.—Examples of different terminologies for AEP.

(1) If additional components need to be labeled, all later components must be renumbered or subscripts must be added to the subscripts, an awkward solution in either case.

(2) In any sequential system, identical components may have different labels at various electrode locations because not all components appear at all locations. The bottom trace shows the terminology we have used for several years for the SER. It is subject to the same criticisms as the other systems but has the possible advantage of dividing the total complex response into a relatively few components. Its crucial disadvantage is the arbitrary and inconsistent method of parcellation; some components being measured base-to-peak, others peak-to-peak. This brings up an important point with regard to nomenclature; we are dealing not only with a system of identification but also of measurement, and the way we measure reflects assumptions—often unstated—about the nature of the activity being studied. A peak-to-peak measurement assumes that the negative and positive portions of a response reflect a unitary neural process properly described by a single measurement. If animal work is any guide, such an assumption is probably wrong. Even the simplest cortical evoked response studied in animals—the primary positive-negative response of the projection areas—is clearly not a unitary potential change. Abundant evidence shows that the positive and negative phases are caused by separate neural events (e.g., Amassian et al., 1964; Bishop and Clare, 1953b; Purpura, 1961; Towe, 1966); that if consecutive responses are measured, there is a zero correlation in the amplitude of the two phases (Tunturi, 1959); and that changes in behavioral state can be associated with opposite amplitude changes (Allison et al., 1966). The neurophysiological evidence, then, indicates that, whenever possible, a potential should be denoted as a base-to-peak change and measured accordingly.

To give an example from human research, Wilkinson and Morlock (1967), in an experiment on the effects of alterations in attention on the auditory evoked response (AER), measured all response components base-to-peak. They found that increases in level of attention (as operationally defined by them) produced a statistically significant increase in the amplitude of three components, no change in one, and a significant reduction in another. The component that did not change was the positive phase of the vertex potential; the negative phase increased. The commonly used peak-to-peak measurement of the vertex potential would have shown an increase but would have obscured the fact that the change was entirely in the negative phase. This might well be important to neurophysiological interpretation of the results.

Taking these factors into consideration, we are now using a method

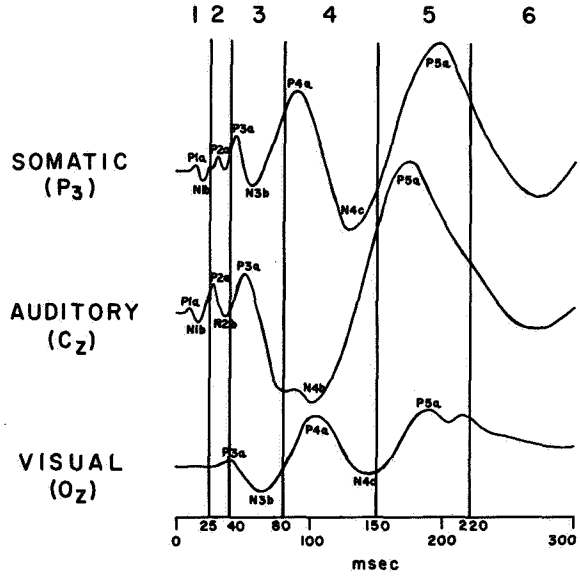

FIGURE 3–4.—Suggested system of nomenclature applicable to the three types of AEP indicated. The total AEP is divided into six latency ranges with limits as indicated by the vertical lines.

of nomenclature illustrated in figure 3–4. It is not the ideal method, but it is a possible basis for standardization. It provides labels that are applicable across modalities, specifies the polarity, and gives a rough indication of latency. Furthermore, modifications can be introduced without a complete revision of the system. The total evoked response is divided into six latency ranges. The choice of ranges was based on latency data for the three modalities in our distribution study. All potentials within each latency period are designated by the same number, with a prefix to denote polarity and a suffix to denote order of appearance within the latency range. If components are added or deleted, only this suffix changes. The first latency range includes intracranial activity probably representing afferent neural inflow to the cortex and possibly the cerebellum. Fast reflex myogenic activity is also included. Latency range 2 covers the period of the first positive scalp deflections of cortical origin from somatic and auditory stimulation, while latency range 3 covers a subsequent positive wave from somatic and auditory stimulation, as well as the first positive potential of the VER. Our purpose in setting up the six latency ranges is to maximize the probability that potentials with approximately the same latency and waveform, which may subse-

quently be shown to reflect similar neural substrates, will have the same name regardless of polarity. Thus, the positive wave at about 200-msec latency, usually called the V-wave or vertex potential, and the only potential which appears to be homologous across all three modalities, is designated P5a. Note that if we use the P_1–N_1–P_2 system, the somatic vertex potential would be designated P_5, the auditory, P_4, and the visual, P_3. This is unnecessarily confusing.

In setting up a nomenclature in this way, we encounter at least two difficulties. First, the latency ranges chosen are appropriate only for responses evoked by moderate stimulus parameters. For example, differences in latency at extreme intensity values might require some readjustment to the latency ranges. Second, we violate a precept mentioned earlier, that terminology should be descriptive only and not make assumptions about what is being measured. In practice, this is probably not completely possible or even desirable because, as mere description hopefully gives way to understanding, this must be reflected in the way in which we name and measure evoked response components. It is true that this terminology reflects some working hypotheses about homologous intermodality potentials. But at worst, if these hypotheses are invalidated, the system still serves equally well as a description of the data; at best we will have a systematic and comparable set of terms for the comparable waves of the response to any stimulus modality.

In summary, we feel that the problem of evoked response nomenclature should be discussed by those active in the field with the goal of improving communications. A uniform and internationally understood terminology is a continuing problem in any scientific discipline. Although the history of such attempts does not justify great optimism, we believe the attempt is worthwhile.

The problem of nomenclature is related to the problem of measurement. We believe base-to-peak measurements should be made. Unfortunately, base-to-peak measurements do not always reveal features that a visual examination of the data indicate are there, especially a component measured at multiple electrode locations or at different intensities. For example, in our distribution study, there are cases in which a component is clearly negative at most locations in most subjects. In some subjects at some locations, however, adjacent positive potentials become very large, lifting the negativity above the baseline. Such cases show a negative-going component with a positive base-to-peak value. Another example involves a component that maintains consistent polarity in relation to the baseline, but "rides" on an adjacent component whose amplitude changes radically. In this case, the component may appear to remain approximately constant, but its distance from the baseline is altered as a reflection of changes in its neighbor.

Data from a cross-modality comparison experiment should be analyzed in a way that underlines communalities and differences across modalities. We prefer to make maximal use of the raw data and to avoid transformations unless they are necessary. After consideration of alternatives, we decided to create topographical maps of amplitudes and latencies of all components that we could differentiate and measure sufficiently. For amplitude, the measurement at each location for a given subject was normalized to the maximum amplitude, taken as 100. On the basis of these normalized values, maps for each component for each subject were constructed; they showed the estimated area in which the amplitude was 75 percent or greater of the maximum and between 50 and 75 percent of the maximum. To derive a group map, medians of the normalized values for each electrode location for each subject were obtained and plotted in the same way as the individual maps.

Figures 3–5, 3–6, and 3–7 present group amplitude distributions for the SER, AER and VER, respectively. The various components of each type of AEP are shown and labeled on schematic responses. Since not all components are seen at every electrode location, different locations are used to illustrate different components. Not all components were mapped since, for reasons discussed earlier, meaningful measurements could not always be made. In figure 3–5, we see that the early positivity P1a has a very extensive bilateral group distribution, while the next three components, N1b, P2a, and P3a are restricted to the general locus of the somatosensory receiving area in contralateral posterior parietal cortex. The SER P3c has an extensive, ipsilateral group distribution. Component P4b is distributed in the region of the eyes, and P4a appears in the contralateral posterior parietal cortex though more diffusely than earlier components in that area. Components N4c and P5a are the negative-positive peaks of the vertex potential; their distribution is as expected. Thus, in the somatic system, the results are fairly neat. If we consider N1b, P2a, P3a, P4a, N4c, and P5a, we see short-latency potentials localized to the posterior parietal area with a gradual diffusion and with increasing latency up to the central distribution of the vertex potential. Exceptions to this scheme are SER P1a, P3c, and P4a.

The auditory system presents a less coherent picture, as shown in figure 3–6. An important question is whether we see short latency components whose distribution suggests that they are generated in primary sensory cortex as we do in the somatic system. We might expect the foci to be in the temporal areas; however, recent evidence indicates that short-latency cerebral AEP components are recorded clearly from the vertex region (Mast, 1965; Ruhm et al., 1967; Celesia et al., 1968).

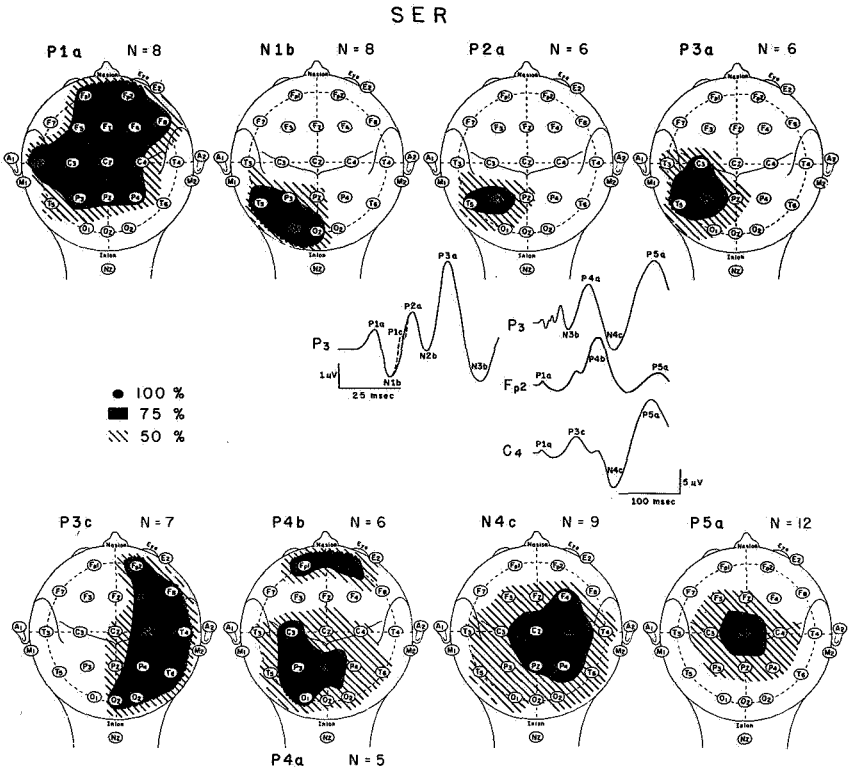

FIGURE 3–5.—Group amplitude distributions for SER components plotted on schematic diagrams of the head. The number of individual subjects (N) contributing to each distribution is indicated. Components are identified on schematic representations of responses at representative electrode locations. (Component P1c, indicated by the dashed line, is seen only in occasional subjects.) Electrode locations according to the 10–20 system plus eye (E_2), mastoid (M_1, M_2), and neck (N_z) locations. The 100-percent points, the distributions of the 75- to 100-percent range and the 50- to 75-percent range are shown. The limits of these distributions were estimated by locating points between electrode locations proportional to the percentage of amplitude of the component and connecting these points in smooth curves. Jagged edges indicate indefinite boundaries resulting from lack of delimiting electrode locations (from Matsumiya et al., in preparation). [In figures 3–5 through 3–10, the electrode locations showing maximum response amplitudes (100%) were indicated by cross-hatching. In reproducing the figures, the cross-hatching filled in. Thus, those locations which appear to be missing from the 75% maps are actually the 100% points.]

Auditory components P1a and N1b have diffuse distributions bearing no consistent relation to the temporal or vertex areas. Components P2a and P3a, however, are short-latency components localized to the vertex region. Components N3b, N4b, and P5a also are localized to the vertex

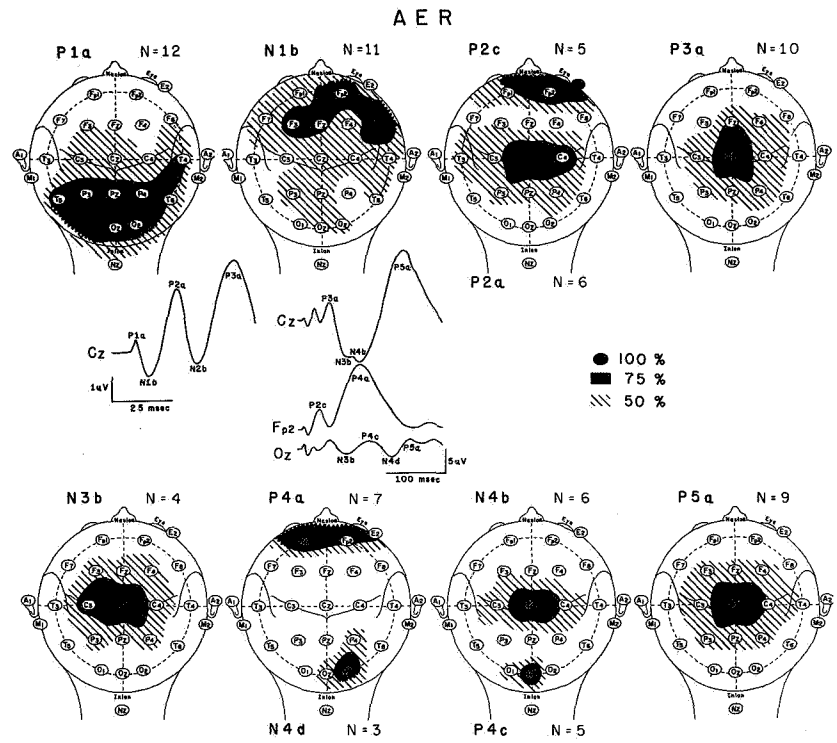

FIGURE 3–6.—Group amplitude distributions for the AER components. Explanation as in figure 3–5 (from Matsumiya et al., in preparation).

region as expected since they comprise the negative-positive peak of the AER vertex potential. We question whether N3b and N4b are really different components. Finally, components P4c and N4d have a restricted focus in the occiput.

In the visual system, component P3a, peaking at a median latency of 41 msec (range 34 to 42 msec), was the earliest visual component we observed. The group distribution shows a bilateral focus in the occiput. Component N3b is much more diffuse in the central occipital region. Both of these components are easily distinguished from the ERG a-wave and b-wave which occur at similar latencies. Component P4a has an occipital focus although the frontal leads picked up an apparently identical component with 50 to 75 percent amplitude. Component P4b distributes around the eye; N4c and P5a are the VER vertex potential. The distribution of N4c is rather different from its SER and AER counterpart in showing a considerable ipsilateral focus.

For distribution data, we think these topographical maps achieve the goal of expressing cross-modality data in ways that elucidate communalities and differences. For example, it is straightforward to identify SER and VER P4b and AER P4a as extracerebral potentials generated by musculature in the eye region. It is easy to see the differences in the distribution of SER and AER components P2a and P3a although these potentials occur with similar waveform and latency at overlapping electrode locations.

An important problem that concerned us is the degree to which these potentials based on a group of subjects represent the distributions for an individual subject. This problem is not unique to cross-modality comparisons; however, our analysis of it was related to the fourth problem which is accentuated in cross-modality comparisons, namely, the problem of separating legitimate cerebral responses from extracerebrally generated potentials. We said earlier that an initial goal in

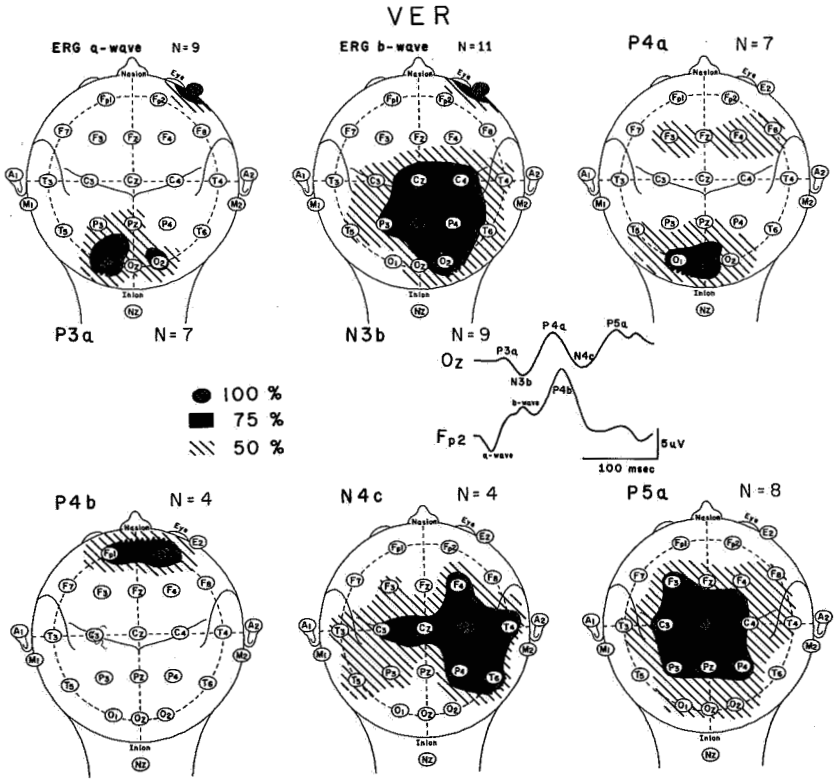

FIGURE 3–7.—Group amplitude distributions for VER and ERG components. Explanation as in figure 3–5 (from Matsumiya et al., in preparation).

these comparisons was to discover components that are "similar" across modalities. "Similar" does not necessarily mean recorded from the same electrode location; nor does it mean modality nonspecific. The SER and AER components P2a and P3a are "similar" in that they have comparable latencies, waveshape, and polarities. The possibility of error in relating cerebral components in one modality to extracerebral components in another is increased because each modality has its own sources of extracranial generators. Thus in the visual system, extracranial sources are the ERG, the "photomotor" response which Bickford (1964; Bickford et al., 1964b) has reported to have latencies of 55 msec in the face and 60 to 80 msec at the inion, and liminal or subliminal contractions of the forehead and orbital musculature which may be triggered by the flash and therefore summed. In the auditory system, Bickford and associates (Bickford et al., 1964a, b; Cody et al., 1964) have given us "sonomotor" responses. Mast (1965) has shown that a diffuse sonomotor response at approximately 30 msec, apparently arising from several head muscle sources, can affect legitimate cerebral auditory responses even at the vertex although this is significant under special conditions such as extreme muscle tension and high intensities—conditions normally avoided in evoked-response studies. Short-latency "somatomotor" responses also have been reported although these are rather easily differentiated from cerebral SERs (Cracco and Bickford, 1968; Goff et al., unpublished observations). Finally, there is the possibility of "startle" motor responses. These have longer latencies than the motor responses just mentioned. They tend to habituate but may be significant in the naive or anxious subject or at the beginning of an experimental session.

On the other hand, comparisons of evoked potentials recorded from the scalp and directly from the cortex in the auditory (Ruhm et al., 1967; Celesia et al., 1968), visual (Gastaut, 1949; Hirsch et al., 1961; Rayport et al., 1964; Corletto et al., 1967), and somatic (Jasper et al., 1960; Domino et al., 1964, 1965; Kelly et al., 1965; Broughton et al., 1968) systems have established that many scalp-recorded AEP components are faithful representations of neuroelectric potentials occurring at the cortical surface except for amplitude attenuation.

There are various ways of minimizing or eliminating particular myogenic responses such as local motor nerve blocks, curarization, or complete voluntary relaxation of a muscle (Bickford et al., 1964a). Obviously, these are not practical for the typical AEP experiment, and their use would not eliminate other sources such as the ERG. In the general and practical case, probably the best way to differentiate cerebral from extracerebral components either within or across modalities is by judicious choice of recording locations based on knowledge of the topography of both types of responses. In our distribution ex-

periment, therefore, we made no attempt to maximize or minimize extracranial components. We examined their distributions under fairly typical recording conditions to determine what components might be admixed under these conditions. The necessity for head restraint for the Maxwellian view gave us a somewhat greater degree of muscle tension than we would get in complete relaxation.

In analyzing the variability of the individual distributions upon which the group distributions presented in figures 3–5, 3–6, and 3–7 are based, it became apparent that for some components the variability was small, and the group distributions consequently were representative, while for others the variability was so great that the group distributions were misleading. An example appears in figure 3–8 in which individual distributions for early SER components are compared with the group distribution at the far left. The individual distributions for P1a are highly variable with multiple foci; those of the other components are quite homogeneous. Initially we thought this a signal-to-noise problem, that is that P1a was too small to be measured accurately. But the median amplitude of both P1a and N1b is equal at 1 μV. Further examination showed that other components that were larger in amplitude had heterogeneous individual distributions. For example, SER P3c (fig. 3–5) had a median amplitude of 3.5 μV, but individual subjects showed disparate foci and even dual foci for this component.

A second possibility is that the heterogeneous individual distribution resulted from coalescence of potentials arising from more than one source. In other words, it seemed possible that for these components showing diverse foci across subjects, there was a mixture of cerebral and extracerebral potentials. If this were the case, we might expect that those components which other types of experiments such as direct cortical recording had demonstrated to be legitimate cerebral components should have homogeneous foci and distributions. Those potentials which on other evidence were likely to be contaminated by temporal coincidence with extracerebral potentials should be the ones having multiple foci and/or more variable distributions. The data were examined from this point of view.

Considerable evidence supports the cerebral origin and lack of contamination of SER components N1b, P2a, and P3a. As mentioned earlier, responses were identical in latency and waveform, though larger in amplitude, were recorded from the cortical surface. Also, Cracco and Bickford (1968) found that these potentials were not changed by local muscle tension and judged them to be of cortical origin. The individual distributions for these components, presented in figure 3–8, show consistency of focus and distribution with the exception of one subject in whom a neck muscle potential similar to P2a is recorded.

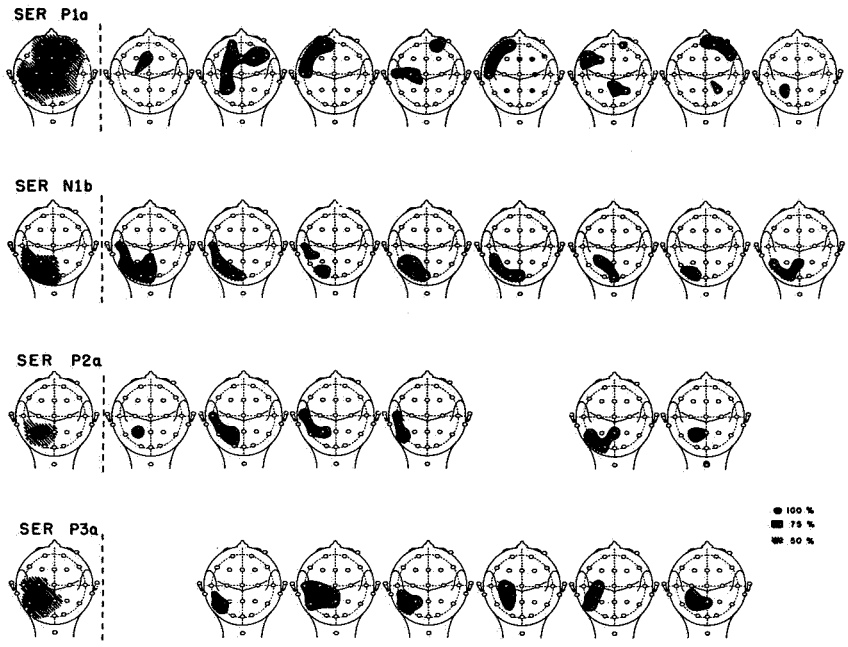

FIGURE 3–8.—Comparison of individual and group distributions for SER components. Group distributions at extreme left. Distributions in columns are from the same subjects for the four components. Some subjects show more than one 100-percent point; this results from inability of the measuring technique to resolve differences between these locations. Derivation of distributions as explained in figure 3–5 and text (from Matsumiya et al., in preparation).

In all three sensory systems, the vertex potential is acknowledged to be cerebral in origin and free from myogenic contamination. Figure 3–9 presents individual distributions for the positive phase of the SER, AER, and VER vertex potential—component P5a in our terminology. For the SER and AER, the consistency of focus and distribution is apparent. There is greater variability in the VER component.

Short-latency auditory responses are reported to be an admixture of vestibular mediated sonomotor responses and auditory cerebral responses (Bickford et al., 1964a, b; Mast, 1965). Recently, however, Ruhm et al. (1967) compared early AER components from the scalp and cortex. The latencies and waveforms of their responses compared favorably to those we record as AER P2a and P3a. They concluded that "there was clear early response componentry at the vertex which was interpreted to be cochleoneurogenic." Figure 3–10 shows individual subject distributions for AER P1a, N1b, P2a, and P3a. Components P1a and N1b show multiple foci which bear no consistent relation to the vertex. Indeed they are mostly focussed at the periphery as would

be expected if they were in whole or in part myogenic. There are more homogeneous distributions for AER P2a and P3a, which are generally focused along the coronal line at, or encompassing, the vertex. This supports their neurogenic origin; however, we may expect some intrusion by myogenic sources in some subjects, e.g., Y.M. for component P2a and E.D. and P.C. for P3a.

On the basis of this evidence, we believe that much of the variability in focus and distribution of scalp-recorded AEPs results from the temporal coincidence and resultant confusion of cerebral and extracerebral-evoked potentials. Extracerebral sources include the shorter-latency sonomotor, somatomotor, and photomotor responses; involuntary, frequently subliminal, twitches of the orbital and forehead musculature possibly associated with so-called startle reactions and, to a much more limited extent, the ERG.

These distribution data illustrate three points. First, they emphasize the distortions inherent in bipolar scalp-to-scalp electrode placement. For example, it is apparent that electrodes placed in frontal regions risk contamination by "eye-blink" potentials with a latency of around 100 msec in all three modalities (SER and VER components P4b; AER P4a; fig. 3–5 to 3–7). In the auditory system, there is a short-latency (median, 32 msec; range, 30 to 40 msec) component that

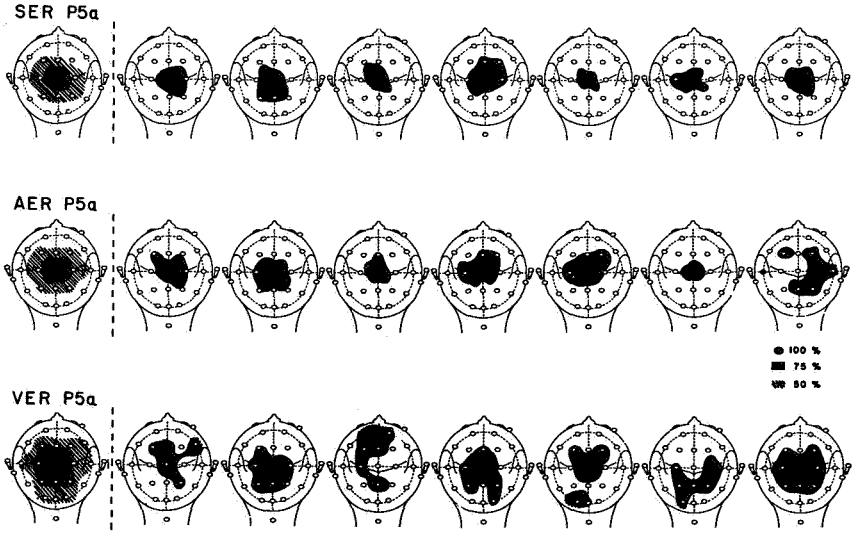

FIGURE. 3–9.—Comparison of individual and group distributions for the positive phase of the vertex potential (P5a) for the three modalities. Group distributions at extreme left. Individual distributions in columns are from the same subjects (from Matsumiya et al., in preparation).

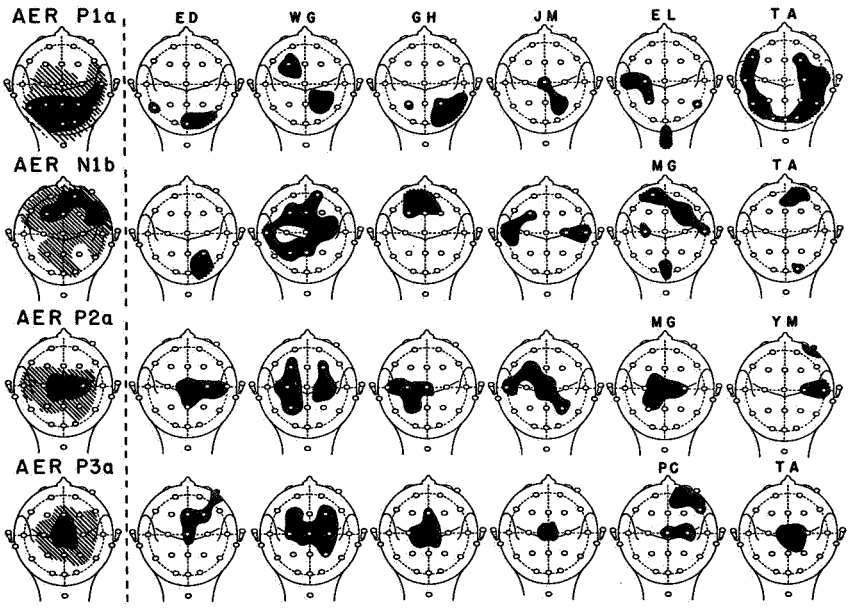

FIGURE. 3–10.—Comparison of individual and group distributions for AER components. Note that these components are comparable to those shown in Figure 3–8 for the SER. Group distributions at extreme left. The first four columns are for the same subjects. In the remaining two columns, different subjects are indicated by initials (from Matsumiya et al., in preparation).

apparently is also a "blink" potential. A frequently used reference for SER recording is located a few centimeters anterior to the interaural circle somewhere between C_3 and F_3 (for right-side stimulation). As we pointed out earlier (Goff et al., 1962), this produces a muddle of monopolar and bipolar recording and can be expected to increase SER variability across subjects. Finally, in the visual system, a parietal-to-occipital bipolar derivation is commonly used. Reference to figures 3–7 and 3–9 (VER P5a) shows that in most cases, both electrodes are active to varying degrees, and the algebraic sum will produce a distorted and highly variable record. The ERG a-wave and b-wave are quite localized and probably would be significant only in the anterior frontal region.

Second, the relation between variability in focus and distribution and cerebral versus admixed components reveals something about the security with which we can attribute given components to cerebral versus extracerebral origins. Third, knowledge of the focus and distribution reveals where to record in the different modalities in order to minimize the possibility of confusing neurogenic with myogenic com-

ponents both within and between modalities. For example, SER components N1b, P2a, P3a, and P4a have homogeneous distributions and are probably of cerebral origin. Location P_3 is within the 75 percent range for all. The SER vertex potential (N4c, P5a) is best recorded from location C_z as are the vertex potentials in the other modalities. If one were restricted to one electrode for the somatosensory system, the P_3 location is within the 50 percent range for the SER vertex potential; thus, P_3 will serve for all SER components. In the auditory system, the focus-variability criterion indicates that components P2a, P3a, N3b, N4b, and P5a are neurogenic cerebral potentials, and the distributions indicate that the C_z location is optimal for recording all of them. The origins of AER P4c and N4d are not clear. The individual distributions are moderately variable and mostly occipital; P4c is within the 75 percent range at the inion in one subject. Finally, VER present the muddiest data of the three sensory systems. The individual distributions for all of the possibly cerebral components—P3a, N3b, P4a, and P5a—show considerable variability in the extent and focus of their distributions, and some show multiple foci. Our data indicate locations O_1 or O_z are optimal for VER components (assuming right-eye stimulation), with the exception of the vertex potential. Therefore, under our stimulating conditions, electrode locations P_3, C_z, and O_1 or O_z referred to the left ear are the optimal AEP recording array for cross-modality experiments.

In summary, we have discussed the problems encountered in an extensive cross-modality experiment, which we believe are of general relevance to the conduct of any such study. We believe that the predominant need for cross-modality comparisons and indeed for all AEP studies is development of standardized techniques so that the work of different laboratories may be compared directly and accurately, thus minimizing overlap and duplication of effort. To this end, we have suggested that the general use of bipolar recording, especially in the absence of adequate consideration of placement, introduces confusion and retards progress in AEP research. We have indicated a common nonscalp reference location that appears to be relatively indifferent for evoked activity in all three modalities. We have suggested the need for uniformity of measurement and of component nomenclature and suggested a system which, while we do not expect its adoption as such, we hope may serve as a basis for achieving agreement. We have attempted to illuminate the question of sources of variability in AEPs and suggested that this is intimately related to the serious problem of "contamination" of scalp-recorded AEPs by extracerebral generators. On the basis of homogeneity in focus and distribution among subjects, we have designated AEP components that appear to be of cerebral neurogenic origin and indicated electrode locations for

the three modalities that are likely to record them without serious distortions from extracerebral sources. These locations suggest another possible basis for standardization.

We have adapted the hypothesis that the neural substrates of sensory information processing in the auditory, somatic, and visual system operate in similar ways and should thus produce homologous AEP components. Such homologies are more likely to become apparent when we have minimized spurious technical variability.[3]

DISCUSSION

DR. LINDSLEY: I would like to ask one question about figure 3–2 in which you show large potentials at the eye, elicited by auditory and somatosensory stimuli, but not by visual stimuli. Why did the visual stimulus not produce any response in this area?

DR. GOFF: I don't know why. Possibly, it is related to the use of Maxwellian-view stimulation.

DR. LINDSLEY: Your bipolar derivations were done with electrodes separated by a considerable distance; is that correct?

DR. GOFF: The ones that we used in our experiment were the P_z–O_z derivations commonly used in visual evoked response work.

DR. LINDSLEY: Have you done any recording where the electrodes might be only 2½ cm apart over the visual area or the auditory area?

DR. GOFF: No, we have not. When we started this experiment, we found (as others did) that it is difficult to record early visual evoked components. We were concerned about the reasons for these difficulties. We came to the conclusion that these components were a function of the bipolar recording and were not comparable to the monopolar analysis that we wanted to do.

DR. LINDSLEY: Assuming for the moment that you could get sufficient potential differences between two electrodes that are close together, wouldn't this method rule out, to a considerable extent, potentials generated at a distance that might influence the response in different areas, particularly extracranial responses? Do you think that it would do that?

DR. GOFF: It would depend upon the distribution of the extracranial generators. Certainly, it is more likely to cancel them out. But you could not be certain. This is one of the points I have been trying to make, that until you know the distribution of extracranial generators, or any other response component, you can't say what contribution they are making to a bipolar record.

Dr. WHITE: My discussion of Dr. Goff's paper will be quite brief. I

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[3] We gratefully acknowledge the assistance of Dr. George Heninger and Mr. Thomas C. Fisher in this research.

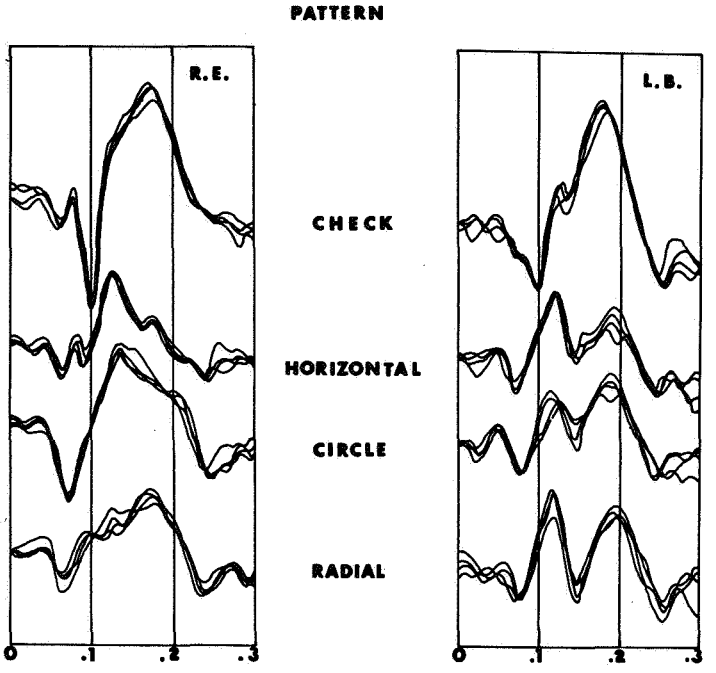

FIGURE 3–11.—Responses to four visual patterns. Four replications for each condition, N=100 for each replication. Binocular stimulation (negative down).

have studied only visually evoked responses and therefore cannot discuss his somatic and auditory work. I would like, however, to note that we also have decided to use the monopolar type of recording exclusively, and we use one or both of the earlobes as the reference.

Most of my comments are more general and are related to earlier papers, and to other things which have been said here. Dr. Clynes mentioned the "quality" of the stimulus. In our work in vision, we have discovered that the most exciting—if I may use this term—responses were in relation to pattern vision. Figure 3–11 presents some examples which illustrate points raised in this discussion.

With regard to individual differences, Figure 3–11 presents AEPs from two individuals responding to four different types of patterns. At the top is a checkerboard; the second stimulus is a horizontal grating in which the distance between the black lines is about the same as the width of the "checks" in the checkerboard. The third stimulus is a group of concentric circles, and the last is a set of radial lines.[4]

[4] The last three stimuli are part of the moire pattern kit available from Edmund Scientific Company. We have found this kit quite useful.

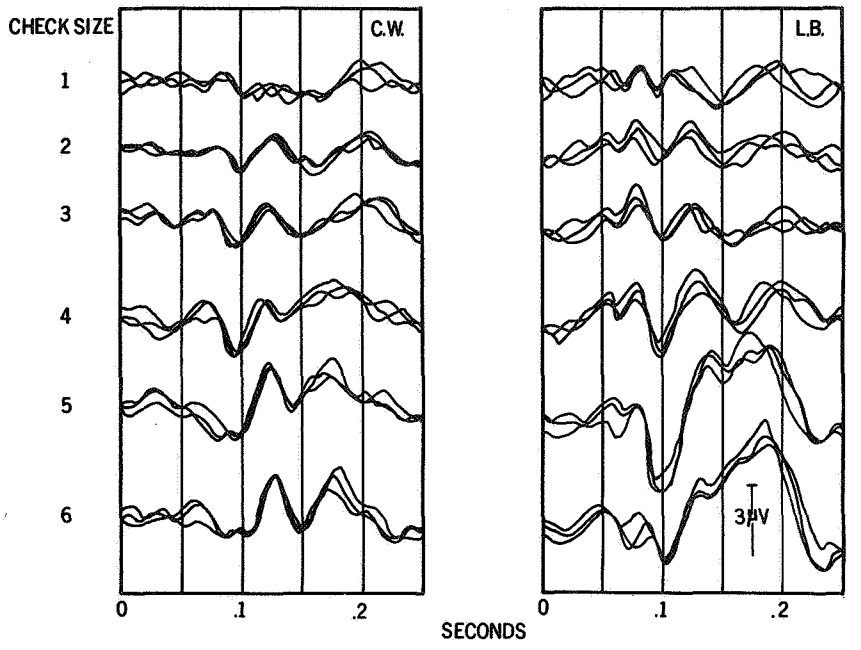

FIGURE 3–12.—Evoked potential and check size. Largest checks at top of record. In "Check 5" each unit subtended 10 min of arc; N=50 per record. Binocular stimulation (negative down).

There were four replications on successive days, and 100 stimuli in each replication. There is a high degree of intrasubject reliability; note also that there is much intersubject variability, its degree depending upon the type of pattern.

The radial lines elicited quite a different pattern in the two subjects. It turned out that there was a good reason for this; one subject was badly astigmatic, and the other was not.

We subsequently conducted a study of the effect of the size of the checks in a checkerboard on the AEP. A similar study was conducted by Rietveld and his associates (Rietveld et al., 1967). Figure 3–12 presents some of the results of this study. The bottom record was elicited by a pattern with 5 minutes of arc per unit check, the next about 10, then 20, 40, and so forth. The independent variable is thus the density of the contour. As contour density increases, there is a very striking increase in the amplitude of response. Note that the increase in response amplitude is most marked at the 100-msec point and at about 180 msec.

These data corroborate the findings of Rietveld and his associates very well. We also find, as they do, that there is a size of the checker-

board element that elicits a maximum AEP and that it subtends a visual angle of 10 minutes of arc.

Figure 3–13 introduces another aspect of the work. This, and figure 3–14 represent work previously reported by Harter and White (1968). Subjects were presented with a checkerboard of the optimum design, elements of 10 to 15 minutes of arc. The stimuli were presented in focus and out of focus to four subjects. The records labeled "front" were obtained when a transparency was placed in front of the diffusing milk-glass light window, while "back" indicates that we placed it behind the milk glass. The front condition produced a clear, sharply-focused image, while the back condition caused a badly blurred image of the checkerboard.

Again there were individual differences, but there were components common to all subjects (we have labeled them A and B). Rietveld and his associates discovered essentially the same two components and called them Gamma and Z. The A is a negative intrusion that occurs at about 100 msec after the flash when there is contour present, and it seems that the amplitude of this negative intrusion is related to both the amount and quality of contour (the sharpness of the contour).

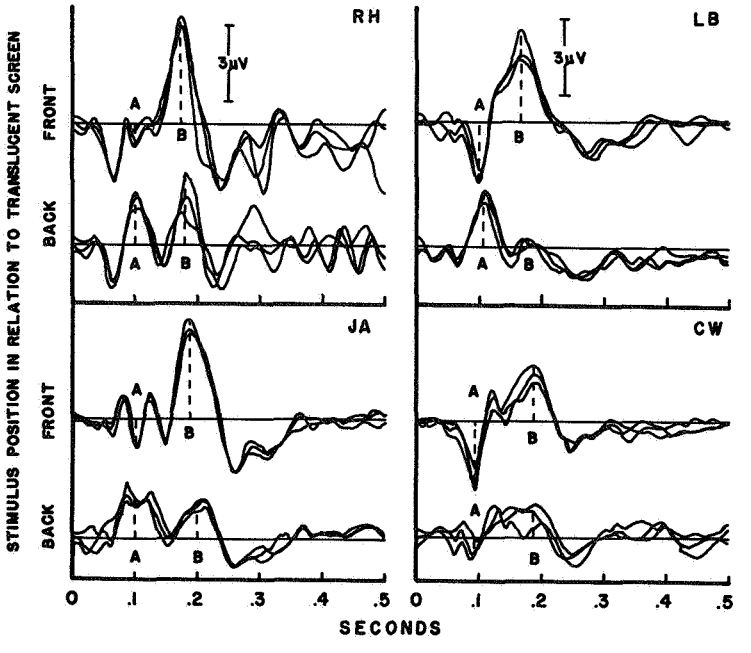

FIGURE 3–13.—Responses to sharply focused (front) and blurred (back) images for four subjects; N=100 per record. Binocular stimulation (negative down).

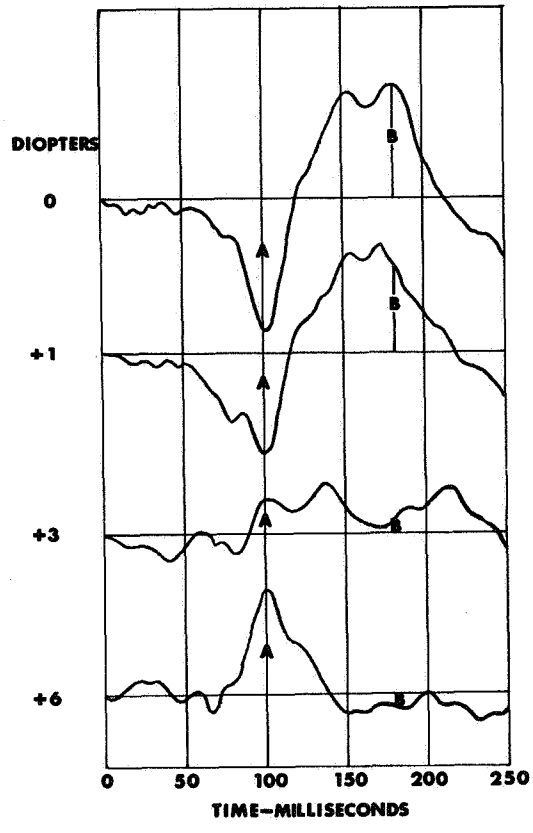

FIGURE 3–14.—Change in responses as a function of degree of sharpness of contour. Most sharp at top of figure; N=100, presentation rate 3 per/sec. Subject LB. Binocular stimulation (negative down).

Our A, in this figure, appears for every individual. Its amplitude peaks when the stimulus is in focus. In subject LB, an actual inversion can be seen from negativity to positivity, depending on whether the stimulus is in focus or out of focus. In the case of CW, the curve never goes positive. This may be a function of age, because the other subjects were all in their early twenties.

Component B is most positive at 180 msec when the stimulus is in focus. This was true in four subjects and in all the replications. We have replicated this study with about 40 to 50 subjects in the past year, and we have generally obtained the same results.

Figure 3–14 shows results obtained when ophthalmic lenses were used to defocus the image in gradual steps, from 1 to 6 diopters. You can see the gradual shift in both the A and B components.

There is evidence that these components are definitely neurogenic and that they are visually specific. These components can only be recorded from a very restricted area of the scalp over the occipital cortex. If you record at the inion, on the midline, and towards the vertex in small steps, a certain point is reached about 2 inches above the inion where these components will disappear. It is a marked and sharp break.

We assume that when we present a very complex figure, such as the checkerboard, that the AEP we record is the sum of the responses to flashes of light, with a nonspecific type of response, as well as a response to the contour that was presented. We were interested only in the contour response. We thought it feasible to eliminate all of the other components by obtaining a set of responses and then subtracting the response to unpatterned light. We thus completely defocused the image and subtracted, by means of the computer, the same number of flashes that we used with the various checkerboard stimuli. Under these circumstances, we hoped to obtain a better estimate of the combination of the contour.

This method is not infallible because there are interactions between the sources of the AEP. For example, with sharp images, there is not as much of the "ringing" after-effect as with a defocused image.

Figure 3–15 shows an example of the subtracting process. At the top left is the standard response of a normal adult human to a sharply focused checkerboard of optimum size; below it are the responses obtained using lenses of 1, 3, and 6 diopters. On the right side of the figure are records from which we have subtracted responses to 50 flashes, with −10 diopter lenses before each eye. At 6 diopters, the record is at the noise level.

Figure 3–16 shows the effects of astigmatism on the AEP of a subject. A grating of fine black lines was presented at different angles—first horizontal, then up to the right, then vertical, and then up to the left. If you know what to look for, you can immediately see that one of these is better than the others; however, the subtraction technique makes it very clear. Good responses were obtained when the grating was horizontal; we obtained just noise otherwise. Under these circumstances, this person could only see the lines when they were horizontal, or 5° or 6° off horizontal. Anything else appeared completely blurred to him.

He is an ideal subject, because his right eye does not have any appreciable astigmatism. The right side of the figure shows the response to right-eye stimulation at horizontal, 45°, 90°, and 135°. After subtraction, the largest response was at 135°; next highest was at 90°, next at 45°, and the lowest at the horizontal. His perceptual response verified this. He could see all of these lines very clearly, but the highest con-

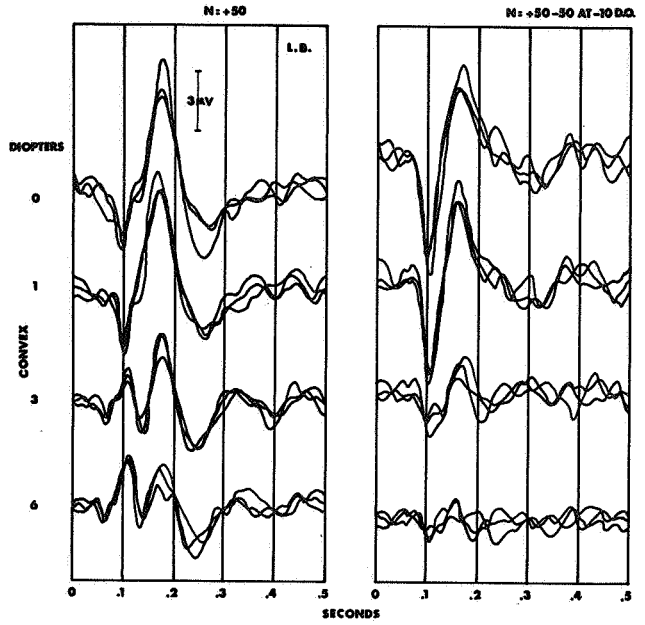

FIGURE 3–15.—Example of subtraction technique. Original records are at left. At right are the results after an equal number of responses to a stimulus with no contour information have been subtracted. Binocular stimulation.

trast was at 135° and gradually decreased to a medium gray. The optometrist who studied him for us agreed with this but said that the degree of astigmatism present in his right eye was so slight that he would not bother to correct it.

DR. DAVIS: I want to support, most enthusiastically, the proposition that Dr. Goff put before us because I think that, as was said earlier, we are now entering a new era—an era of almost infinite complexity, and I am afraid also infinite confusion. One follows directly from the other. At the outset, he gave us some factual recommendations for reducing the degree of confusion and a way of establishing certain conventions and a nomenclature by which we can communicate. It is going to be very important for us to communicate across our various interests and specializations. Otherwise, we are going to be like the blind men feeling the elephant from different aspects. But if we can have a certain degree of commonality, it will allow us much greater and more successful communication.

I like Dr. Goff's particular recommendations because they coincide almost precisely with the conclusions that we have reached—I won't

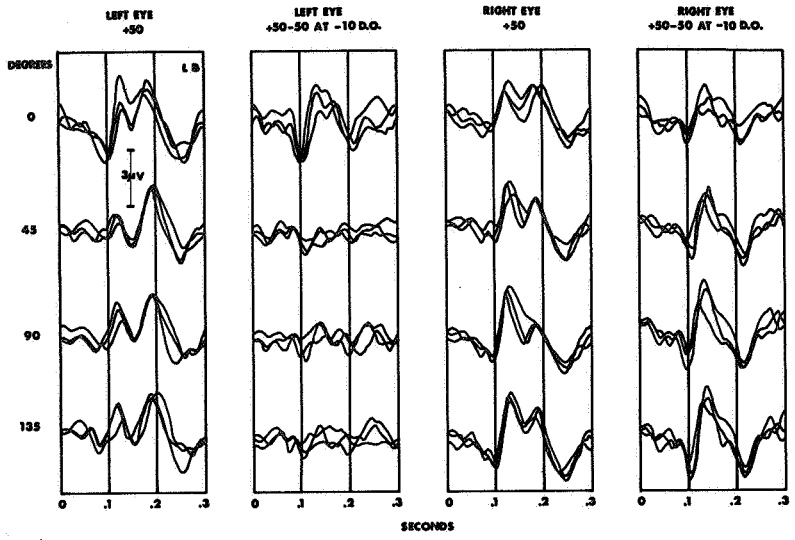

FIGURE 3–16.—Example showing the effect of astigmatism on the evoked response. Stimulus was a grating pattern consisting of fine black lines. Subject had marked astigmatism in the left eye and a very slight amount in the right eye (negative down).

say completely independently, but pretty much independently in our own laboratory—although we were definitely oriented to the auditory system and dealt right from the start with the vertex potential. But I am a monopolar man from the early EEG days, and I have found empirically that the vertex-to-earlobe or mastoid arrangement seems to give us the greatest stability and reproducibility of the responses.

Recently we began venturing away from purely auditory stimulation and encountered some of the complexities of somatic and visual stimulation. Incidentally, I want to support the proposition that "somatic" stimulation must be defined very carefully and that one should specify exactly what the somatic stimulation is. Electric stimulation of a nerve and tactile stimulation are really quite different. We came to the same choices of electrode placements in parietal, occipital, and vertex areas as has Dr. Goff's group.

On nomenclature, all I can say is that we have been using the one that was illustrated on Figure 3–3—the N_1–P_1, P_2, P_3—and we are dissatisfied with it for exactly the reasons that Dr. Goff cited. I offer the general proposition that we cannot in principle find a satisfactory nomenclature that will work across modalities without specifying at least four items. We will have to specify something about the stimulus that is employed, something about the time zone in which the component appears, and then the various subdivisions. Whether we can

agree on any practical nomenclature as a group, I'm not sure. I very much hope we can. It would be very nice if we could also agree which side is right side up. I reversed the polarity of my records a few years ago to make them negative-up in order to become aligned with clinical electroencephalography. I am ready to reverse again if it is really going to help. I hope we can make that decision also, but I am not sure we can.

DR. LEHMANN: I would like to question the notion that the ear is an indifferent reference point. Evoked responses recorded between ear and occiput are very similar to responses recorded between mastoid and occiput, and we know that the mastoid is not an indifferent location. In general, it is very difficult to localize electrical sources and sinks of evoked potentials on the scalp when two sources are to be expected, as is the case when we stimulate both eyes or one eye of a subject. We investigated a simplified visual system in a subject with a longitudinal split of the chiasma, where input presented to one eye reached only one hemisphere directly. In this subject, we studied the electrical fields on the scalp (fig. 3–17) that were generated by monocular light stimulation (Lehmann, Kavanagh, and Fender, 1969). Almost all of the evoked potential during the 250 msec after the flash could be accounted for by a single occipital source ipsilateral to the stimulated eye. The electrical field showed considerable strength near the mastoid area.

DR. WALTER: In response to Dr. Goff's plea for nonprejudicial words, may I direct our attention to the word "latency," which suggests events that are prepared covertly and, after a latent period, expressed overtly. Particularly since our attention earlier in the day was directed to possible partial cancellation between spatially distinct generators, I think the epistemology that is latent in the word "latency" ought to be rejected. As a less prejudical word, I suggest the word "delay" or perhaps "delay after triggering." At any rate, some comment about the use of the word "latency" should improve our thoughts.

A second prejudicial word is "potential." My sister-in-law, who performs what is euphemistically termed "special education" for emotionally disturbed children, thought that "evoked potentials" referred to the psychosocial results of successful special education. But more specifically, we all know, if asked, that what we record is a difference of electrical potential that must be produced by electric currents flowing in the brain, the skull, and the scalp. We all know that, if asked, but we seldom talk that way. I think the only cure for the disease of talking about potentials when we should use some words which suggest the unknown neural source or sources of marks on

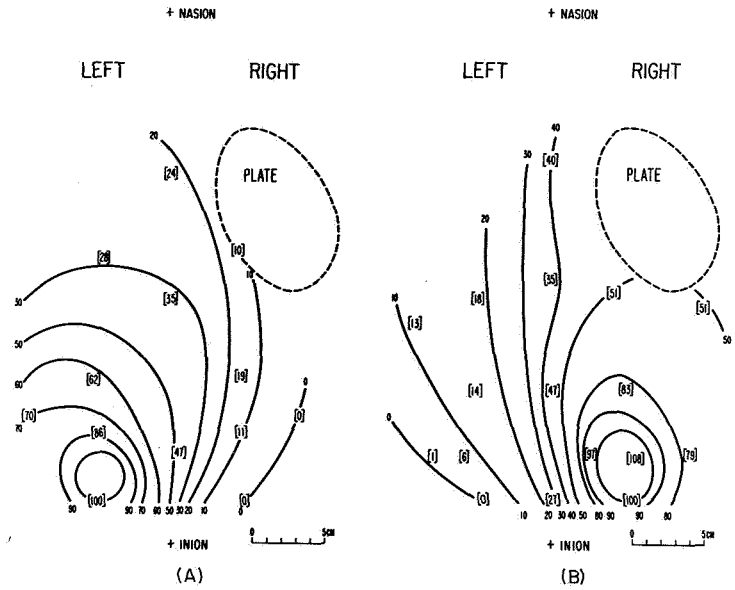

FIGURE 3–17.—Distribution of the electrical field evoked by monocular stimulation (A) left eye and (B) right eye, 92 to 140 msec after the flash in a subject with split chiasma. The figures in square brackets indicate relative amplitudes (from Lehmann et al., 1969).

paper will be to wait for the payoff on Dr. Vaughan's promissory note about a volume model for whatever we should call them, "evoked current records," or something of that kind.

I would like to call your attention to the electric model of Remond and collaborators. They reproduced the temporality and the topography of their "average alpha" records with marvelous fidelity, using only two to four oscillating punctiform monopoles. But this model should alert us to the fact that even a physical, electric model may not necessarily produce indisputable objectivity because I personally doubt that the cortex consists of two to four punctiform oscillating monopoles.

DR. BRAZIER: Dr. Goff's schema seems very rational indeed for the normal adult. Has he thought how those of us who look for changes in clinical cases, and those who look for changes with drugs, anoxia, and anesthesia are going to describe these changes when the nomenclature is on a time base. Also, how are we going to describe these potential differences on a time base when we are working with children?

DR. SUTTON: I admire very much the systematic way in which Dr. Goff has approached these problems which have concerned all

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of us. Nevertheless, I would like to sound a discouraging note. I don't think we should try to solve finally these problems at this time. For example, Dr. Goff has come to the conclusion, as we have in our own laboratory, that it is more satisfactory to measure amplitudes from a baseline defined at stimulus onset rather than to make peak-to-peak measurements; the reasons he gives are highly cogent. But he also notes, as we have noted, that when a waveform is riding on a slow potential, measuring amplitude from baseline may become meaningless. Under such conditions, a peak-to-peak measurement makes more sense.

Secondly, with respect to the nomenclature problem, there also is a paradox. If you use sequence of appearance to name the components, then you can't cope with the fact that under some experimental conditions or with some subjects, there might appear an extra little pip. How large must that little pip be to be counted as an extra component and alter the sequence? If you use latency, there is the variety of experimental conditions, by no means limited to the intensity of the stimulus and intersubject differences to which Dr. Brazier referred, which also alters latency.

I wonder whether the wisest course is not to attempt an immediate solution of these problems. I would be very unhappy if we started talking routinely about a 300-msec component or a 200-msec component, when I have experimental conditions that can take the 300-msec component over to 800 msec (Sutton et al., 1967). Perhaps what we must wait for—and this is an endeavor that I know Dr. Goff has also been involved in—is the discovery of experimental operations that uniquely alter a particular component. In other words, if we are so fortunate as to find a drug, or a lesion, or perhaps a scalp distribution of potentials that would eliminate one component and leave the others essentially unchanged, then nomenclature would become really meaningful. I think we have to remain open-minded with respect to nomenclature until such development.

Dr. Goff: Of course these points are valid. First, with regard to drugs or anesthesia (I am responding here to Dr. Sutton's comments), in order to be able to denote alterations in the first place, you have to have some idea of what the shape of the response is in the normal case. Perhaps we could apply the nomenclature to the response as it is seen in the normal case, and then keep the same nomenclature for the response as the latencies change. What I had in mind initially, of course, were normal data.

With regard to children, mentioned by Dr. Brazier, and developmental studies in general, maybe what we have to do is to establish norms, latency-range norms, or some norms, in categories of age groups. This brings up something I didn't mention in the formal presentation,

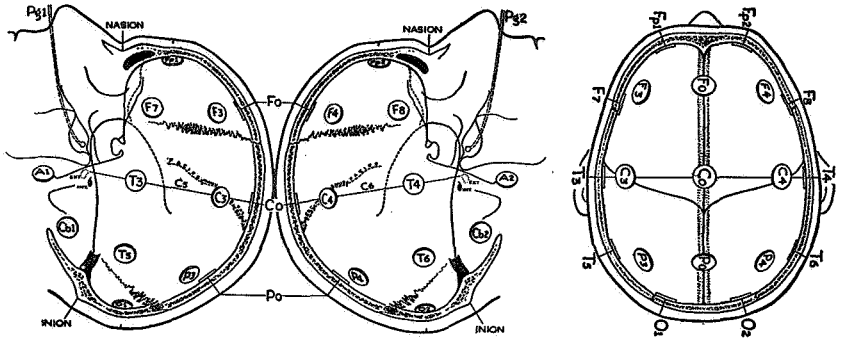

FIGURE 3–18.—Scalp electrode positions of the international 10–20 system. (Jasper 1958). The electrode positions take into account the size and shape of the head, are very reproducible in a given subject, are usually adequate and can be supplemented with intermediate electrodes, when desirable.

but which concerns me. For example, clinical neurologists come to me with a patient having a sensory deficit and ask if his evoked potential is normal. I have to admit that we really don't know what a normal evoked response is. What we need is a vast amount of data, which I don't believe any single laboratory could collect, but which might be gathered from different laboratories if standard recording methods could be established. With computer facilities, means and standard deviations of latencies and amplitudes for these normative data could be established. Of course, this would have to be done for several age ranges. But then we might be able to establish, in terms of means and standard deviations, what is a normal response, and could then specify in terms of probability, based on knowledge of variability, whether a given response deviates from normal.

DR. BROUGHTON: I believe that this part of the discussion is very important since we are considering decisions that would help standardize techniques and so facilitate interlaboratory comparisons. Four aspects appear of particular relevance. The first concerns standardizing the electrode placement positions by adopting the International 10–20 System (Jasper, 1958). This system (fig. 3–18) takes into account the relative size and shape of the head. It has many advantages over other systems used by some experimenters in which constant distances from various reference skull points are measured (Dawson, 1950; Goff et al., 1962; Vaughan and Katzman, 1964; Shagass and Schwartz, 1964; Giblin, 1964; and many others).

If a midline occipital electrode (O_z) is added, the International 10–20 System is quite satisfactory for at least the somatosensory, visual, and auditory evoked potentials. Moreover, supplementary electrodes can be added as desired.

For somatosensory stimulation, the standard central electrode is found—in the absence of atrophy of a temporal lobe—to be regularly over the Fissure of Rolando and at, or near, the point where direct cortical stimulation produces sensation referred to contralateral hand areas innervated by the median nerve (Broughton, 1967). Intermediate electrodes between the standard central electrode and the midline central or midtemporal electrodes are located at, or near, somatosensory cortex representing the face, and sensorimotor cortex representing the leg, respectively. This is valuable for facial or lower extremity stimulation.

In relationship to the early auditory evoked potential, the midtemporal electrode is truly over the midtemporal region as is shown in the illustration. But there is increasing evidence in our own work and that of others that the earliest potentials arising apparently from the primary auditory cortex (muscle contamination excluded) are recorded best at, or just lateral to, the midline. This suggests that the primary auditory projection area in the superior temporal cortex acts as a vertically oriented generator, which is quite reasonable.

The earliest parts of the visual evoked potential were shown long ago by Cobb and Dawson (1960), using bipolar arrays with short interelectrode distances, to be maximal at the midline several (3 to 6) centimeters above the external occipital protuberance or inion. We have confirmed this location of the earliest VER on the lateral hemispheric cortex near the midline by using direct cortical recording of the mesial and lateral surfaces of the occipital lobe (unpublished studies, two cases). It is therefore suggested that an intermediate parieto-occipital electrode be added to the International 10–20 System for recording the early components arising from the visual striate cortex. Later components of all modalities are recorded satisfactorily with this system.

The second point concerns referential recording. There is a palpable tendency at this meeting to accept, suddenly after many years of searching, that we in fact do have an indifferent electrode—the earlobe. I have been using the earlobe reference for over 6 years, having previously rejected the chin, nasal bridge, cervical seventh spine, and other references for various reasons. Although it usually is the best reference for all modalities, the earlobe can be active and shows, in particular, cerebral activity following auditory stimuli, myogenic potentials after auditory stimuli, and oculomotor potentials following visual stimuli. It has become apparent that certain problems are best solved by combining simultaneous bipolar and referential derivations.

Thirdly, I believe that we could take an important step at this meeting by deciding arbitrarily—because it is an arbitrary decision—whether we want "positive down" in referential recordings. It is a small point; however, the visual aspect of these curves is important,

especially when comparing one's own results with those of others, often shown at different analysis times.

Fourthly, I would like to suggest that peak-to-peak measurements of evoked potentials have many advantages over baseline-to-peak measurements. In the latter, you have the problem of establishing the baseline. More seriously, when you have a "component" or deflection of constant polarity and onset and offset latencies which varies from one summed response to the next by reaching and possibly crossing the baseline, the problems are very considerable. If positive-going, it will be called negative when it does not cross the baseline to the positive side; when it does, it will be considered positive. Nevertheless, the physiological event remains the same phenomenon. But very different data will be measured according to where the event is situated in relation to the baseline. One cannot consistently use both a positive-negative nomenclature (e.g., P1, N1, P2, N2, etc.) and employ baseline-to-peak measurements unless the letters indicate only the direction of polarity change.

Peak-to-peak measurements of components are purely descriptive and do not have these important inconveniences, particularly those of having both the polarity and amplitude dependent upon the dc level of the potential at the time of a component's onset.

Dr. Ornitz: I would like to add a word about latencies of peaks, and how we label them with respect to the state of consciousness because a little bit of drowsiness in the subject will begin to alter peak latencies markedly. We work with sleeping children (Ornitz et al., 1967b), and in these subjects age as well as sleep-stage influence latency. We must decide how to label wave N_2, which is not on Dr. Goff's scheme, and also P5a, which is (we call it P_2) the point when the latencies shift. Latencies are usually longer in children in deeper stages of sleep than they are in waking adults. To make matters worse, during sleep in children, peaks P3a and N4b often disappear. Therefore, it becomes difficult to discuss a wave P5a, and so forth. The real issue is not the labeling, but rather the choice between accepting these waves as completely different in different age groups or in different sleep stages, or accepting that there are some homologies across different states of wakefulness and sleep and across age groups. I think we must now define what is the normal latency range in respect to states of consciousness and developmental level.

Dr. Donchin: I would like to make two points. The first concerns the "bipolar-monopolar" arguments. One major advantage of monopolar recording is that it is possible to retrieve bipolar from two monopolar records by simply subtracting one monopolar record from the other. It is impossible, however (without a common reference), to retrieve the monopolar records from the bipolar records.

The other point I wanted to make concerns the notion of homologous components. Dr. Goff—if I understood him correctly—defines components as homologous if they have similar distributions over the skull. However, components, as have been pointed out by many here, tend to change with the conditions of the experiments. Thus, it is quite possible to find that the same spatiotemporal distributions reflect two different components under different circumstances.

Let me give you an example. We know that the evoked response waveform is quite dependent on stimulus intensity. As we reduce stimulus intensity, there are consistent changes in the latency of some components as well as a change in the amplitude of other components. As the intensity is reduced to near threshold levels, a fairly marked change in the AEP waveform is observed (Wicke et al., 1964). The common two-peaked waveform is replaced by one component, a rather slow positive-going shift. Vaughan has interpreted this as an indication of a shift from photopic to scotopic mechanisms (Vaughan, 1966). While this is a very plausible explanation, it is important to point out that as the intensity is reduced to very low levels, the subject's task becomes considerably more difficult. He is now quite uncertain when, if, and where, he is going to see the stimulus. Now, if stimuli that resolve uncertainty produce a large P_3 component, as Dr. Sutton has reported (chapter 6), the near-threshold stimuli might elicit this component, which is then only indirectly related to the effects of intensity on the AEP.

In a study of AEPs elicited with near-threshold stimuli (Donchin, 1968), the subjects were presented with a very dim stimulus and were instructed to report the position of the stimulus (which could be in one of eight possible positions), as well as to indicate whether or not they were certain about their position judgments. Whenever the subject was certain about his judgment, whether or not he was correct, a very large positive component with a latency of about 250 msec appeared in the AEP. This component thus appears to be related more to the subject's task than to the purely psychophysical aspects of the stimulus. When we did this experiment, we believed that we were running a pure, well controlled psychophysical study. However, the experimental design introduced nonstimulus-related factors that greatly affected the AEP. It is, thus, very important when defining homologies among AEP components obtained with different stimuli, or with "the same" stimulus, to specify clearly the circumstances under which the AEPs are recorded and to specify carefully all the variables that might affect the response. Thus, I am not sure how we are going to identify homologies between components if we don't include in the definition some notion of the variables that we are operating with when we are recording the evoked response.

DR. VAUGHAN: I would like to comment on some aspects of Dr. Goff's presentation and to state my position concerning the problem of ERP nomenclature. I am in substantial agreement with the views of Dr. Sutton on the latter question. It would, I believe, be unwise to crystallize a nomenclature about any limited set of evoked potential data. The effects of stimulus parameters, state of subject, maturational factors, and other variables are so significant as to preclude at this time any physiologically significant designations. What is needed is redoubled effort to specify with precision the effects of these various factors on waveform and spatial distribution since only parametric data on these questions can provide a substantive basis for some future descriptive system. As a corollary, it seems to me that premature designations will confuse, rather than clarify, attempts to relate findings of different studies. For example, the appelation P_2 carries with it connotations concerning latency, distribution, and even of the physiological processes underlying its generation. The erroneous assumption of the "nonspecificity" of this so-called vertex potential has for some time colored interpretations of evoked potential data. It seems to me that the fewer the interpretive assumptions concerning evoked response waveforms, the better, until substantive evidence has been obtained to support such assumptions. For this reason, the notion of component homology across modalities espoused by Dr. Goff does not appeal to me as a basis of evoked response classification. The differences in physiological organization of the various sensory systems would seem to be reason enough for caution until more parametric information is at hand. My own preference, stated in my paper, would be for a specific designation of electrode placements and of the peak latencies of each component. This method is precise, noncommittal, and tends to call attention to the details of spatio-temporal configuration that become obscured in more summary designations. This proposal, I think, provides greater clarity at the current stage of research in this area.

I have some comments on the apparent discrepancies in the distribution data presented by Goff and myself. Actually, there is substantially greater agreement than might perhaps be apparent at first glance. We have, of course, come to somewhat different conclusions concerning the late "vertex" wave, but I think that Goff's own data on the loss of this component after unilateral interruption of the lemniscal pathways, as well as the conclusive transcortical recordings by Goldring, make it absolutely clear that the P200 components in each modality are associated with activity in their respective primary projection areas. The major reasons for the differences in our findings are the choice of reference and the placement of the cranial electrodes. I can confirm the difficulties encountered by Goff in the use of nose or chin reference. We decided that these were preferable to the ears, however,

when it became apparent that the latter site was not inactive for auditory ERs. We worked to eliminate the artifacts present at nose and chin and found that in our experienced subjects, these placements could be employed quite satisfactorily. Unfortunately, the 10–20 system is not adequate for ERP distribution studies since it does not provide sufficient spatial resolution near the vertex region. Since the observed ER distributions are the sum of fields from bilateral generators, the distributions all peak at or near the midline. It is these subtle distinctions that are absolutely critical for differentiating the intracranial generators. I was quite amazed to see what small spatial differences were associated with rather gross alterations in generator configuration. Only when one has looked at this problem quantitatively do these facts become clear. I believe that workers in the evoked potential field have been "brainwashed" by views long held in electroencephalography, and expressed earlier by Dr. Knott, into the belief that these phenomena are extraordinarily crude and unreliable indices of underlying brain activity. Although volume conduction theory has been invoked at several times during the history of EEG research, one can search the literature in vain for any substantial effort to make a quantitative application to empirical data. Some tentative attempts were made by Roth and colleagues, but these were doomed to failure for reasons already noted. Other workers (e.g., Geisler and Gerstein, 1961) have failed to obtain adequate empirical data to test their model. It is not surprising, therefore, that one can cite a number of "failures" of the volume conduction treatment. In fact, a volume conduction analysis cannot be invalid; it may at worst be inaccurate. Since field distributions within the cranium are defined by the same physical laws as any conductive system, volume conduction cannot "fail" to occur although its lawful operation may not be apparent to an observer who does not know what to expect. In the future, these comments will appear both self-evident and trivial, but at the present time it is necessary for workers in this field to recognize that physical laws are as applicable in this field as in any other, and that their quantitative assessment can serve to define more clearly the potentialities and limitations of ERP analysis.

Dr. Storm van Leeuwen: I agree with Dr. Donchin that it is in a way immaterial whether one uses bipolar linkages or leads to a common reference, because the one can be derived from the other. It is only a matter of convenience which combinations of derivations should be used. In fact, in some cases it can even be useful to record to a common reference electrode situated in an area of maximum amplitude, for example, in the case of visual responses to a common occipital electrode.

As far as terminology is concerned, I have always objected to the use of the term "monopolar." We all know that we are recording the

difference between two poles; thus we are always recording bipolar, and monopolar recording does not even exist. Therefore, I urge calling it recording to a common reference and dropping the term "monopolar," which is not correct and which is misleading.

I agree also with Dr. Vaughan that the temporal areas are not always indifferent. Particularly in epileptic patients, responses sometimes occur in these areas. Therefore, a point which is really indifferent under all circumstances does not exist, and one should adapt his recording technique from case to case as the situation demands. What one should try to do is to construct a proper topographic potential distribution over the head of the electrical phenomena.

DR. LANSING: We have been impressed not only with the variability of evoked potential waveforms from one subject to another, but also with the complexity and variation produced for a single subject by varying the physical parameters of the stimulus. As Drs. White and Clynes have shown, different components of the visual evoked potential can be enhanced selectively by manipulation of color, contrast, pattern, background illumination, and so forth. Since in addition to this dependence on experimental conditions, these components occur at somewhat different latencies for different subjects, it is not surprising that we have had difficulty arriving at a uniform system of labeling wave components.

It seems to me that one direction in which we might move is to identify components on a functional basis, according to the manner in which they change in response to change in a given stimulus dimension. This would be difficult if just the extremes of a dimension were sampled; however, if a parametric study is done, progressive shifts in latency and amplitude can be observed, and the components properly identified. We have found for example in our visual recovery cycle work (Lansing, Landis, and Crown; 1968) that wave components may be selectively reduced or enhanced according to the interflash interval; however, the total waveforms produced are so complex that the identification of wave components is frequently impossible, with only a few widely spaced, paired flash intervals. When the successive flash intervals are spaced more finely, the waves can be identified successfully as they emerge, disappear, or change in amplitude and latency.

I suppose the real problem in using these functional classifications (for example in clinical investigations) is the time necessary to carry out such parametric testing. A convenient means of quickly manipulating critical stimulus dimensions would be required so that you would not have to carry out a month's experimentation with each subject before you could begin testing him.

DR. CLYNES: I would like to reiterate that latency is a stable measure in distinction from the variability as found in amplitudes. That is one

of the physiologically remarkable phenomena that we encounter. There is much greater stability in latency than there is in the amplitude of the components that can be identified. I would like to show data from different individuals on this matter. Figure 3–19 shows the AEPs of different individuals elicited by the same stimulus, namely, an area of red presented after black. The visual angle is important because any one of these waveshapes appears with stimuli of a particular size. If one studies these AEPs in detail, he will note that there is enormous variability in one particular lead. However, if he studies the data from one individual, something methodical and systematic emerges, and it becomes clear that the variability that is found is only a mask for the order that really exists there.

All of the data can be shown to contain the three specified components. What is remarkable about these three components is the stability of their latency and the fact that they are in themselves rather simple. Figure 3–20 shows a similar finding; different types of com-

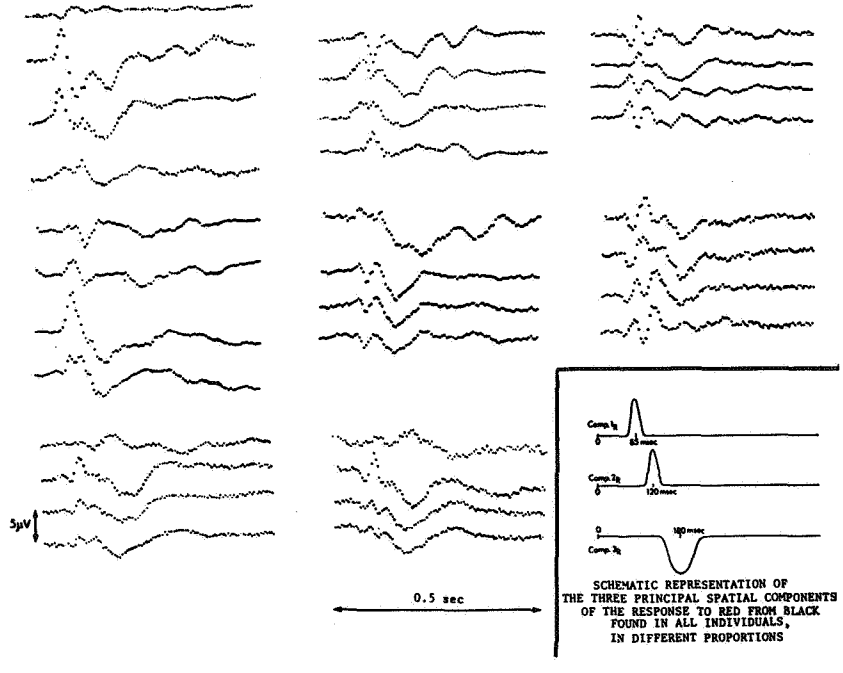

FIGURE 3–19.—Comparison of the responses of eight adult males to the same stimulus—red from previous black. Three principal components 1R, 2R, 3R, may be distinguished in each of these response groups. The relative amounts of these components are different, but their timing is similar for different individuals. Note the similarity between the two groups of responses on the right of the figure and also between the bottom two groups.

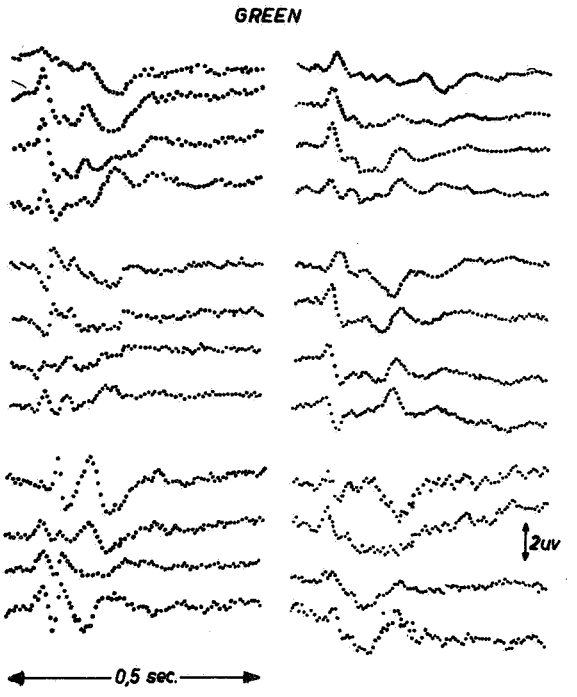

FIGURE 3–20.—Comparison of green-black responses of different individuals. Main components peak at 70, 110, 200 msec ±3 percent approximately. At least two other characteristic components of rather small amplitude are present between 70 and 150 msec.

ponents are shown to be characteristic when green is presented after black for the same area.

Table II shows the latencies for red grouped together for different individuals. They are comparatively stable across different individuals. The standard deviation across individuals is only 5.4, around a mean of 86 msec. The σ of the second component latency is 6.5 for a mean of 199 msec. For the third component, σ is 10.4 msec. Thus the standard deviations increase in proportion to the mean latency.

For a given individual, the latency stability is at least an order of magnitude greater than it is for the group. In fact it is so stable that no statistically significant latency variation can be detected by averaging 200 or even 500 responses, under similar experimental conditions, with sessions spaced up to a year, while amplitudes may vary readily as much as 30 percent.

To sum up then, there is the importance of the difference between latency and amplitude in establishing the stability of a spatiotemporal

TABLE II.—*Red-Black Components for Different Individuals*

Peak locations
(CAT address numbers, each address = 5 msec)

	Comp. 1_R	Comp. 2_R	Comp. 3_R
	16	23	34
	16	23	37
	18	26	35
	17	24	33
	16	23	39
	19	23	36
	17	24	32
	18	25	35
	19	26	39
	18	22	36
	17	25	34
	18	24	36
	16	23	37
	18	22	33
	16	22	37
	17	24	36
Mean peak time	86 msec	119 msec	178 msec
Std. dev	5.4 msec	6.5 msec	10.4 msec

Polarity relations of components for the 4 traces

Comp. 1_R[a]				Comp. 2_R				Comp. 3_R[a]			
0°	45°	90°	135°	0°	45°	90°	135°	0°	45°	90°	135°
0	+	+	+	−	0	+	+	0	−	−	−
+	+	+	0	−	−	0	+	−	−	−	0
+	+	+	0	+	+	+	0	−	−	−	−
−	0	+	+	−	0	+	+	−	−	−	0
0	+	+	+	−	−	+	+	+	−	−	−
−	0	+	+	−	0	0	+	+	−	−	−
−	0	+	+	−	0	+	+	−	−	−	0
0	+	+	+	−	−	0	+	0	−	−	−
−	+	+	+	0	+	+	+	0	−	−	−
0	+	+	+	0	+	+	+	0	−	−	−

[a] 1_R and 3_R, often null near the 0° direction, are of almost opposite polarities, while 2_R generally tends to null nearer the 90° position.

pattern. The "spontaneous" variability that one sees in different people as well as in the same person is accounted for to a considerable extent by variation in amplitude of the separate components that are mixed together in different amounts. The various uncontrolled factors giving rise to variability tend to affect the amplitude rather than the latency.

That is why I like the idea of identifying these spatially separate components on a functional basis (not on a simply empirical basis) in terms of latency rather than amplitude.

DR. GOFF: It seems to me that the discussion and comments of the opponents of possible standardization might be summarized as follows. We can all think of conditions under which standardized nomenclature or any other kind of standardization might prove a little awkward. Therefore, there is no point in trying to do it at all.

With regard to Dr. Donchin's comments about homologous components, I did not specify homologous components as those having similar distributions. We think there is a good possibility that the early auditory and somatosensory components (in my nomenclature, P2a and P3a) may be homologous components in the sense that they subserve similar functions in the processing of sensory information. The distribution is quite different, as we have shown.

The comment was made that the bipolar versus monopolar discussion was rather trivial because you can always recover one from the other. But if one is trying to make sense out of a publication, one does not have the data available to make these transformations from monopolar to bipolar, and indeed, unless the data are recorded on some kind of storage medium, such as magnetic tape, from which it can be recovered and transformed by computer, it is difficult and probably impractical for another investigator to compare records. Furthermore, bipolar records can be generated from monopolar, but not the reverse.

Of course, I would not suggest that we label components without specifying the conditions under which they were recorded. In our work on sleep (Goff et al., 1966), for instance, there are components that are not seen in the waking subject; they are only seen during the synchronized stages of sleep. Obviously we could not really label them without specifying the conditions under which they are recorded.

In sleep studies, it has been said that these late, large-amplitude components that appear during the synchronized phases of sleep are the sleeping state counterparts of the waking state vertex potential; I think this is deceptive. We have some evidence—which we are exploring further—that these waking and sleep evoked potentials may not have the same neurophysiological substrates at all. Perhaps it would be better not to label them as the same components with different latencies until we are sure that they are.

It is rather curious that the discussion was initially directed towards refuting the possibility of using the earlobe as an indifferent reference and then progressed from the earlobe to the mastoid process to the temporal area. I never said that the temporal area, or the mastoid process, was indifferent. I should perhaps have included in figure 3–2 records from the mastoid process showing that it is not indifferent. It

is near the postauricular area which Bickford has shown to give myogenic potentials. What I said was that the earlobe appears to be relatively indifferent and is the best for all three modalities. In our previous work, we used the nose, and we would continue to use the nose, except that, as I showed, it is not good for the other senses, and perhaps not ever good for the somatic response. All I said was that the earlobe appears to be the most practical, relatively indifferent electrode as a common reference for recording in all three modalities.

I agree with the majority of points ably made by Dr. Vaughan. He has done us a valuable service in proposing a formal classification of the several types of "event-related potentials." I want to clarify some apparent misunderstandings of the purpose of our paper and to discuss certain points upon which I disagree with Dr. Vaughan.

We did not mean to suggest that we thought it possible to formulate immediately a complete, comprehensive, descriptive nomenclature for AEPs. We were emphasizing the manifest need to direct our attention to the problem. Since much AEP research is done on normal, alert adults, using moderate stimulus intensities, we suggested that we start with this group. While agreeing with the need for continued careful parametric analysis of factors affecting AEP configuration, we disagree with the "wait and see" approach espoused by Drs. Donchin, Sutton, and Vaughan. We do not think that continued specification of parametric data, however precise, will by itself eventually reveal a proper descriptive system. Increased knowledge of factors producing configurational differences will not eliminate these differences; thus a nomenclature capable of coping with the differences is needed now and will be needed in the future.

We certainly did not mean to suggest component homology as a basis of evoked response classification. The classification suggested was based on similarity of appearance in components in terms of waveform and latency. We suggested that components that appear similar were candidates for homology pending further analysis. Rather than dwell on the differences in physiological organization of the somatic, auditory, and visual sensory systems, we are impressed with the similarity of the primary thalamocortical and association area activity of these modalities including single-unit organization and mechanisms such as revealed when the work of Mountcastle is compared to that of Hubel and Wiesel. Therefore, we are inclined to think that a system that permits similar descriptions of similarly appearing AEP components is preferable.

Our suggestions for standardization were not restricted to nomenclature but included electrode locations and recording conventions as well. Frankly I am tired of reading repeatedly in the literature the meaningless "escape clause" that discrepancies between the findings of

X and Y probably are caused by differences in recording techniques when these differences could be eliminated easily in many instances.

I must also disagree with Dr. Vaughan's comments regarding the use of peak-to-peak measurements, especially with respect to the vertex potential. We found differences in the base-to-peak amplitude distributions of these two phases of the potential especially in the somatic and the visual systems. Furthermore, it has been demonstrated (Wilkinson and Morlock, 1967) that the negative and positive phases of the vertex potential can vary independently with different subjective states of the subject. Thus the use of peak-to-peak measurement seems to violate Vaughan's own well-spoken admonition that AEP analysis must recognize the impact of behavioral variables on the validity of the observations.

I think there is no disagreement in our respective interpretation of vertex potentials. We have suggested previously on the basis of our data to which Dr. Vaughan refers that these late potentials are modality-specific in the sense that they depend upon the integrity of the projection to primary cortical areas.

Finally, we have data that are compatible with Dr. Vaughan's suggestion that late VER components arise from two generators. In individual subjects, we have seen a more occipital distribution for VER than for SER and AER. In two subjects, we have seen a secondary amplitude focus in the occiput. Data from our analysis of the effects of intensity on VER waveform from which figure 3–1 is adapted suggest that the appearance of one or two amplitude foci for Vaughan's P200 component (our N4b–P5a) is a function of stimulus intensity. At low intensities, such as used by Vaughan, peak-to-peak component amplitudes measured at P_z and O_z are similar. A distributional analysis at this intensity might well reveal two foci. With increasing intensity, the peak-to-peak amplitude at P_z (and by inference at C_z) increases more rapidly. Thus, at the higher intensities, such as used in our experiment, the distributional analysis indicates in most subjects a single maximum amplitude focus at the vertex.

CHAPTER 4

Very Slow Brain Potentials Relating to Expectancy: the CNV

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INTRODUCTION

SINCE THE publication by W. G. Walter and his colleagues (1964), in which the contingent negative variation (CNV) was initially reported, there has been a steady growth of interest in this phenomenon. Grey Walter's findings were confirmed and extended in several laboratories. The clinical applications of such techniques are now being explored.

Dr. Walter's group reported that the effect consists of a slow shift in the average baseline potential that is correlated with conditional expectancy and thus represents a cerebral response in the Pavlovian sense. They hypothesized that the CNV is a shift in the apical cortical dendritic potentials in the direction of depolarization that "primes" the cortex for action and that reducing the excitability threshold facilitates cortical responsivity, with the result that the efficiency of overt activity is increased (Walter, 1964b).

In this paper, I shall review studies of "steady" cortical potentials, sometimes referred to as dc shifts or very slow potential changes. This includes phenomena with a latency of 200 to 300 milliseconds and a duration of 0.5 second or more. There is no implication of a dc generator as a source of a steady potential between the surface of the brain and a neutral reference. I am dealing with activity slower than delta waves (1 to 4 Hz). Sensory evoked responses (ER) have rapid primary components with a latency of about 50 milliseconds, later secondary components with a latency of 100 to 200 milliseconds, and often "slow" components from 200 to 500 milliseconds with variable durations.

There has been interest in the study of baseline changes since the development of stable, high-input-impedance dc amplifiers. Caspers

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(1961) concluded from his investigations and those of others that the steady-potential gradient between the surface of the brain and an extracerebral reference electrode is built up in the upper cortical layers in the apical dendritic network. He hypothesized that the slow changes in potential are synchronized in large numbers of neurones. Clare and Bishop (1955) demonstrated that dendritic excitation does not conform to the "all or nothing" principle of axonal discharge. Accordingly, either direct electrical stimulation of the cortex or neuronal stimulation from ascending fibres would cause a negative dc shift at the cortex. Goldring and O'Leary (1951, 1958) have demonstrated actual shifts in the dc level of the cortex using both electrical and physiological stimuli. They have recorded long-lasting slow potential shifts during spontaneous spike discharges of epileptogenic foci (O'Leary and Goldring, 1960). Kohler et al. (1952, 1955a,b, 1957) demonstrated a slow potential shift that accompanied prolonged visual and auditory stimuli in cats, humans, and monkeys. They found the maximal negative shift at the vertex rather than near the primary sensory projection areas as they had expected. Contrary to results with animals in which they found a steady negative potential shift over the visual cortex, they found in humans a positive potential because they used an electrode at the vertex as the reference lead and the occipital position as the active lead. Since we have found the vertex to be the area of greatest negativity of the CNV and it is often the position for recording the maximum amplitude of the secondary components of ER, it is the least neutral area that could be chosen for the electrical reference.

Caspers (1961) demonstrated a slow shift in rats in the negative direction in connection with locomotion, exploratory behavior, alerting, and orienting behavior. Grooming behavior, on the other hand, was accompanied by a positive shift. He found the shift to be nonspecific to the type of stimulation and maximal in the central and frontal areas of the rat's brain. It related to increased firing of cell units in the reticular system. The steady potential shifted to positive polarity when the animal's alertness decreased in the transitional stage between waking and sleep. Arousal from sleep was accompanied by a shift in cortical activity in the negative direction.

Rowland (1961) reported slow-potential shifts in cats after a conditioning signal. It was initially positive and then shifted to negative during a 10-second application of clicks that signalled that electric shock was to follow. He measured negative shifts of 300 to 500 μV, lasting up to 30 to 70 seconds, and demonstrated the extinction of the response during nonreward trials and also a swing from negativity to positivity after several such trials. The maximal negative shift occurred in the early acquisition trials, and the positive shift in nonrein-

forced trials appeared after only a few extinction trials. He also showed that the degree of negative shift was related to drive-induced states caused by food deprivation and feeding reinforcement (Rowland and Goldstone, 1963). Somewhat similar slow potential shifts in rats caused by electrical reinforcement following conditional signals were reported by Wurtz (1966).

A potential shift in humans preceding a voluntary motor response by a half second was reported by Kornhuber and Deecke (1965). They termed that slow negative potential the "readiness potential" and found it to be bilateral, but maximal on the contralateral side to the responding limb. This was also observed by Gilden et al. (1966) who described its distribution and amplitude, attributing it to a generator in the Rolandic area corresponding to the neural area involved with the initiation and control of a voluntary movement. The readiness potential will be related to the CNV in the discussion.

DESCRIPTION OF THE CNV IN HUMANS

The original experimental paradigm that was utilized in the early work of Grey-Walter et al. and subsequently adopted in many other laboratories, involved a first, or conditional, signal (S_1) such as a click, a constant delay of 1 second or more, and then a second or imperative stimulus (S_2) such as a series of repetitive flashes to which the subject responded by pressing a button. The development of the CNV in such a paradigm is shown in figure 4–1. The baseline measure of potential is established to each of the signals when presented alone, and then when paired, no change in slow potential is seen in the interstimulus interval. With instructions to press the button, a slow wave shift of about 20 microvolts at the vertex is seen arising in the interval just after the ER to S_1 and ending with the ER after S_2. Averages of ten to twelve 4-second intervals are commonly taken to enhance the signal-to-noise ratio in order to make the electrical response clearly visible. Figure 4–2 shows the CNV in a series of single trials in a subject with a high-amplitude CNV that is seen clearly without averaging.

METHODS OF RECORDING

We have recorded the CNV in this basic paradigm in more than 100 normal individuals of college age and adults and also in about 90 children. The CNV response is present in practically all normal and cooperative adults. In the few cases of failure, we have observed that the recording equipment or the experimental procedures were faulty.

Presently we record the EEG on an Offner type TC EEG recorder with the time constant altered to either dc or 8 seconds. In working with children, however, we find it sometimes necessary to record

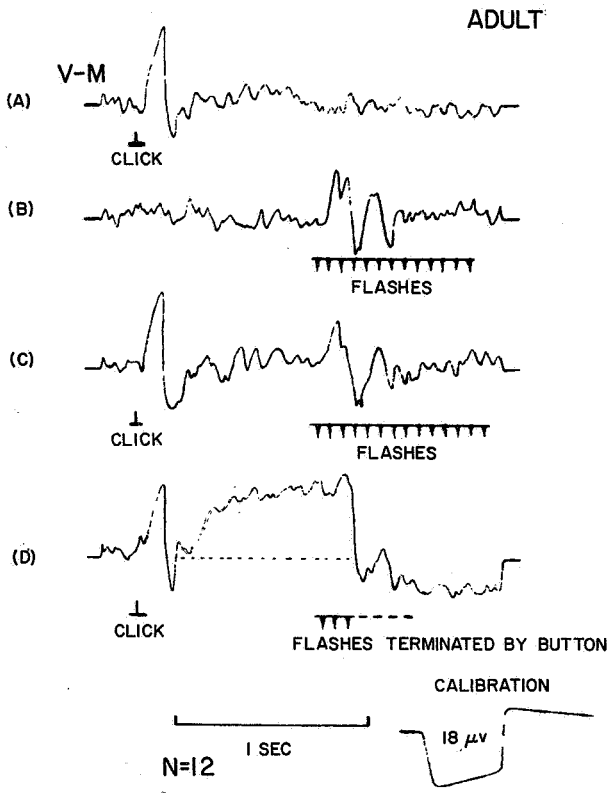

FIGURE 4–1.—Development of the CNV as a conditional response. (A) Vertex response to click alone, (B) response to series of flashes, (C) response to click followed by flashes, and (D) CNV appears as slow negative wave following the click when subject presses button to stop flashes.

with a 1-second time constant to obtain sufficient stability. Silver chloride disc electrodes are attached to the skin with collodion after the cleaning of the skin with ether and application of conducting jelly. The resistance is reduced to 3 to 4 kilohms, and the offset potential between electrodes is minimized by keeping them shorted together in saline solution when not in use.

The physiological stimulus and response data are recorded on an 8-channel P.I. Co. magnetic tape recorder; two channels of data are monitored on the CAT averager on line. After the experiment, all data channels are analyzed by the CAT and written out on a plotter from which data are measured by hand.

REVIEW OF RESEARCH ON THE CNV

After the initial discovery by Walter's group of the CNV as the electrical correlate of expectancy, related work has been done in other laboratories. Cohen and Walter (1966) found that the CNV is seen in anticipation of a pictorial presentation with no overt response on the part of the subject as well as when an operant response is required. There have been many attempts to define the psychological process as associated with the CNV. Cohen and Walter take the view that it relates to the psychological state of "expectancy" and have sometimes used the term "E Wave" as an interchangeable term for the CNV.

Irwin et al. (1966b) studied the CNV as a function of motivation and reported that the amplitude of the response is subject to attitudinal effects. Chiorini (1966) demonstrated the CNV in cats during the acquisition of a conditioned avoidance response; however, in humans, Irwin et al. believed that the motivational aspects of the response are more significant than the conditional expectancy.

Low et al. (1966a) demonstrated the CNV in humans as a conditioned response. They considered conation as the important part of the mental state relating to the response and suggested the term "conative negative variation" as more appropriate. They also reported the scalp distribution of the CNV and assessed the possible role of eye movements as its origin. Low et al. (1966b) were the first workers to record the CNV in monkeys as a conditional response in a paradigm similar to the one used with human subjects. The animals pressed a lever to terminate a shock as the second stimulus, following an auditory stimulus. Discrimination training showed a negative shift follow-

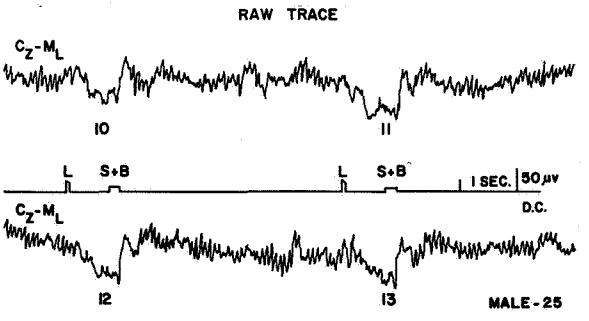

FIGURE 4–2.—CNV in original record. The vertex-to-mastoid record is negative down, showing a high-amplitude CNV and alpha blocking in response to a light flash L, followed by a sound and terminated by a button S + B.

ing punitive reinforcement trials and almost no slow response to a stimulus that was not reinforced by shock, so that no motor response was made after sufficient training. Cant and Bickford also reported the presence of CNV in a monkey in an avoidance conditioning paradigm (personal communication). Even in animals the CNV appears to be stable only during operant conditioning, when the subject is prepared to respond to the stimuli and not in cases where it must passively endure reinforcement. Cant and Bickford (1967) also observed the CNV in humans and found that its amplitude is related to changes in motivational level. Hillyard and Galambos (1967) produced similar results to the work of Walter in demonstrating the CNV as a brain conditional response. They also demonstrated a relationship between the average amplitude of the CNV and the rapidity of response in a reaction time experiment with a constant foreperiod.

The current work in this area represents elaborations of the original paradigms to include a variety of stimulus response sequences of greater complexity. Walter et al. (1967) telemetered EEG from free-ranging human subjects in order to study brain responses in a naturalistic, unrestrained setting. The CNVs recorded from four subjects by telemetry were identical to those recorded under restraint. A rubber ball thrown to the subject on the first signal produced a CNV that bore close resemblance to the trajectory of the ball. Records were made while subjects were sitting, walking, talking, riding a bicycle, and affected by distracting activities.

Walter (1967) found the CNV to be similar whether the stimuli were presented to the subject at random time intervals or whether the subject initiated the presentation of stimuli by pressing a button to start the procedures himself. When he pressed a "start" button, the action was preceded by the "readiness potential" already described, or as Walter calls it, the "intention wave." This wave merges with, and becomes the CNV before the flashes, which the subject stops either by pressing a button or producing a negative shift above a trigger threshold to stop the stimuli. In this case, the physiological response controls the stimuli rather than an overt action, termed by Walter, "autostart" and "autostop." The temporal relationships of the CNV to different delay intervals have been reported both by Walter et al. and by Irwin et al.

The temporal course of the CNV is found to have a similar pattern by all of the workers who used similar experimental paradigms. The time course of the response relates specifically to the temporal relationships of the S–R intervals. The CNV is maintained until the S_2 and its reaction. McAdam et al. (1969) found that maximal average amplitudes are significantly greater for 0.8 and 1.6 seconds than for 1.8-second intervals between stimuli. The point in time at which

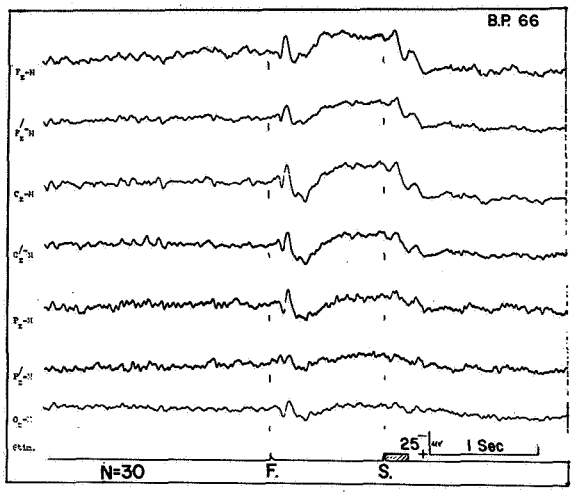

FIGURE 4–3.—A–P distribution of the CNV in a normal subject. Average of 30 trials of dc recording from six monopolar leads referred to mastoid. Positions are standard and intermediate locations from the midfrontal to the midoccipital.

maximal amplitude is reached depends on the time at which the response is to be made; if the interval is broken up into quarters, the growth of the CNV by quarters of the total interval between S_1 and S_2 is similar for the different intervals. The rise time for the shortest interval is the fastest. McAdam (1966) showed that the CNV developed during trials of time estimation and that it was maximal in amplitude during acquisition trials, decreasing during later practice trials. (See figs. 6–23 and 6–24.)

Irwin et al. (1966b) varied the amount of effort needed to press a bar for operant response. They found the CNV to be significantly larger when it was necessary to exert 14 pounds of force than 2 pounds.

DISTRIBUTION OF THE CNV

The combination of multichannel tape recorders and averagers or other specialized computers allows responses from several scalp positions to be compared simultaneously. We have recorded from all of the standard electrode positions of the 10–20 system in order to compare the CNV response from various locations. Figure 4–3 shows the anterior-posterior distribution of the CNV in an adult. Large—but consistent—individual differences can be observed.

In agreement with Walter (1964b), we found that the maximal amplitude is usually seen at the vertex lead, with a mastoid reference.

Walter thought the response to be mainly frontal and, in some subjects, to sweep back in time from the frontal pole, reaching its peak at the vertex. We were able to establish normative spatial distributions of the CNV which provide a baseline for the study of development in children and also pathological changes by recording from all of the standard positions during several sessions.

About 20 subjects were tested using bipolar combinations of leads from both standard and nonstandard electrode placements in the A–P line, as well as across the head in the standard coronal positions, M1–T3, T3–C3, C3–Cz, etc. Bipolar recording permits use of higher gain, and some of the movement and skin artifacts common to wide areas of the scalp are reduced. Measurements from bipolar leads are comparable to the unipolar data cited in the last figure. Figure 4–4 shows the distribution of the CNV in seven channels of bipolar combinations in a normal subject, with the maximal amplitude of the CNV at the vertex. The amplitude peaks a bit earlier in the frontal leads, indicating that it is not always a standing wave but that it may move from the front to the center of the head confirming Walter's observation. The maximal posterior gradient usually is seen between the vertex and the Pz position, and the maximal anterior gradient lies between the frontal and frontal pole position.

We have tried many reference positions and found none that was sufficiently neutral to be more stable for slow components than the mastoid leads. Most of our left and right comparisons were made to the linked mastoids to provide a common lead for both sides since one mastoid may be more active than the other. On many runs we have used a mastoid lead linked to a lead just over the middle of the brow of one eye through a potentiometer, so that we could compensate for eye movements in the vertical direction as was suggested by Walter. The resistance between the two reference leads is adjusted so that the contribution of voltage induced by an eye blink is sufficient to cancel the blink artifact at the vertex electrode. This also partially reduces the blink artifact to the frontal leads. One argument for continuing to use the mastoid reference is that the data from many laboratories will continue to be comparable.

We have found the average maximal amplitude of the CNV at the vertex in 60 young adults to be 21.4 microvolts with a standard deviation of 4 microvolts. This is in close agreement with Walter (1964b) and with Low and his colleagues (1966a). CNV below 5 microvolts is very difficult to detect with our averaging methods against the background activity; a CNV of 35 microvolts is the largest value measured in my laboratory. The amplitude seems to be fairly stable if the same situation is repeated. Subjects who were retested during two sessions separated by 2 to 8 days had a product moment correlation of 0.8

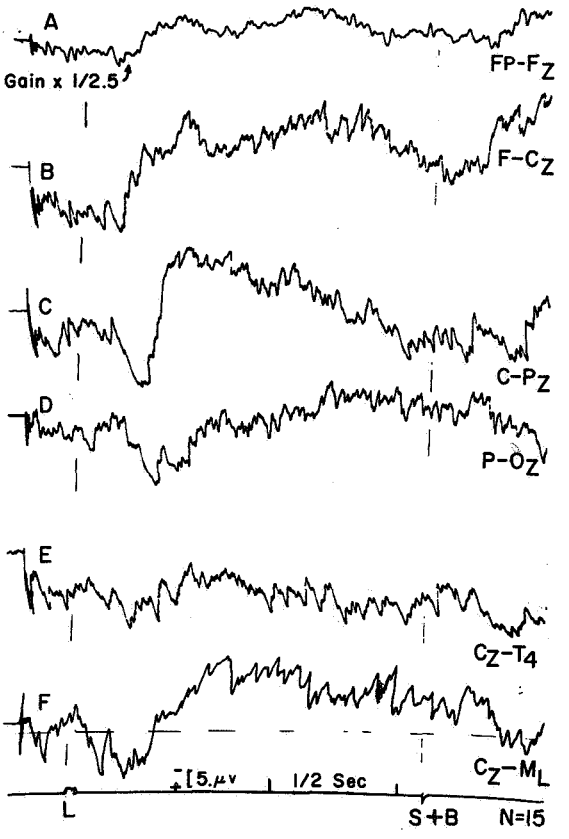

FIGURE 4–4.—Bipolar recording of CNV. The first four traces are a standard midline bipolar run. The trace E is vertex to a midtemporal lead, and F is a vertex-to-mastoid lead, indicating the shape of the CNV.

between average maximum vertex CNV on the test and retest trials (N=34).

The amplitude of the CNV is reduced in the frontal positions, more so in the parietal positions, and is minimal in the occipital and posterior temporal positions. It is quite small also in the frontal pole positions, which is evidence against its generation by the electrical field of the eyes, or even its being primarily a frontal lobe phenomenon. The CNV is reduced fairly symmetrically as the transverse distance from the vertex is increased, reaching a maximal gradient between the mid-Rolandic and midtemporal positions. There is still a considerable CNV in the midtemporal positions, but using the mastoid references probably minimizes its amplitude because of the small separation of

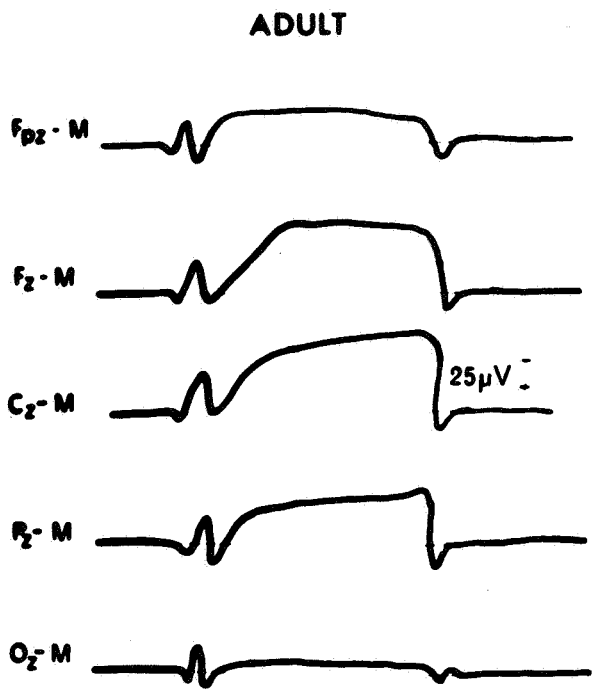

FIGURE 4–5.—Typical A–P distributions of the CNV in average adults.

the active and reference leads. The amplitude in the anterior temporal positions is quite minimal but greater than in the posterior temporal leads. Figure 4–5 shows the amplitude at the various standard lead positions (see Table I).

Low et al. (1966a) presented data comparable to ours in 30 subjects in a similar S–R paradigm. They observed an earlier maximal amplitude in frontal regions and a later maximal amplitude in posterior regions. They also confirmed Walter's and Cohen's observations that the modality or intensity of the stimulus has no significant effect on the CNV. The decrease of CNV amplitude with distance from the midline is comparable to our findings. The distribution in the A–P longitudinal plane is not in complete agreement although the average amplitude at the vertex is the same. Their study shows an almost linear reduction in amplitude from about 23 microvolts in the frontal pole position to about 19 microvolts in the occipital-parietal position, while we obtained an average maximum of about 12 microvolts in the frontal pole position and 9 microvolts in the midoccipital position.

TABLE I.—*Spatial Distribution of Maximal Amplitudes of the CNV**

	FP_1	FP_z	FP_2	
	11. 3	12. 1	11. 9	
F_7	F_3	F_z	F_4	F_8
12. 3	16. 3	18. 7	15. 5	12. 9
T_3	C_3	C_z	C_4	T_4
14. 2	17. 7	21. 4	18. 3	14. 8
T_5	P_3	P_z	P_4	T_6
7. 4	12. 2	16. 6	13. 7	8. 3
	O_1	O_z	O_2	
	8. 1	9. 3	7. 6	

*Entries are the means of average maximal amplitudes of the CNV in microvolts in 60 adult subjects. Standard deviations ranged from 2.4 to 3.8 at different positions.

FORMATION AND MORPHOLOGY OF THE CNV

The form of the CNV is characteristic of both the individual subject and the experimental parameters as shown in figure 4–6. About 40 percent of the adults tested produced a ramp-shaped CNV as in (A), and about 33 percent produced a rectangular CNV as in (B). The other 27 percent were divided among the mixed or atypical shapes remaining. In some individuals, the CNV remained for a short time after the imperative signal, or it dropped for about 0.1 second and then resumed a marked negativity, returning only gradually to a baseline within 1 or 2 seconds. This is an identifiable effect that has been called "rebound" by Dongier's group in Belgium (Bostem et al., 1967).

When a novel stimulus is first presented, there is in addition to the sensory evoked response an indication of the alerting or orienting response. The alpha rhythm is blocked; there may be a decrease in skin resistance or change in skin potential, and a slow negative potential shift lasting 300 to 500 milliseconds and about 10 to 15 microvolts at the vertex often occurs. This is best seen with stable electrodes in a small number of trials in the average. This response becomes habituated rapidly unless the stimulus is given significance by its association with a response; in this case, it blends with the "intention" wave, which then remains as long as the person voluntarily responds.

If the first stimulus is a click and the click is followed by an imperative stimulus such as flashes, the slow negative potential blends into the early part of the CNV by rapidly lengthening in duration and increasing in amplitude. At that stage, it is impossible to separate the brain response of orienting and conditional expectancy since psychological expectancy is a consequence of novelty. The CNV is acquired fairly rapidly as a conditional response. Figure 4–7 shows the percentage of subjects reaching their maximal CNV amplitude as a function of

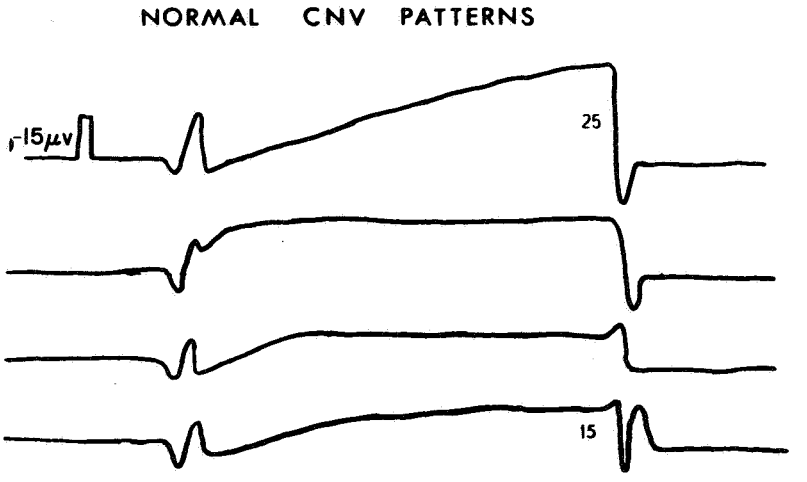

FIGURE 4–6.—Typical patterns of the CNV in normal subjects. A calibration pulse is shown on the top trace, and the CNV is shown between the evoked responses to the first and second stimuli. The numbers represent the usual range of amplitudes.

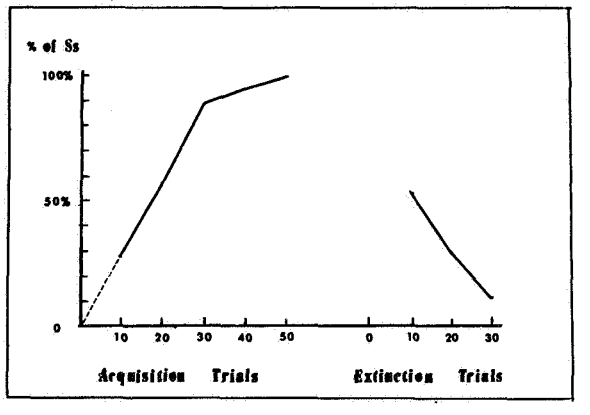

FIGURE 4–7.—Mean CNV during acquisition and extinction trials.

number of trials when the subject pushed a button to terminate a tone (S_2) as quickly as possible after the onset of the tone. First, 25 trials of tone alone—without a conditional signal—were presented in order to establish the baseline of reaction time, and then the conditional signal of a single light flash was introduced 1 second before the tone. With anticipation of the response, the average reaction time

shortened from 360 milliseconds to 190 milliseconds in the last set of trials. Over one-half of the subjects reached their maximal CNV within the second set of ten conditional trials. The CNV stayed near its maximal level indefinitely as long as the experimental conditions remained constant. Several hundred trials were presented to two subjects at single sessions lasting over 3 hours with no appreciable change in CNV amplitude as their motivation and responsivity continued at a satisfactory level.

RELATION OF THE CNV TO OTHER BRAIN POTENTIALS

The maximal amplitude of the ER to light flashes and sounds was measured for each subject from repeated presentations of the stimuli alone at 4-second intervals and from presentations during CNV trials. There is a tendency for subjects with large ER also to have large CNVs; however, many subjects with low-amplitude ER also have high-amplitude CNV. Several examples of the various types of relationships are shown in figure 4–8. The maximal average amplitudes of the ER derived from the vertex to mastoid are compared with CNV amplitudes from the same derivation. The peak-to-peak deflection of the

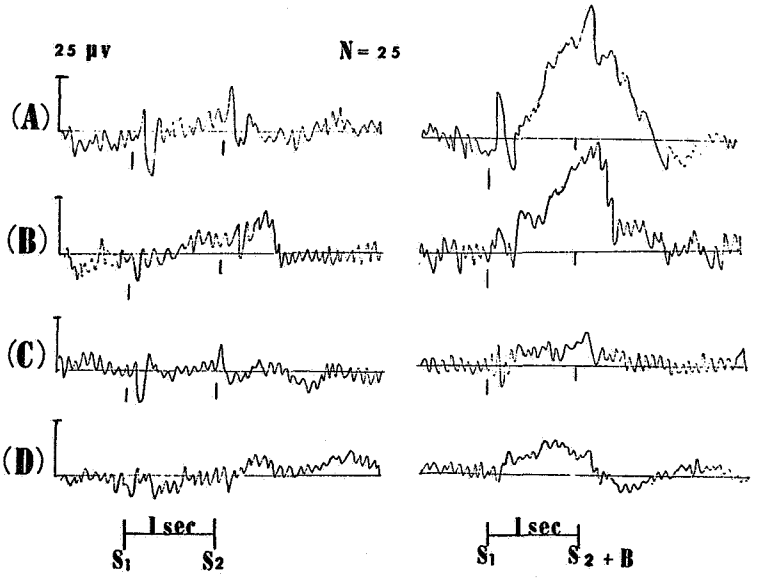

FIGURE 4–8.—Comparison of evoked response and CNV amplitudes. The left-hand traces show averaged records when the subject makes no response to S_2, and the right-hand traces show the CNV when the subject pushes a button to end the S_2. (A) shows a subject with high-amplitude ER and CNV, (B) a subject with small ER, but a large CNV, (C) a subject with large ER and a small CNV, and (D) a subject with both small ER and CNV.

highest negative to the highest positive potential of the ER components within about 300 milliseconds of the stimulus is taken as the maximal amplitude.

The ER amplitude to light flash varied from 6 to 19 microvolts with an average of 12.4 microvolts and a standard deviation of 2.6 during trials when the flash had conditional signal value. During flash presentations alone, the mean amplitude of the AEP was 10.7 microvolts with a standard deviation of 2.4 microvolts. The hypothesis that the mean amplitudes under the two conditions are not different was rejected, using a t test at the .05 level of significance. The increase of the ER with significance of the signal agrees with the finding of Sutton et al. (1965a) in which the amplitude of an ER is increased as stimulus uncertainty is increased and the subject guesses what stimulus is going to occur.

The product-moment correlation of the mean amplitudes of CNV and ER to flash as a conditional signal for 60 subjects is 0.43, significant at the 1-percent level. The greatest response to flash did not always occur at the vertex lead, and the correlation might have been higher if more posterior leads had been considered; however, a uniform lead position seems advantageous.

The ER to S_2 is usually obscured by the CNV, and no accurate measurements of amplitude may be made. Often the negative peak extends beyond the CNV, but it is not quantifiable since the neutral baseline is not known. We did not present a sound stimulus as a first stimulus to a sufficient number of subjects to make a meaningful correlation of its amplitude. Observation so far, however, indicates that results are similar to the flash response. The amplitude seems a little larger when the signal is given conditional significance, and it bears some relationship to the amplitude of the CNV.

The latency of the CNV is difficult to measure since it develops out of the complex secondary ER to the S_1. It seems on the average to begin within 200 to 400 milliseconds after the onset of the S_1 and to reach its peak within 400 to 900 milliseconds after the S_1 when the interstimulus interval is 1 second. The latency and delay time to peak value are of course related to the characteristic shape of an individual's CNV with the "rectangular" shape leading to shorter latencies and a rapid rise to the peak amplitude.

Visual inspection suggests that the average latency for a 1-second interval is 260 milliseconds and 295 milliseconds when the subject is conditioned to expect a 2-second delay. The difference in time to reach peak amplitude is more marked. It took an average of 820 milliseconds to reach the peak with a 1-second delay and an average of 1530 milliseconds to reach peak amplitude with a 2-second delay, a significant difference at much below the 1-percent confidence level.

The motor potential—or the intention wave as called by Walter (1967)—mentioned earlier is thought by some to bear a relationship to the CNV. We have not yet looked systematically at that variable; however, in a few subjects tested, there seems to be no strong relationship. It has a more restricted distribution, is much smaller in amplitude, and is found by Vaughan et al. (1968) to be bilaterally asymmetrical. The strongest evidence against it as a possible basis for the CNV is that no overt motor response is necessary to elicit a CNV; CNV to a variety of S–R acts are quite similar indeed, even when the response is subjective or ideational. At first, Walter thought the CNV to be a cortical priming response preparatory to making a voluntary action, but he now conceives the CNV as related to the psychological state of expectancy (Walter, 1965b). It can be elicited by the expectancy of almost any discrete event in time that bears significance for the subject. It is convenient for research purposes to endow significance by asking the subject to press a key when a stimulus occurs. If the key press becomes a passive act, the CNV amplitude is reduced. If the act is given operant significance by controlling something in the situation, then the CNV is maintained at a high level.

Figure 4–9 shows what can happen when a motor response loses its

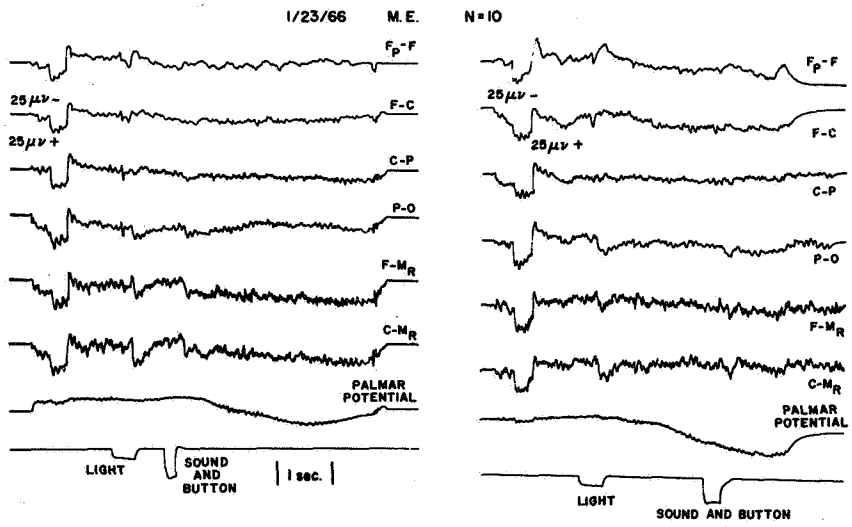

FIGURE 4–9.—Drop in CNV with change in stimulus-response conditions. Top five traces are a midline bipolar run and a frontal monopolar run. The sixth trace is vertex-to-mastoid, the next is average palm potential, and the last line is the stimulus program. The left-hand traces show a fully developed CNV, and the right-hand traces show the flattening of the CNV with increasing the interval and removing the function of pressing the button.

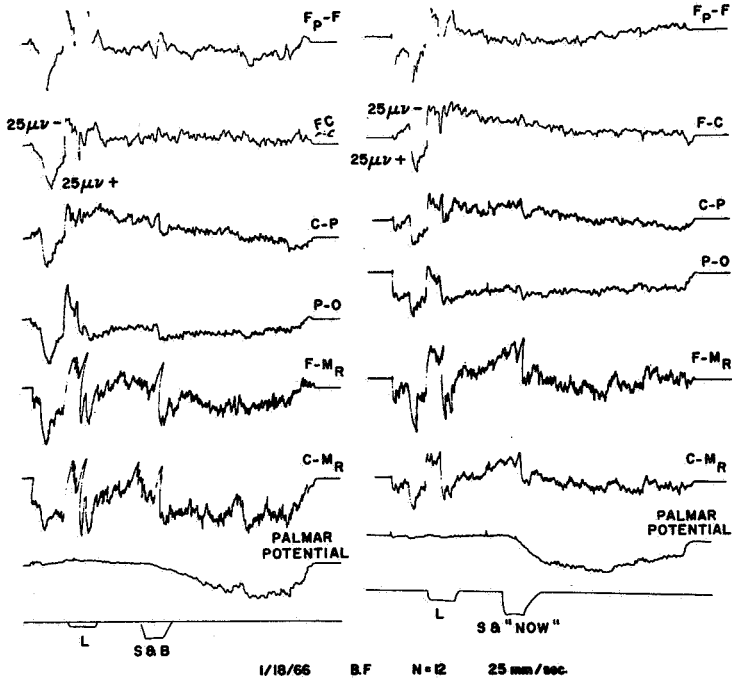

FIGURE 4–10.—The CNV terminated by a thought. The left side traces show the CNV and palm potential response in the conventional situation of flash, sound, and button. The right side traces show the CNV response in the same subject to the instruction, "Think 'Now' at the time that you would press the button, but make no movement." There is very little difference either in the CNV or the skin potential response between the two situations.

operant value. We routinely ran an experimental extinction series by presenting S_1 alone after the subject was well trained. The CNV extinguishes as the subject perceives that he no longer has any task. When the S_2 is restored, the CNV returns to its former value as the subject again expects to press the button and stop the sound. In this case, by accident, the push-button jack was loose, and the subject could not terminate the sound with the push button; although he continued to press the button to the sound, it accomplished nothing. He was no longer motivated, and the CNV remained at a minimal level.

An ideational response alone is sufficient to produce a CNV in a well-trained subject, so that instead of pressing the button to S_2, the subject is instructed to just think "Now" at the time that he normally would press the button. An electromyograph revealed no movement of his hand during the CNV response seen in figure 4–10.

The CNV also is present in a situation in which subjects expect a projected picture as the S_2; the CNV is similar whether or not he is to make an overt response (Cohen and Walter, 1966). Actually, although the CNV is a fairly generalized response, the distribution over the head is often slightly more posterior when a picture is presented than when the subject makes a motor response, as shown in figure 4–11.

The CNV is elicited when the subject responds with a word to S_2 which he freely associates to a word presented as S_1. It does not matter whether he says the word aloud or merely "thinks" the word to himself as an ideational response (fig. 4–12). In this case, the subject has a higher amplitude CNV to a verbal series than the motor reaction series of trials. This probably reflects his value system since the subject is a professional writer and is more interested in words than fast hand reactions.

SUMMARY CONSIDERATIONS

The CNV develops in human subjects as the electrical response of the brain to a conditional signal that an operant response is to be made after a delay. As illustrated, a wide variety of S–R paradigms result in the CNV in human beings even when verbal or ideational responses are made instead of overt motor acts.

The CNV varies in amplitude, shape, latency, consistency, and distribution over the head in different subjects. The experimental parameters of the stimuli may vary in relation to temporal sequences, sensory modality, prior number of trials, instructions to the subject, and in countless other ways. The electrophysiological response is related to psychological events or states of mind identified as expectancy, decision (Walter, 1964b), motivation (Irwin et al., 1966b; Cant and Bickford, 1967), volition (McAdam et al., 1966), preparatory set or conation (Low et al., 1966a), and arousal or the physiological state of excitability (McAdam, 1969).

The evidence that eye movements do not account for the CNV is conclusive. The CNV is similar when recorded from surface or intracranial electrodes (Walter et al., 1964), it has a different spatial distribution than the eye field, and it has been reported in a subject with glass eyes when no electroocular field (Low et al., 1966a) was present. Data from a subject who moved his eyes in opposite directions as an overt response and careful recording of eye position during the production of the CNV also confirm this opinion, as seen in figure 4–13. However, the fact that eye movements can simulate the CNV makes it imperative to monitor them for both experimental and clinical work.

We should consider another possible internal brain source for the CNV, that is, the generator for the motor potential (MP) described by Gilden et al. (1966), who report the maximal negativity of up to

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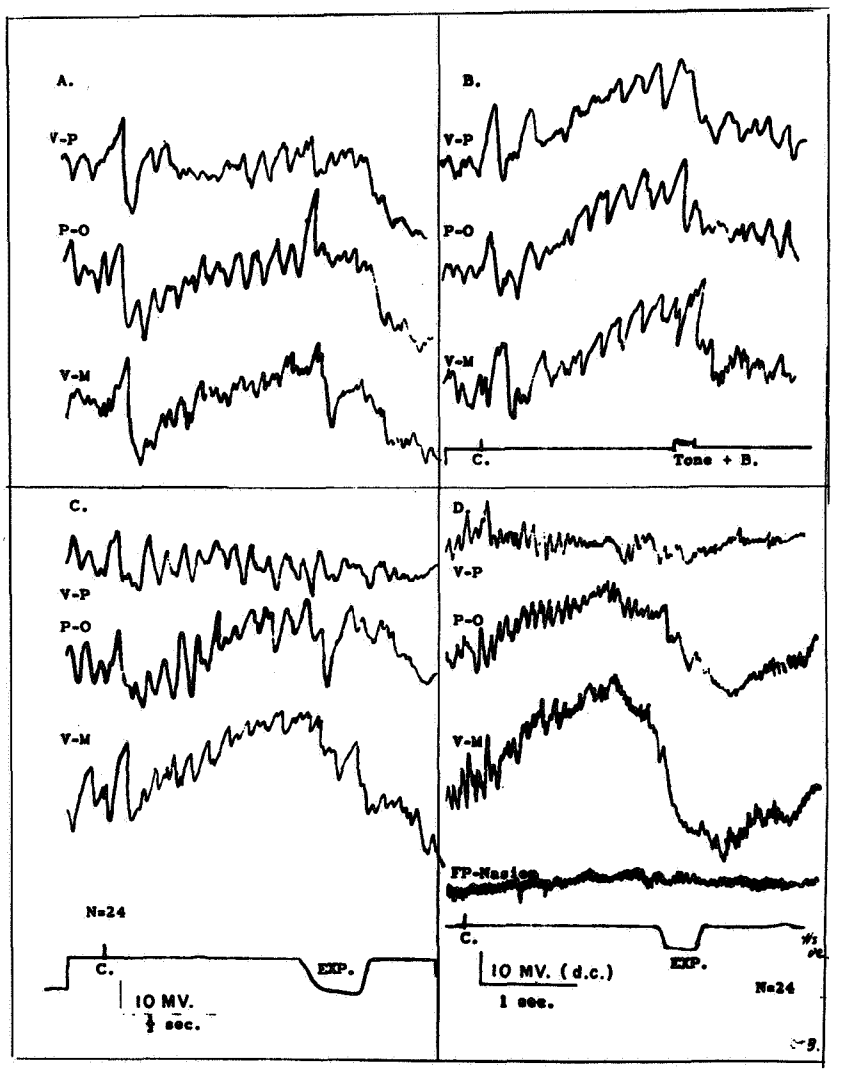

FIGURE 4–11.—Comparison of the CNV in anticipation of making a motor response and of seeing a picture; (A) and (C) are two sets of averages showing that maximal gradient of the CNV is posterior between the P and O leads when a picture is expected; (B) shows that the gradient is more anterior when the subject expects to make a motor response (same subject); (D) shows the result when the subject must press a button to make the picture appear, indicating a larger CNV than either alone. The last trace shows the stability of the leads around the eye.

25 microvolts beginning from 0.5 to as much as 2 seconds before a voluntary movement. The most compelling argument against the CNV being nothing but "motor potential" is the finding that CNVs are recorded in situations that do not involve movement such as

anticipation of meaningful visual or auditory presentations as shown in the previous figures. It is conceivable that the MP is a special instance of a CNV, with the S_1 and S_2 both being internalized, the hand movement being the response that operates to satisfy the induced set of the subject. The internalized realization that it is "now time to press the button" or make another instructed response is S_1; the initiation of the voluntary action that has been delayed until the "proper" time is analogous to S_2 in the S–R paradigm of the CNV. The electrophysiological event mediating the time between the origin of the wish and the consummation of the act is a slow negative shift, and the

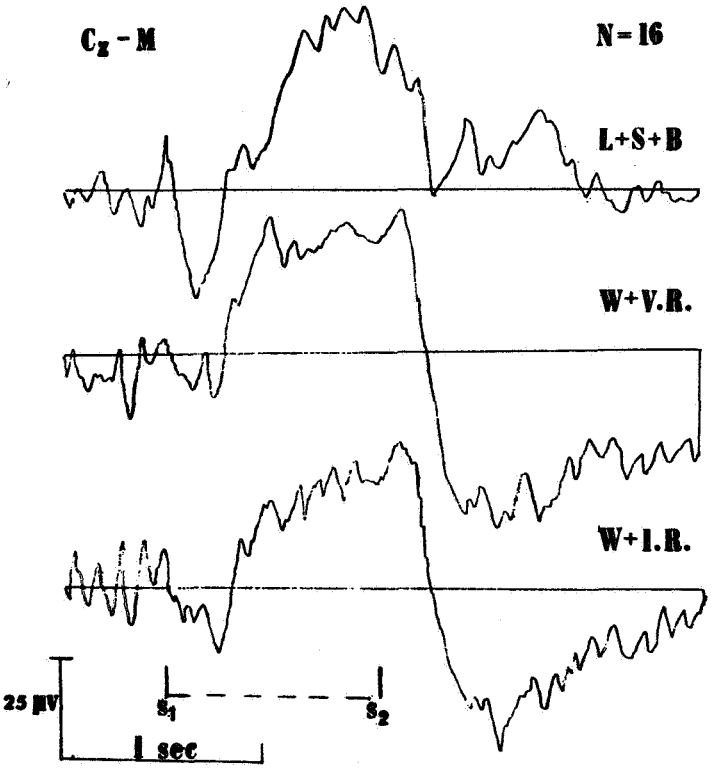

FIGURE 4–12.—The CNV to verbal stimuli.

A. The average of 16 trials recorded at the mastoid to the usual light, sound, and button trials.

B. Same subject when a word is called to the subject as S_1 and he responds aloud with an associated word as S_2.

C. Same situation, but subject merely thinks a word to the sound of S_2, making a subjective or ideational response.

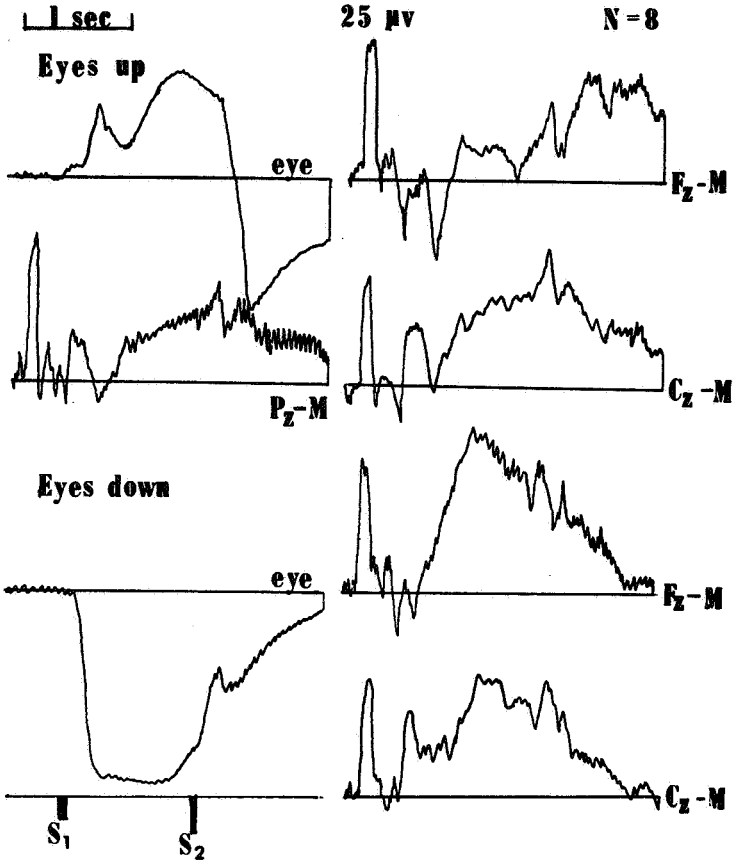

FIGURE 4–13.—Independence of the CNV from eye movement artifacts. The subject makes a voluntary eye movement response to a visual stimulus as S_1 and returns the eyes to the original position at S_2 (recorded at the Burden Inst., Bristol, England).

psychological correlate may well be expectancy or, in other terms, preparatory set.

Walter's original hypothesis that the CNV relates to efficiency of action such as shortening of reaction time because of "cortical priming" is confirmed by the other investigations. McAdam (1969) found that late components of somatosensory AEP between 200 to 400 milliseconds are shorter when the stimulus is presented during the CNV trials compared to presentation during the resting state. Other measures of levels of arousal are consistent with the hypothesis that the CNV is present, representing heightened arousal or alertness, but no change is seen in the early components of the ER.

The work on one very slow potential wave—the CNV—has been reviewed here. We are continuing our work toward understanding the physiological origins and the psychological significance of the CNV as well as exploring its clinical utility (Walter, 1966). We are now exploring a variety of psychiatric and neurological disorders and developmental problems in children. We still conceive of the CNV as the electrical correlate of psychological expectancy and prefer the generality of the term "contingent" since there is such a variety of contingencies which it can represent.

DISCUSSION

DR. LOW: The CNV certainly is contingent upon something. The question is, upon what? Is it always contingent upon the same thing? If and when these questions are answered, we may find some reliable clinical or diagnostic application for CNV studies.

Since this is supposed to be a workshop session to consider problems involved in conducting and interpreting experiments related to the study of AEP, I would like to begin this discussion of Dr. Cohen's review by emphasizing the most serious methodological problem in CNV experiments. It is obvious that eye movements can introduce a very significant contaminant into recordings of slow activity at the scalp or from the brain surface. These movements must be accounted for in any CNV experiment. In humans, this may be done in several ways. One method, described by McCallum and Walter (1968), consists of "balancing out" eye movement between the active electrode and the reference. Another simple method—and the method we prefer with cooperative subjects—is to make all recordings with the subject visually fixating a target.

In animal work, accounting for and eliminating eye movement is not so simple. We have solved the problem in two ways. The obvious method is to enucleate the eyes of the animal, as first suggested by Chiorini (1966); however, this is not always practical or desirable. Another method uses a subcortical reference electrode. This works well if both the surface and the reference electrodes are away from the anterior frontal regions, and this point will be discussed in more detail later.

The most extensive work quantifying the relationship between eye movement and the CNV in man was done by Hillyard (1968). He partitioned the CNV into two components, the Eye Artifact Potential (EAP) and the true CNV (tCNV). In experiments performed with the subject's eyes closed, the mean contribution of eye movement artifact to the total negative shift at the vertex was 23 percent over all subjects. Significantly, the EAP introduced as much variability into the vertex potential as did the tCNV. He concluded that changes re-

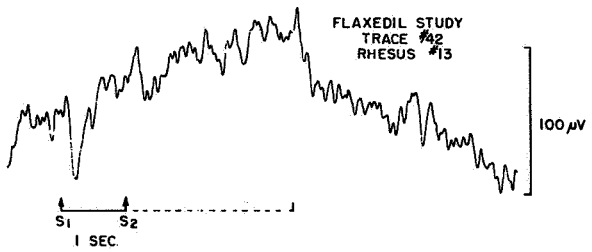

FIGURE 4.–14.—CNV recorded from a chemically paralyzed monkey. Trace is an average of 48 trials, recorded with the active electrode on frontal cortex referred to a reference in occipital bone (negative up).

ported in the CNV by other workers without controls for eye movement effects may have been determined by ocular rather than brain potentials. His data are in general agreement with those of Low (1966).

If ocular movements are excluded as the source of the CNV by proper experimental procedure, then what is the source of this potential? Our major research effort in Houston was directed towards attempting to answer this question, and I will show some of the results of this work.

A CNV-like potential may be recorded from Rhesus monkeys using a variety of stimulus-response conditioning paradigms. The simplest paradigm—and the one most closely resembling the S_1–S_2–R situation in human studies—is escape-conditioning with a warning cue. Using such a paradigm, we have recorded CNV from monkeys with and without eyes; with and without chemically induced paralysis; with cortical surface electrodes; with bone, cortical, and subcortical reference electrodes; and with intracortical, extracellular microelectrodes.

Figure 4–14 is a sample CNV recorded from a monkey that was completely paralyzed by Flaxedil. The animal had been trained using a variation of our usual S_1–S_2–R paradigm. The S_1 was a loud click, and S_2 was a 1000-Hz tone lasting 2.5 seconds, with a shock, across the feet occurring at the end of S_2. The tone could be terminated, and the shock avoided if a lever was pressed during S_2. Lever presses in the S_1–S_2 interval were punished by shock. After training to criterion, i.e., 90 percent correct trials, this animal was paralyzed and intubated, maintained with a respirator, and given a series of S_1–S_2 trials. The illustration is an "average" of 48 trials recorded from frontal cortex and referred to an occipital bone reference. The form of this potential is very similar to CNV recorded in humans without the sharp cutoff at S_2, possibly because the animal was not able to make the required response.

Figure 4–15 illustrates similar shifts recorded with an identical paradigm from a different animal. This monkey's eyes were surgically removed 8 days before this experiment. Each of the three traces is an "average" of 40 trials and is a result of cortical-cortical simultaneous multichannel recording. Frontal cortex to parietal cortex leads show a marked anterior-dominant negative shift in the S_1–S_2 interval and beyond. When the recording is from frontal cortex to sensory-motor cortex, the more anterior electrode is still recording the greater negativity. Sensory-motor cortex to parietal cortex leads show relatively little potential difference between the two, with only a small, late rise of the baseline in the S_1–S_2 interval.

Figure 4–16 illustrates the positions of the electrodes in this animal.

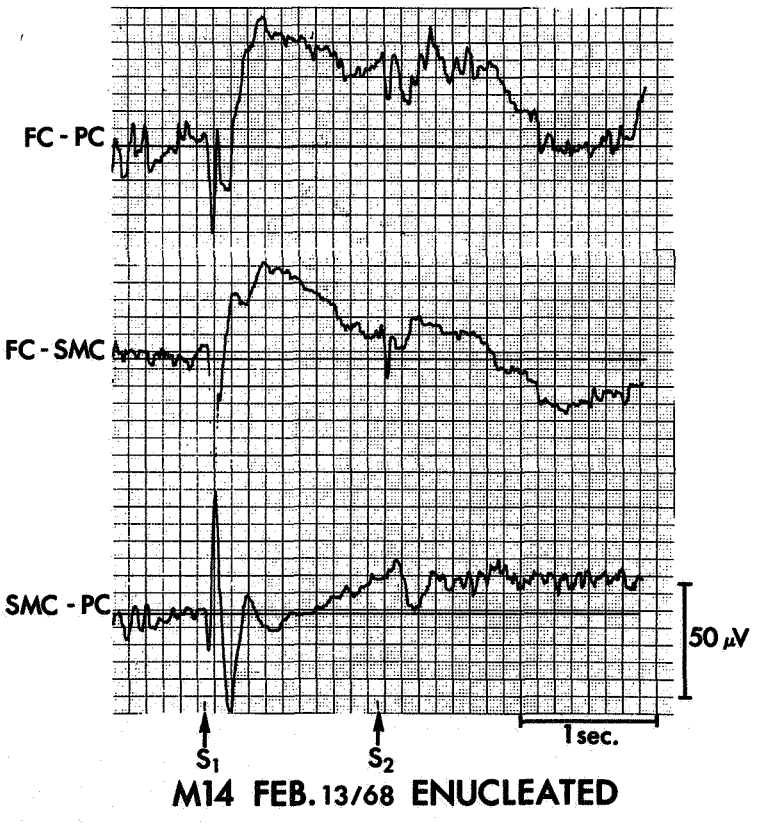

FIGURE 4–15.—CNV recorded from an enucleated animal. Cortical-cortical recording. Each trace is an average of 40 trials, and the epochs are simultaneous (negative up). FC=frontal cortical, SMC=sensory-motor cortical, and PC=parietal cortical.

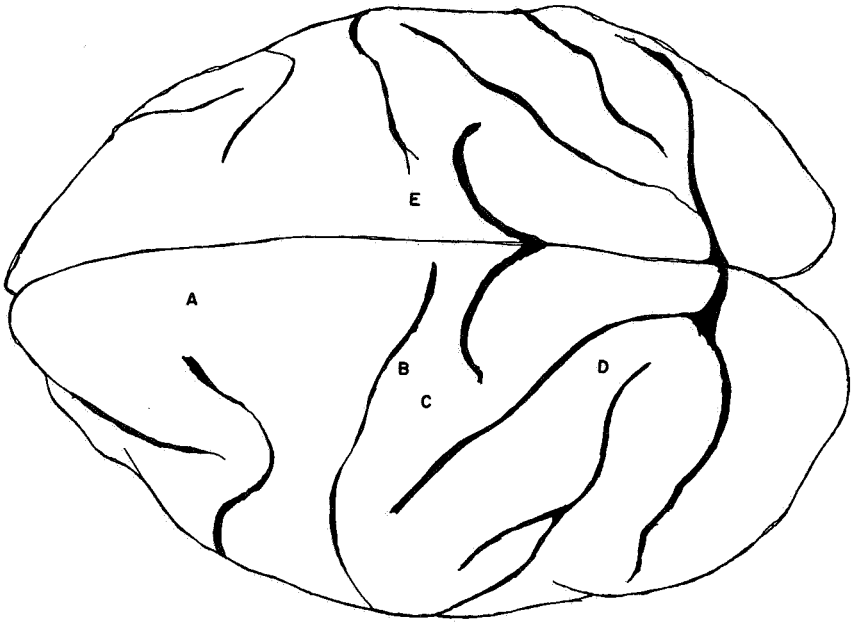

FIGURE 4–16.—Electrode positions for Figure 4–15 and Figure 4–17. A=frontal cortex, B=sensory-motor cortex, C=subcortical reference, D=parietal cortex, and E=subcortical reference.

The frontal surface electrode (A) is well anterior to the motor region. The sensory-motor electrode (B) is near the motor-arm area, not as close as we intended, but certainly closer to it than electrode (A). Electrode (D) is on posterior parietal cortex. Marks (C) and (E) indicate the insertion points of subcortical reference electrodes. For technical reasons, electrode (C) could not be used, and the subcortical reference for the following illustration was in the opposite hemisphere to the surface electrodes, a circumstance that introduced no significant variation as compared to similar recordings using an ipsilateral subcortical reference in another animal.

Figure 4–17 shows three traces, each an average of 40 trials using the same "enucleated" animal. The first trace is from the frontal cortex, the second from sensory-motor cortex, and the third is from parietal cortex, each referred to the same subcortical reference. There is an obvious early rise of the negative shift in the anterior region, with a later, slightly delayed peaking in the sensory-motor and parietal regions.

Using this same technique in the same animal before enucleation produced very similar findings except that the negative shift in the anterior lead was greater before than after the eyes were removed.

There were no significant differences noted in amplitude measurements of the CNV at the sensory-motor area referred to the subcortical reference when comparing pre-enucleation and postenucleation records.

Other recordings from three other monkeys produced similar results, i.e., a potential shift between S_1 and S_2, which was negative at the surface of the cortex with respect to subcortical reference. While this particular observation may be modified with more careful measurement, there were no apparent differences noted whether the reference

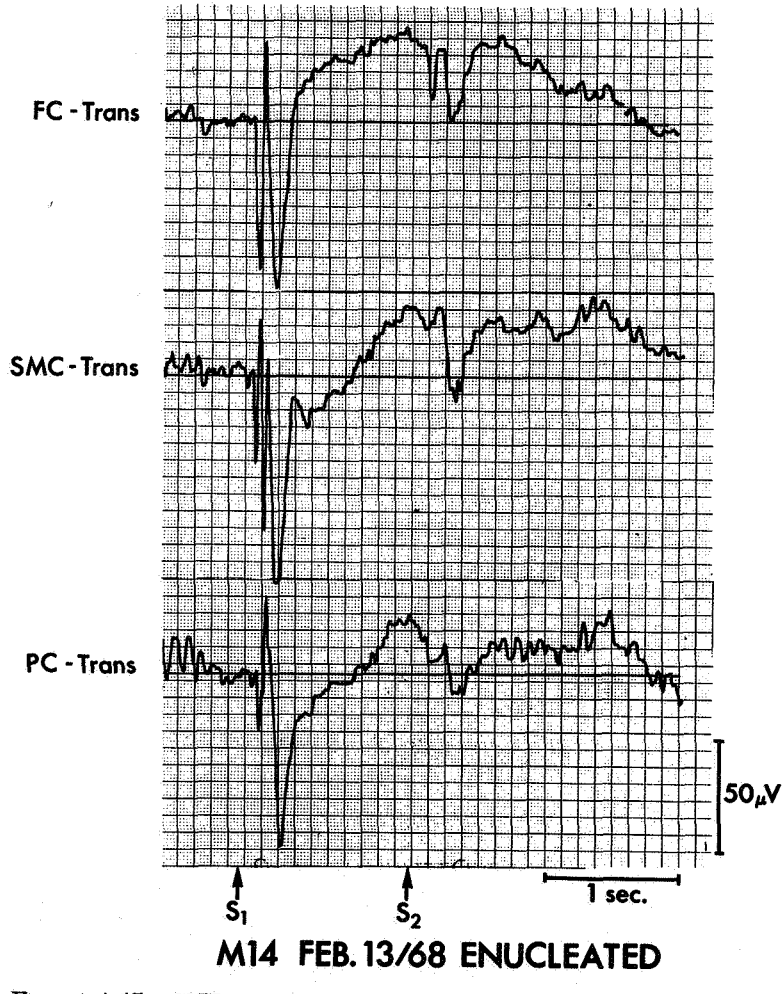

FIGURE 4–17.—CNV recorded from an enucleated animal. Cortical-subcortical recording. Each trace is an average of 40 trials, and the epochs are simultaneous (negative up). FC=frontal cortical, SMC=sensory-motor cortical, PC=parietal cortical, and Trans=subcortical.

was 3, 7, 10, or 15 mm deep, as long as the contact was in white matter. In every animal, the anterior cortex became negative first, with reference to more posterior cortex, with a later increase in negativity of posterior areas.

Whether this potential in Rhesus monkeys is the same thing as the CNV in man is a moot point. It looks very similar to the human CNV; it appears in apparently analogous situations; its distribution is similar, and we have considered it to be that which serves as the CNV for monkeys.

Regarding another point, i.e., the relationship of the CNV to arousal and/or alertness in man, we have acquired some clarifying data. By varying the intensity of S_2 around threshold, it was demonstrated (Low et al., 1967) that CNV magnitude is correlated positively and CNV variability is correlated negatively with level of attentiveness in man. The question then arose concerning whether this increased CNV magnitude is simply a reflection of generalized arousal.

Another experiment was done with nine volunteer subjects, using essentially the same procedure; i.e., the subject's threshold for clicks was determined using the Bekesy trace method. Then a series of flash-click pairs was given with the intensity of S_2 systematically varied around threshold. Twenty flash-click pairs were given at each arbitrarily chosen intensity level of S_2, and the trials were averaged in blocks of ten, giving two CNV measurements for each level. A figure called percent variance of CNV magnitude was calculated as σ/μ where σ was the difference between the two CNV measurements at any given level multiplied by $1\sqrt{2}$ (analogous to the standard deviation), and μ was the mean value of the two measurements at the same level. The CNV measurements included peak amplitude and area.

Correlations were then made between these measurements and several variables, including attenuation of S_2 in decibels. Figure 4–18 shows the relationship for all nine subjects of percent variance of CNV area to S_2 intensity. The variance is markedly lower when S_2 is at threshold than at other intensities, and the differences between the variances at T and at T+3 dB, and T and T—10 dB are significant at the 0.05 level. Pearson product-moment correlation coefficients were then calculated for S_2 intensity against CNV area, CNV amplitude (peak), reaction time, heart rate, respiration rate, and GSR reactivity. Table II shows these coefficients of correlation. There are three significant correlations, i.e., a strong negative correlation between S_2 intensity and CNV area, and positive correlations between S_2 intensity and respiration rate and S_2 intensity and GSR reactivity.

These data were interpreted as indicating that the mechanisms responsible for the increased magnitude of the CNV with increased

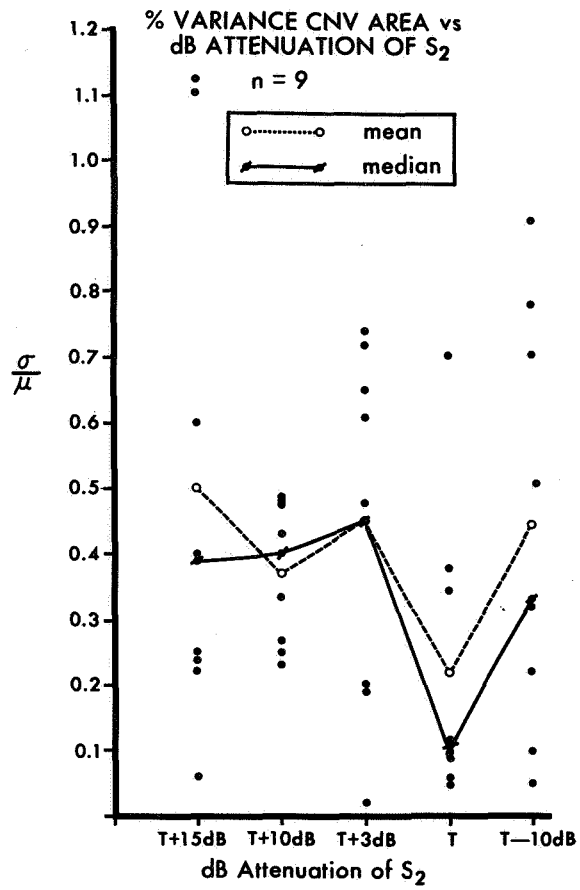

FIGURE 4–18.—Percentage value σ/μ of CNV area vs dB attenuation of S_2. See text for explanation of σ/μ. Nine subjects, 20 trials at each intensity level for each subject.

attentiveness are not necessarily part of a global, physiological arousal response.

The method of measuring the CNV is a matter of concern. It is evident that a single-point amplitude measurement, whether it is peak amplitude or amplitude at a given time after the warning signal, or before the command signal, is not alone a sufficient descriptor of the CNV. The shape of the CNV varies markedly, depending in part upon the length of the interstimulus interval (McAdam et al., 1969), and yet it is difficult to accommodate multiple measurements such as rise time, amplitudes at different points along the CNV, duration, etc.

TABLE II.—*Correlation Between S_2 Intensity and Other Variables*

Variable	r	p
Heart rate	−0. 210	0. 100
GSR reactivity	+0. 405	*0. 005
Respiration rate	+0. 323	*0. 025
Reaction time	−0. 222	0. 100
Peak CNV amplitude	+0. 176	0. 150
CNV area	−0. 612	*0. 005

*Significant correlation.

Also, it is often difficult to measure peak amplitude with accuracy because of the fast activity superimposed on the curve of the CNV.

For these reasons, we have adopted the method of measuring CNV area as well as peak amplitude. Figure 4–19 illustrates the area of a CNV as we measure it. The area is obtained as an integration of CNV amplitude as a function of time between point A and point B. Point A is the point of origin of the CNV, and B is its point of termination; both points are obtained by inspection.

Using the data obtained in the last described experiment, correlations were determined between CNV areas and S_2 intensity, peak CNV amplitude, CNV duration, reaction time, and the other measured physiological variables. Table III shows the correlation coefficients in table form. The only significant correlation was between area and S_2 intensity. There was little or no correlation between area and peak amplitude or duration of the CNV, or between area and reaction time.

It was concluded that the area measurement is a useful parameter, without which valuable information may be lost and that the area of a CNV is not necessarily a simple function of peak amplitude, duration, or reaction time.

One other point should be stressed. The exact relationship of the CNV to background rhythmic activity or to the so-called resting dc level has not yet been satisfactorily resolved. For example, we have obtained traces such as those in figure 4–20, indicating that, at least in some cases, the resting dc level of the brain moves positively as the CNV increases in magnitude, as though the CNV were momentarily returning the cortex to the zero state. Knott and Irwin (1967) have shown that low-anxiety subjects will develop higher amplitude CNV than high-anxiety subjects in a stressful experimental situation. They postulate that the cortex may have a fixed capacity for shifting negatively and that the CNVs of the high anxiety subjects "run into" this ceiling from a variable baseline, with anxiety or arousal factors af-

fecting the level of this baseline. The specific CNV generators presumably provide a transient negative rise toward the postulated "ceiling."

Low and McSherry (1968) have shown that in the usual low-stress single S_1–S_2–R paradigm, the physiological system for generation of the CNV is not saturated since the CNV magnitude may be increased by superimposition of tasks in time.

Finally, I feel less brave about making assertions regarding the psychological-physiological significance of the CNV than I once was. It may well be that what we call the CNV is not a single entity but is several different potentials with similar appearances, occurring alone or recorded together in a variety of circumstances. All negative shifts recorded at the surface of the brain do not necessarily signify the same physiological-neuronal process. Since there is no general agreement about the question of whether a cortical surface-negative potential always indicates either excitation or inhibition or some mixture of both, it would seem quite adventurous to speculate about the physiological function of a phenomenon that may not even be a discrete potential.

DR. LOMBROSO: I would like to make some remarks on this subject, and I apologize if they will further add to the complexity—already alluded to—of this phenomenon. It has been stated earlier that cortical

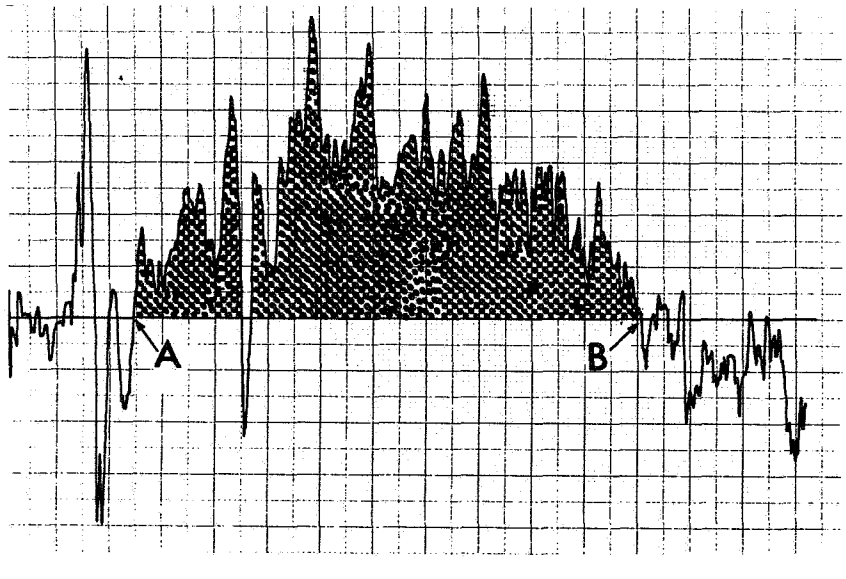

FIGURE 4–19.—Sample CNV (monkey, sensory-motor cortex-to-subcortical reference) illustrating area of the potential (stippled); (negative up).

TABLE III.—*Correlation Between CNV Area and Other Variables*

Variable	r	p
S_2 intensity	−0. 612	*0. 005
Heart rate	+0. 138	0. 200
GSR reactivity	+0. 002	>0. 500
Respiration rate	−0. 004	>0. 500
Reaction time	−0. 040	0. 450
Peak CNV amplitude	−0. 002	>0. 500
CNV duration	+0. 090	0. 300

*Significant correlation.

or scalp-derived dc shifts (1) are synchronized with behavioral processes; (2) may form an integral part of the bioelectric activity of the cortex; (3) may provide information on the functional state of the cortex.

We have made some observations that may be interpreted as raising some questions on these claims (Lombroso, in press). These were obtained on adult subjects, and the usual technique for the study of the CNV was used. The only difference in our setup was that 1 second following a flash (2 logarithmic units above threshold) the subject received via earphones a 10-msec tone delivered to either his right or left ear according to a program provided by a random pattern generator. There was background white noise. After baseline trials with no instructions, the subject was asked to respond to each tone regardless of the ear it reached. Thus, we could observe the development of the CNVs obtainable when the tone reached either ear and "averaged" separately on a CAT–1000 from an FM tape deck. There was no difference between these CNV, as could be expected. We also were recording and averaging both vertical and horizontal EOG, as well as the EMG derived from the "acting" arm, and from two pairs of electrodes placed orthogonally presumably over the sensory projection area of the contralateral hemisphere. The response requested was the activation of a microswitch that in some cases gated an electronic counter that measured reaction time. For some experiments, the response was "mental"; i.e., a serial subtraction. A continuous strip-chart monitored all parameters and permitted discarding of trials with mistakes or blinking and other artifacts.

After the CNV became established, the subject was asked to respond only when the tone reached one of his ears, and not to respond when it reached the other. Two to four trials were run consecutively in the same manner. Then the subject was asked to reverse his response to the time when the tone now reached the opposite ear. This again was

repeated for two to four trials. Finally, runs were made with the subject instructed to ignore the tone to either ear.

Figure 4–21 shows what happened consistently in the CNV obtained separately when the tone reached one ear or the other at random. Each graph is the average of 12 flash-tone sets. The broken lines indicate when the flash and the tone were given—1-second apart. In the left column are displayed the CNV developing when the tone reached the left ear, for which the subject was asked not to respond (NR) during the first three runs, and to respond (R) during the subsequent two. Conversely, in the right column are the CNV developing when the tone arrived at the right ear, for which a response was required in the first three runs, and none for the two consecutive ones.

Note the similarity of the CNV developing when the tone had reached the left or the right ear during the first run when a choice had to be made. Remember that the subject was performing (correctly as monitored all the time) a different task for each stimulated ear—press a switch or subtract a number in one case, or do nothing in the other. As the program continued, however, note the difference developing at the termination of the CNV. Naturally, none would occur during either the first evoked response nor during the development of the negative dc shift since no difference in the program became known to the subject until the imperative signal arrived.

As you can see, at the second such trial (run 4 of fig. 4–21) the CNV tends to terminate earlier when the tone reaches the ear for which

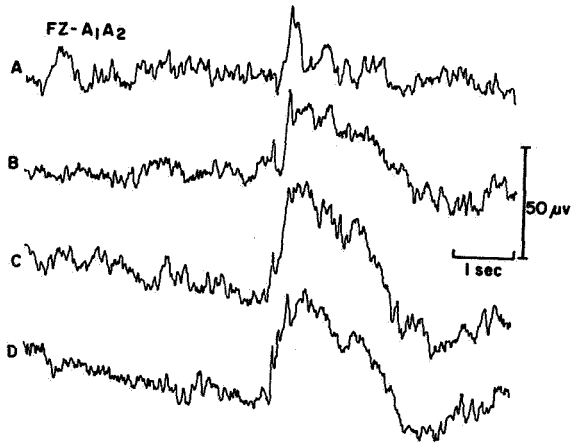

FIGURE 4–20.—Sample CNV (man, vertex-to-paired ear reference) obtained while recording for 4 sec before and 4 sec after the occurrence of S_1. Each trace is an average of 12 trials (negative up).

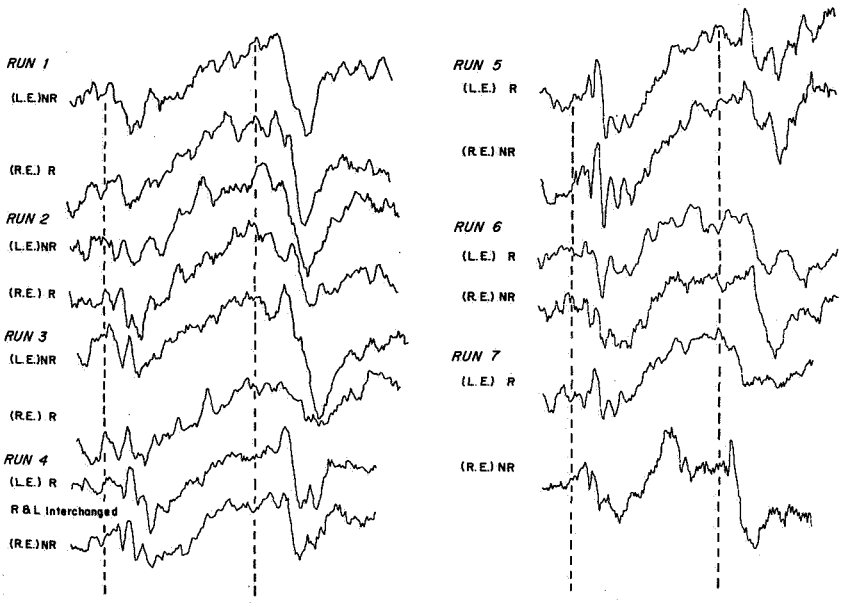

FIGURE 4–21.—Broken lines indicate times of flash-tone stimuli, 1 second apart. The CNV, obtained when the tone reached at random the left or the right ear, are displayed in the left and right columns, respectively. R and NR denote "response" and "no response," respectively. During runs 3, 4, and 5, the subject was responding only when the tone reached his right ear, while during runs 6 and 7, the instructions were reversed. Note the difference in the termination of the CNV between R and NR that appears at run 4 and its rapid reversal at run 6. During the last run, the subject was told not to respond to tones reaching either his right or left ear. All runs were performed consecutively and consisted of 24 flash-tone pairs, with tones distributed randomly to right or left ear.

the subject was told to respond. More strikingly, the positive deflection of the CNV when the tone reaches the ear for which no response is requested now has "grown"—so to speak—becoming notably greater than it was for the previous trial and falling below "baseline". Conversely, note how much smaller the positive deflection of the ending CNV has become when the stimulus reaches the ear selected for response. These differences become even more marked at the third consecutive trial (run 5 of fig. 4–21). Note what happens when the response parameters are reversed, that is, when at run 6 the subject is told to respond only when the tone reaches his left ear. The CNV termination sweep has changed also quite markedly, becoming less than one-half of its value for the previous one. Conversely, the end sweep of the CNV developing when the tone reaches the right ear for which now no response is requested, is about double what it was for the

previous run. Similar differences are seen for the next consecutive trial (run 7) and for the last (run 8). No differences are seen between the two sides when the subject is told not to respond to any tone, and no CNV develops.

These differences in the termination of the CNV were not caused by muscle or eye contaminants although I argue—like many others—that strict monitoring of both is necessary. Also "averaging," especially of eye movements, should be done in conjunction with CNV averaging since only by "averaging" one may discover their contribution. Likewise, there was no significant contamination in our CNV from the SER because of the contralateral fingering of the microswitch. These differences in the termination of the CNV occurred equally over both hemispheres and were unrelated to the subject's errors.

Now, I would like to illustrate briefly a second observation. This shift in the morphology of the CNV termination, with the reversing of instructions, can occur right away following the change in instructions and in response. But in other instances, we found a remarkable lag in the shift of the CNV morphology as it related to the behavioral response. Figure 4–22 illustrates this point. Here the two CNV (each an average of 12) are displayed in pairs. Note again the little difference between the NR and R CNV on the first trial, and the developing of a marked difference as trials progress (runs 2 and 3). But now, when the instructions are reversed at run 4, there is no immediate and parallel shift in the CNV termination. If anything, the end of the R CNV is still greater than the NR CNV. Only at run 6 and especially at run 7 do we see a well-established reversal of the CNV positive deflection. In other words, while the subject performed the requested shifts in his response immediately and correctly, there was a considerable time lag for a parallel shift to appear in his CNV.

It is possible that the described differences in the termination of the CNV obtainable when the subject responds or does not respond, may be related to a surge of negativity and to a further positive dc shift, respectively, and that these relate to aspects of discriminatory behavior such as "attending to" or suppressing" and so forth. Interesting as these differences I have described might be, I find it strange that the electrical signals accompanying these high-level neuronal processes should lag, at least in some subjects, so far behind their performance. It would seem reasonable to question, for example, the concept that the CNV represents a "priming" process of the frontal cortex preparatory for the discharging of its motor neurons, when it may take so long for an aspect of its morphology to "catch up" with a change in motor performance. For the same reasons, how could we relate these changes to either "excitation" or "inhibition" in neuronal assemblies, as has been claimed?

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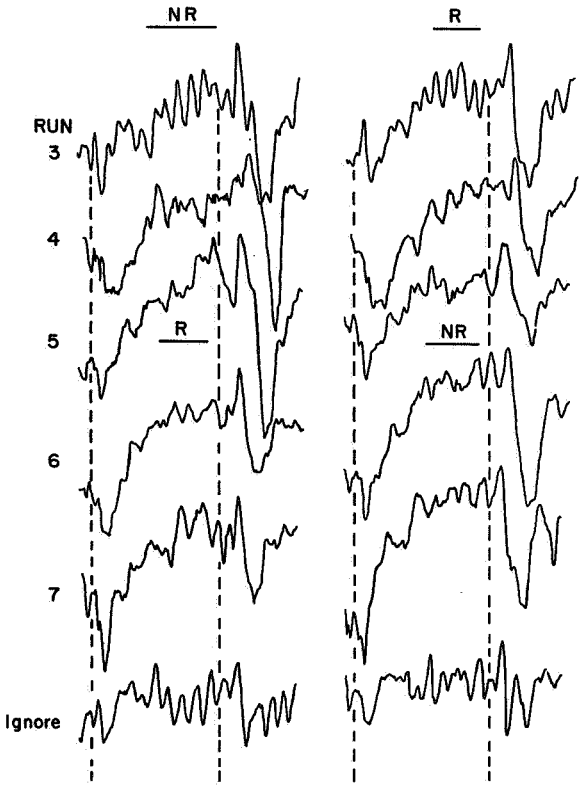

FIGURE 4–22.—The experimental situation is the same here as for the preceding figure and the CNV are displayed in pairs, those obtained when the tone reached the left ear being the first for each run. R and NR denote "response" and "no response," respectively. A notable difference develops in the termination of the CNV as the trials progress, being maximal at run 3, when the instructions were reversed. At runs 6 and 7 the reversal in the CNV termination takes several trials to become clear.

While it is conceivable that some components of the CNV are "neuronal" in origin—and we would agree that the AEP to flash and tone were indeed "neuronal" events—it is at least plausible that others may be non-neuronal. Referring in particular to the dc shifts, we should remember that parallel to neuronal events of excitation or inhibition, many metabolic and physiochemical processes are occuring in glial cells, capillary endothelium, and the like, all capable of inducing slow current shifts. Adey (1963), for instance, has shown that rapid changes in impedance of small volumes of cortex closely relate

to relatively rapid shifts of blood flow and gas exchange, and that the impedance of dendritic structures has been noted to change in several of those behavioral states during which negative dc shifts have been measured on the cortex. It is conceivable that a phenomenon such as the one we have described before, namely, the time lag between reversing changes in CNV when behavioral parameters are reversed, might be explained easily on the basis of such extraneuronal sources whose time basis is much less rigid than one would expect from neuronal populations.

DR. CHAPMAN: I would like to make two points—the first about the various ways that eye movements might affect electrical responses and the second about the relation between CNV and AEP. We all know that eye movements can cause much difficulty, and this holds equally true for the slow potentials, as well as the faster ones which we categorize as evoked potentials. I would like to point out that there are several ways in which such eye movements might affect our responses. The one that has been discussed primarily is the direct electrical effect resulting from movement of the eye. The voltages recorded from the eye as the corneoretinal potential or electrooculogram (EOG) may be carried by volume conduction to electrodes at other sites on the head.

There are also indirect ways in which eye movements might affect the evoked potentials that we ought to keep in mind because the effects may be larger although the mechanisms are more subtle. I call them indirect because they involve the visual pathways themselves, rather than simple spread of potential. There are at least two ways in which the indirect effects might occur.

One kind of indirect effect is caused by displaced retinal images producing neural activity in the visual system. A static light pattern moved across the retina by eye movements is a very effective stimulus for retinal activity because both on and off responses are produced as the light moves onto fresh retina and off of previously stimulated retina. This effect was demonstrated in experiments by Gaarder et al. (1964), who had their subjects fixate a static target and obtained an AEP by synchronizing the computer with the subject's eye movements. The AEP they obtained depended upon stimulus characteristics showing that it was mediated by the visual system. This indirect effect may be large enough to be seen as lambda waves in the EEG. This indirect effect can be eliminated in many experiments by keeping the subject in the dark and keeping the presentation of visual stimuli so brief that the retina does not have time to sweep across the light. It is to be noted that experiments purporting to use nonvisual stimuli are not immune from this eye movement effect if a visual field is present, since the nonvisual stimulus may synchronize eye movements, which in turn

result in visual evoked responses. If we are interested in differential effects, we might worry about differential eye movements producing the differences between the evoked responses or CNV.

The second indirect effect of eye movements concerns direction of gaze and is not so easy to cope with. A light stimulus may not reach the same retinal locations from one stimulus presentation to the next, even within an averaging run. Even having an experienced subject fixate is only an approximation to reproducible conditions since eye movements are so ubiquitous (Riggs, Armington, and Ratliff, 1954). The eye need move only little for the light stimulus to reach a fresh piece of retina, and it is well known that adaptation effects in the visual system are very large. Also a shift in gaze may shift the visual stimulus onto a part of the retina that contributes more or less to the AEP (Rietveld et al., 1965; Tepas and Armington, 1962); for example, consider the difference between peripheral and foveal representation. We need to consider the problem that differences in electrical responses associated with independent variables of interest may be caused by differences in gaze direction, and the problem is more complicated than knowing the average gaze during an averaging run. Reviewing briefly, eye movements may have direct effects from the EOG and indirect effects via the visual system—i.e., retinal image displacement during the individual stimulus presentation and from one presentation to the next.

The second issue concerns the relation between slow wave potentials and the AEP. The data in figure 4–23 were obtained in a study of AEP (Chapman, 1965); however, slow wave effects show up. Two classes of stimuli, numbers and letters, were presented in a sequence that was fixed for a given run of trials. For example, the data in the top row were from runs when each trial had the following sequence of light flashes: number, letter, number, letter, blank. The particular numbers and letters in each position were randomly selected. The subject was given a task that involved one set of stimuli. In the top row, the letters were relevant to the task, and the numbers irrelevant. In the second row, the same physical stimuli were used in the same sequence, but the numbers were relevant to solving the problem, and the letters irrelevant. Vertical comparisons showed the tendency for larger AEP when the stimuli were task-relevant.

These AEP appear to be superimposed on a slow wave change running across the trials. This experimental design has features in common with the one used to obtain the CNV, namely, trials in which there are fixed temporal relations among the stimuli; also, the subject must respond to certain imperative or relevant stimuli.

The question is whether the enhanced positive response (positive is up in fig. 4–23) to the relevant stimulus might be caused by the

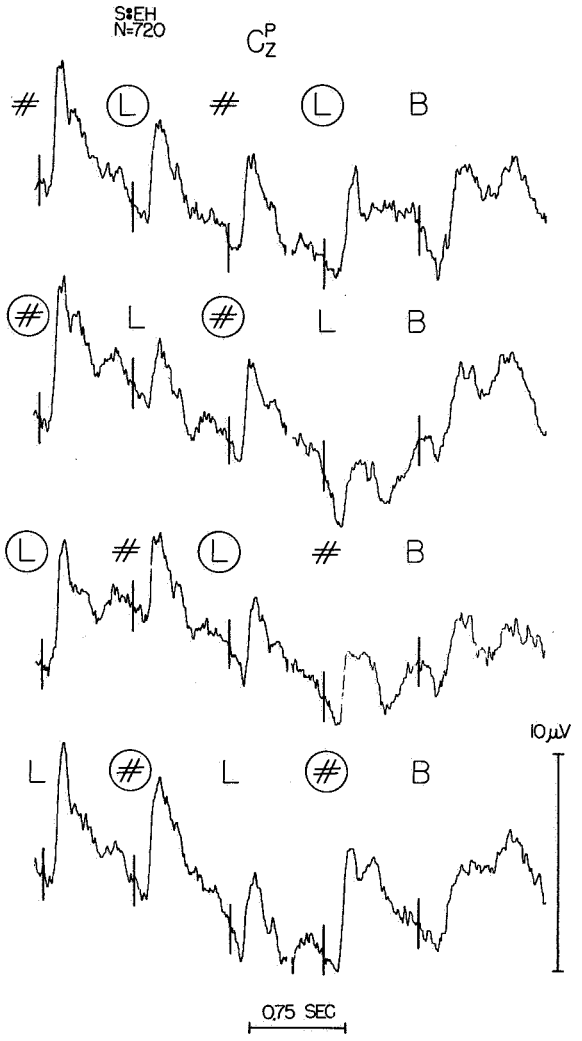

FIGURE 4–23.—Averaged evoked potentials to numbers (#) and letters (L) during runs when one stimulus class was relevant (circled), and the other irrelevant. Monopolar recording from electrode between C_z and P_z with reference to linked earlobes (negative down). Time constant was 0.4 sec. Onset time of brief visual stimuli shown by vertical lines on traces.

termination of an anticipatory negative wave. If so, AEP and CNV investigations may be studying the same process.

The data from this subject suggest that they are independent to some extent. For the sake of this discussion, the AEP is defined as

the amplitude of the major positive component with reference to the voltage level at the time of the stimulus (vertical lines in fig. 4–23). The slow wave is defined as the voltage levels "across" the trial at the times of the stimuli. Although there is a statistical tendency for higher AEP peaks to occur when the trace at the time of the stimulus is more negative, this does not appear to be a tight, causal connection. For example, the largest AEP tended to occur at the first stimulus on all types of trials (first AEP in each row) although for this subject the most negative part of the slow wave occurred later in the trial when the fourth stimulus was flashed. Moreover, the pattern of slow wave change across the trials was different in other subjects although there was a tendency for the relevant stimuli to evoke higher-amplitude AEP.

Aside from the question of the relation to CNV, these data illustrate a problem with regard to AEP measurement. Most of us take our AEP measurements in relation to the particular response we are looking at, and not in relation to the entire sequence of responses or an absolute reference level. For example, many of us establish a baseline using the very first part of the response or the potential level found a short time before the stimulus was delivered and measure amplitudes from there. The data in figure 4–23 show that the AEP amplitudes would be profoundly different if they were measured from a common baseline for all the AEP in the sequences.

DR. WALTER: Dr. Low's espousal of the area under the CNV curve raises a question. Why not use a low-pass filter on the data? It would seem that this would be an entirely equivalent operation. Is there some positive reason for not treating the data that way, rather than waiting until the Linc can process it?

DR. COHEN: To answer Dr. Walter, I guess my reason for not filtering that way is that I am interested in the faster responses as well at the same time.

DR. WALTER: It still might be easier if you separated them onto two channels.

DR. COHEN: In regard to Dr. Lombroso's finding, we have made similar observations. When stimuli are to be discriminated, the negative stimulus is followed by a positive wave. I wonder whether he thinks that positivity, in that case, represents inhibition. If the negativity is priming excitation, do we have an opposite process in the positivity? I realize we must have some balance.

There is a lag in the CNV compared to the behavioral response. I think that the reason for the lag is that we are looking at synchronous activity. We don't know what in the cortex is mediating a particular behavior and how that is reflected electrically at a given point. However, unless there is synchrony, we won't see a wave at the surface.

Young children can perform the tasks used in CNV experiments before the CNV can be recorded. This is also found in children with learning problems and behavioral disorders. There, behaviorally they may be able to perform the task, but the CNV is very much retarded for the age level and may be absent. We obtain behavioral changes before we see a synchronized electrical activity at the scalp. But that should not be too surprising since I think maximal cortical response is not required in order to mediate a simple task.

DR. ALLISON: I have a question for Dr. Vaughan which was triggered by one of Dr. Cohen's figures (fig. 4–5). He showed the topography of the CNV, and it was largest in the vertex region. It is curious to me that there is a whole variety of evoked responses, all of which are largest in the vertex region. Of course, there are the vertex potentials themselves, which may or may not be largest at the vertex. There are certainly differences between modalities that are focused in the region of the vertex.

Some of the early auditory responses that Goff described this morning are largest at the vertex. Goff and I have recently been recording odorant evoked responses (Allison and Goff, 1967). This response is a long latency response that is also largest at the vertex. It seems unlikely to me that the area of the brain under that electrode is really responsible for all this activity. I gather that you are rather optimistic about your volume conduction model, allowing you to infer the generators of scalp-recorded responses. I am wondering how your model would accommodate this conglomerate, all of which seems to be large at the vertex.

To be specific, would the model allow us to specify superficial generators, as the CNV might be, for example, if it were generated transcortically, as opposed to a deep generator, as I would expect the odorant response, for example, to be?

DR. VAUGHAN. As I have noted in Chapter 2, there are several steady-potential shifts (SPS) that differ both spatially and in their behavioral correlates from the CNV. My present evaluation of this situation is tentative at best, both because of the artifact problem and the somewhat ephemeral nature of these phenomena. Because of these uncertainties, I have not published more data obtained over the past few years in my laboratory. I have serious reservations concerning the reliability and interpretation of some of the published observations made elsewhere. For a time, we were convinced that the CNV was, in fact, merely the early slow component of the motor potential (MP) (the "readiness potential" of Kornhuber and Deecke, 1965). Our evidence was the somatotopic distribution over motor cortex and the fact that it seemed to be more closely time-locked to the motor response than to the stimulus in both the reaction time paradigm and the time esti-

mation paradigm (Vaughan and Cost, 1968). We have never been able to confirm conclusively the existence of a frontal SPS independent of the MP or the EOG. The issue has been complicated further by our confirmation of the early observations by Köhler, et al., (1955a, b) of SPS associated with novel stimulation and the discovery of SPS over visual cortex in discrimination tasks. Since these seem to be specific potentials comparable to those recorded by Gumnit and Grossman (1961), the SPS to auditory stimulation is maximal at the vertex. Only for visual stimuli has it been possible for us to make a clear spatial differentiation of the SPS associated with sensory set or orientation and those which seem to be related to preparation for a motor response.

My own bias on this problem is that the physiological origin and functional significance of the SPS need to be elucidated in experimental animals. At the present time, there is virtually no reason even to suppose that they are either wholly or partly of neural origin; nor do I feel that the phenomena are sufficiently reliable within or across subjects, even under the quite close behavioral controls we employ, to feel very comfortable about suggestions that these phenomena might have diagnostic value in clinical populations. Although much of the interest in steady potentials in man has derived from the presumption that "complex" psychological variables exist which may be defined by such vague terms as "expectancy," I suspect that observations made in animals under carefully controlled behavioral conditions will provide the insight into the functional significance of these potentials.

DR. DONCHIN: I want to support Dr. Chapman's comment on the relationship between the CNV and the AEP. Dr. Smith and I have obtained very similar results (Donchin and Smith, 1968). I would like to stress that whatever we decide about the CNV, its nature, its physiological source, and its functional significance, we must consider the relationship between the CNV and the evoked response. While an investigator might have no interest in the CNV in a particular study, the subject determines to a large extent the nature of the experiment. If the instructions produce constraints that make the contingencies between the stimuli in a series important to the subject, as for example when the stimuli follow each other at a fixed interval and each becomes an S_1 to the following S_2, a CNV might—and usually does—develop between the successive stimuli. If there is a relationship between the CNV and fast responses—and we have no information on that yet—then the results of such an experiment would be difficult to interpret. In the study I refer to, we were basically interested in the task-relevance of stimuli and its effect on the AEP. The stimuli were presented randomly, and averaged evoked potential differences were indeed found that depended on task-relevance. However, if the

stimuli are presented at a fixed rate and the proper amplifiers are used, a CNV develops between the stimuli. Any relationship between the CNV and evoked response thus would greatly affect our results.

DR. KNOTT: I want to give Dr. Dale McAdam an opportunity to comment on the matter of evoked response and the CNV. He may answer your question for you. However, I would like to return to the data presented by Jasper at the Cold Spring Harbor conference of 1936. Using rather long-time-constant amplifiers, he recorded very slow potentials in the electroencephalogram. At that time, Jasper made some analogies between shifts to a negative polarity and increases of excitability, and shifts to a positive polarity related to a decrease in excitability. In this, he led the field by many years.

Our data on the anxiety problem did show that there was a lesser rise in the CNV in moderately anxiety-prone individuals placed under stress than in less anxious subjects under stress; this led us to believe that there is a finite dc level that can be achieved. This has been followed up by my collaborator, Dr. Don Irwin, who has been able to show that while the dc level of the cortex can be increased by constant stimulation, there consequently is a limit to the remaining shift under the expectancy paradigm. This is important, because I think it may explain the Chapman data, and I think it clearly is related to the comments just made by Donchin.

DR. MCADAM: I would like to summarize briefly some recent work (McAdam, 1969) showing changes in somatosensory evoked potentials to noncue stimuli presented during a CNV. Figure 4–24 shows sample CNV and the procedure we used. We generated CNV by asking subjects to respond as quickly as possible to the offset of an 1800-msec tone. On a random one-half of the trials, shock to the median nerve was given 1 second after tone onset. The median nerve shocks were of sufficient intensity to cause a small but reliable thumb twitch. Subjects were instructed to pay no attention to the shocks, but to attend only to the tone and respond as quickly as possible to its offset. Shocks were also delivered during the intertrial intervals, i.e., when no CNV was present.

In addition to recording the CNV from a vertex-mastoid derivation, evoked potentials to median nerve shock were recorded from contralateral frontoparietal scalp using RC-couplied amplifiers. Examples of these potentials are presented in figure 4–25. These are tracings of responses from two subjects, A and B, under conditions when the shock was presented during the CNV (A′ and B′), and when it was presented in the intertrial interval (A and B). The lower set shows the most complex potential, while the components in the upper set were seen in all 24 subjects. All scoring was based upon the seven compo-

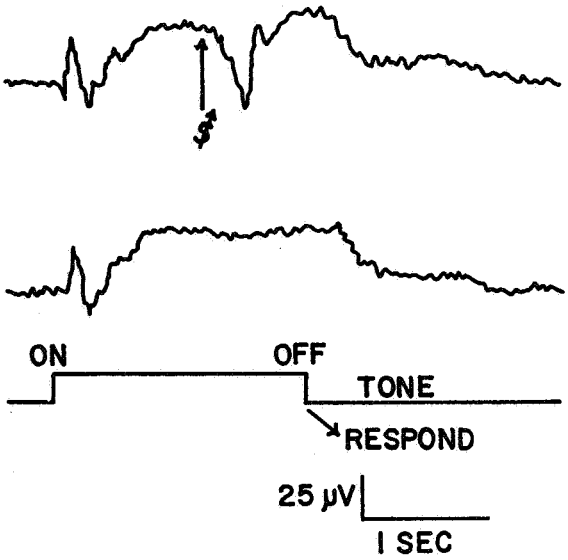

FIGURE 4–24.—CNV from one subject. Averages of 50 responses each. Vertex-to-mastoid reference. Upper record: trials when median nerve shock was presented. Lower record: trials with tone alone (negative up).

nents that were common to all subjects; the component numbers used in tables IV and V are those shown in this figure.

In addition to the 16 subjects in the experimental group, 8 subjects were run under a "tone-control" condition. These subjects were given the same stimuli as were those in the CNV group, but made no responses. No CNVs were seen in this group.

Analysis of amplitude changes between potentials recorded when the shock was given during the tone as compared to those recorded when shock was given during the intertrial interval showed an across-the-board decrease in amplitude of nearly all components when the shock was presented in combination with another stimulus (see table IV). These amplitude decreases during tone were present whether a CNV was generated or not.

Latency changes, on the other hand, were found to be unique to the CNV group; the latencies of components 9, 10, and 11 were significantly shorter when the shock was given during the CNV than when it was given during the intertrial interval. No corresponding difference was found in the tone-control group data (see table V). This result lends support to the hypothesis advanced by Walter, et al. (1964) that the CNV represents "the electric sign of cortical prim-

ing." There is, however, nothing in these data that would limit the mechanism for the observed responsiveness changes to a cortical site. In fact, since the changes in the evoked potentials that were unique to the CNV group were seen only with the later components (beyond 200 msec), subcortical structures such as the reticular formation are very probably playing a role in producing these changes.

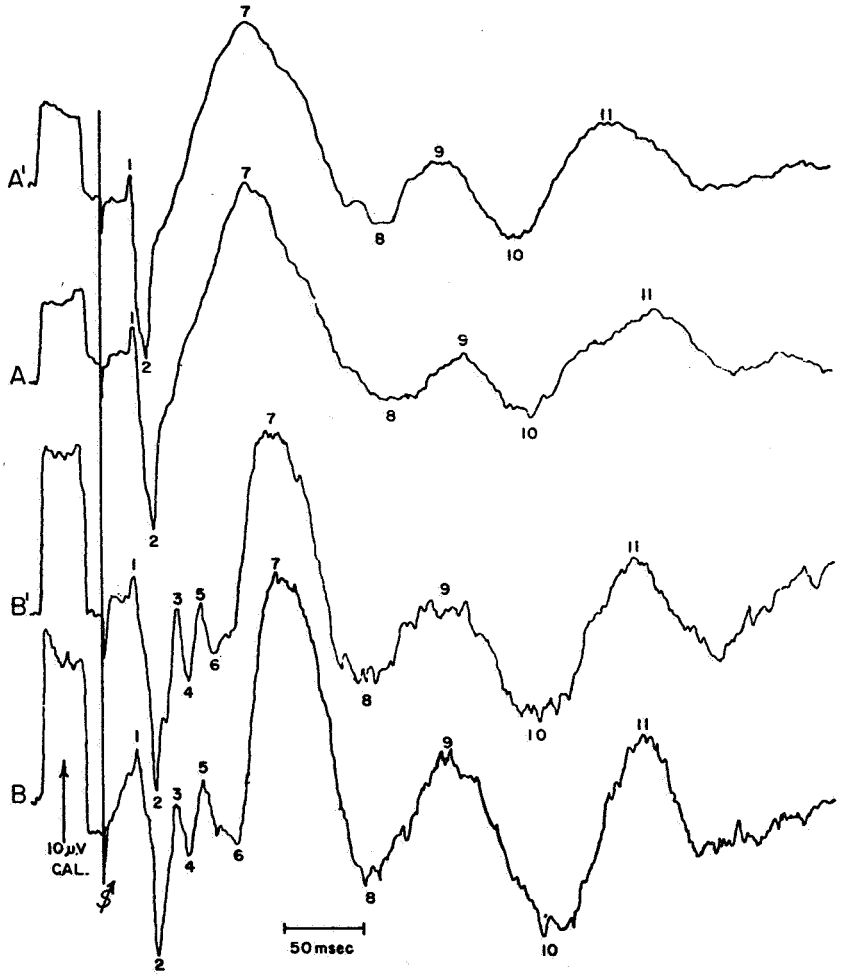

FIGURE 4–25.—Somatosensory evoked potentials from two subjects, A and B, in the CNV group. Averages of 50 responses each. Parietal electrode relative to a reference placed 6 cm anterior to it. Square wave at left of each trace is 10–μV calibration signal; A and B responses obtained during the intertrial interval and A′ and B′ are responses obtained during presentation of the tone (negative up).

TABLE IV.—*Mean Differences in Peak-to-Peak Amplitudes of Evoked Potential Components*

Components[a] (and mean peak-to-peak amplitudes, in μV, response during intertrial)	Tone control group		CNV group	
	Difference (μV) (intertrial-tone)	t	Difference (μV) (intertrial-CNV)	t
1–2 (14.5)	1. 3	[b] 3. 33	0. 9	1. 02
2–7 (19.0)	1. 6	[b] 2. 71	3. 7	[b] 2. 75
7–8 (11.4)	1. 2	[b] 2. 67	4. 1	[b] 4. 17
8–9 (8.9)	2. 0	[b] 5. 00	2. 7	[b] 2. 48
9–10 (9.5)	1. 6	[b] 2. 71	1. 9	3. 92
10–11 (9.4)	−0. 4	0. 585	1. 1	1. 43

[a] Identified by numbers as in figure 4–2.
[b] $P<0.05$; all others not significant.

TABLE V.—*Mean Differences in Peak Latencies of Evoked Potential Components*

Component[a] (and mean latency, in msec, response during intertrial)	Tone control group		CNV group	
	Difference (msec) (intertrial-tone)	t	Difference (msec) (intertrial-CNV)	t
1 (18.7)	0. 4	. 800	−0. 2	. 610
2 (33.4)	0. 1	. 164	0. 1	. 151
7 (104.9)	1. 4	. 318	−2. 2	1. 93
8 (158.1)	−4. 1	. 579	3. 6	1. 26
9 (210.6)	2. 0	. 769	6. 5	[b] 2. 20
10 (273.7)	2. 6	. 565	7. 3	[b] 4. 68
11 (343.9)	−0. 8	. 333	10. 3	[b] 4. 11

[a] Identified by numbers as in Figure 4–2.
[b] $p<0.05$, all others not significant.

I would like now to discuss another point in Dr. Vaughan's support by helping bridge the gap between what he calls the "motor potential" (Vaughan et al., 1968) and the CNV. The motor potential consists in part of a slow, surface negative shift recordable over motor cortex, which occurs before the performance of a voluntary motor act. It is topographically distributed over the motor area, the site of maximum amplitude being determined by the muscle groups involved in making the response.

The motor potential was first described by Kornhuber and Deecke (1965), and they gave it the name *Bereitschaftspotential* or "readiness potential" (RP). They noted that the RP is enhanced by "intentional engagement" on the part of the subject in the performance of the response, but they do not report quantitative data on this point. "Intentional engagement" sounded a lot like motivation to us, and since a number of papers on the CNV had expressly implicated motivation as one of its most potent psychological determiners (Irwin et al., 1966a, b; Rebert et al., 1967; McAdam et al., 1968), David Seales and I decided to look at the RP under conditions of varying motivation (McAdam and Seales, 1969).

Figure 4–26 shows examples of RP that we recorded from electrodes located at C_3 and C_4 (contralateral and ipsilateral motor areas, respectively) while the subject was making a simple button-press response with his right thumb. Two conditions were run; in one, labeled "baseline" subjects were instructed simply to make a response every 3 or 4 seconds. There was no consequence whatsoever. Under the "reward" condition, the subjects were given purposely vague instructions that if they responded in the "right way" or at the "right time" they would receive a monetary reward for the response. In fact, they were rewarded on a random 50 percent of the trials in this situation.

Figure 4–27 summarizes the data from the 11 subjects tested under these conditions. Analysis of variance on these data showed no interaction effect between conditions and electrode placement. However, RP amplitudes were significantly larger under the "reward" condition than under the "baseline" condition for both ipsilateral and contralateral placements, and RP amplitudes were larger for contralateral placements than for ipsilateral placements under both conditions. It appears, therefore, that the RP changes with increased motivation in much the same way as does the CNV; i.e., larger amplitude responses are found. Since the changes in RP amplitudes were the same for both ipsilateral and contralateral electrode locations, it implicates a general activating system (possibly the reticular formation) as a neural substrate for these changes.

It is interesting that a laterality effect has never been reported for the CNV. This is certainly caused in most cases by the fact that experimenters did not look for it; the CNV is "traditionally" recorded as a midline phenomenon. Nonetheless, both Low et al. (1966a) and Cohen (in this volume) report that the CNV is distributed symmetrically in the coronal plane with a peak amplitude at the vertex. It may be that the increased complexity of the CNV situation over that used to evoke an RP and the fact that stimuli have been presented bilaterally, served to wash out any laterality effect. Mr. Seales and I are currently exploring this problem, but we have no data which we can report as yet.

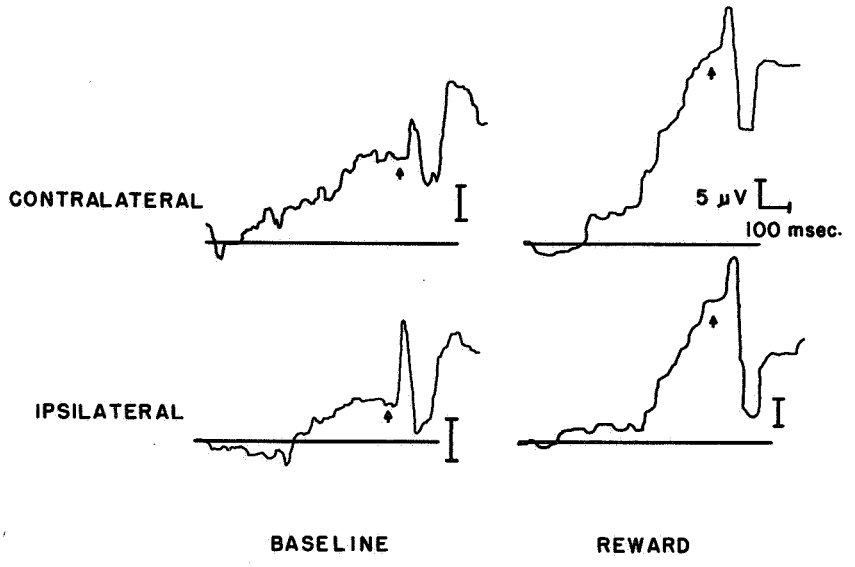

FIGURE 4–26.—Sample RPs obtained from one subject. The active electrode is C_3 or C_4. Arrow indicates occurrence of response (negative up).

DR. LEHMANN: I would like to ask Dr. McAdam if he measured the amount of pressure exerted by the subject in the reward and non-reward situation.

DR. MCADAM: I would be very happy to say that I did, but I didn't. We were not equipped to do it.

DR. HILLYARD: Both Low and Cohen pointed out that the corneoretinal potential can be a source of artifact in the CNV, and I would like to present some data that will document the seriousness of this problem.

Figure 4–28 (Hillyard and Galambos, in press) shows computer-averaged tracings of the CNV from the vertex-mastoid derivation and the simultaneous transorbital EOG, recorded with dc electrodes above and below one eye. These recordings were taken in the standard S_1–S_2-lever-pressing situation, wherein S_1 was a click and S_2 was a tone that signalled the motor response. These are typical records from nine different subjects, each of whom displayed a different, characteristic pattern of eye movements during the S_1–S_2 interval.

In the top row, for example, the waveform of the CNV is paralleled closely by the waveform of the EOG deflection (lower tracing). An upward deflection in the EOG indicates a negative shifting of the supraorbital electrode, caused by elevation of the negative, posterior end of the corneoretinal dipole. Most commonly, there was a downward eye rotation in the S_1–S_2 interval if the eyes were closed; however,

the mechanisms and significance of such involuntary eye movements preceding lever presses remain a mystery. Some subjects, however, did not display any sizable eye movements under identical circumstances.

My next task was to relate the amplitudes of these transorbital potential shifts to the artifacts produced concurrently in the vertex-mastoid montage during different-sized eye rotations. Accordingly, the recorded CNV was subdivided into one component caused by the corneoretinal fields called the Eye Artifact Potential (EAP), and a second component which I called the "true" or tCNV, which probably comes from the brain. These two potentials are summed and confounded in most recordings of the CNV unless special precautions are taken.

A separate "calibration" procedure was designed to relate the amplitude of the EOG deflection to that of the EAP induced at the

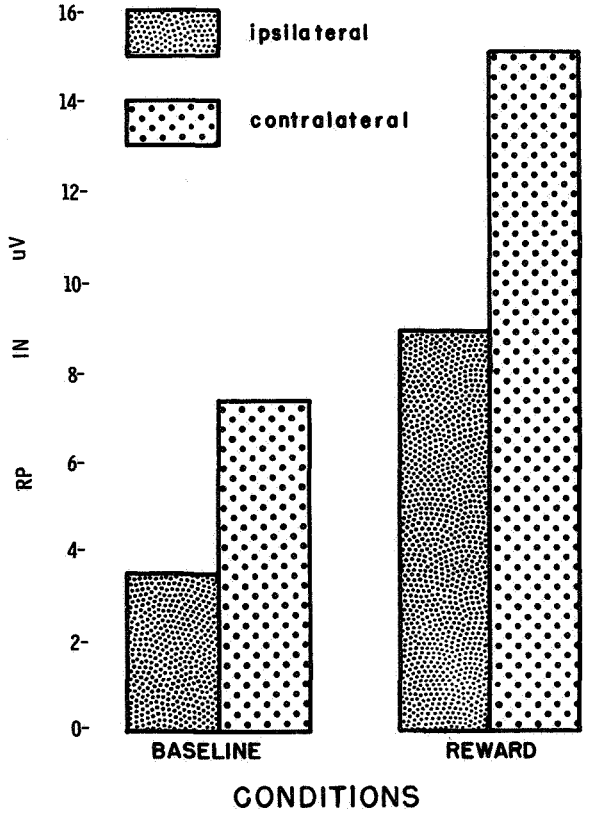

FIGURE 4-27.—Group means of RP amplitudes for ipsilateral and contralateral locations under baseline and reward conditions.

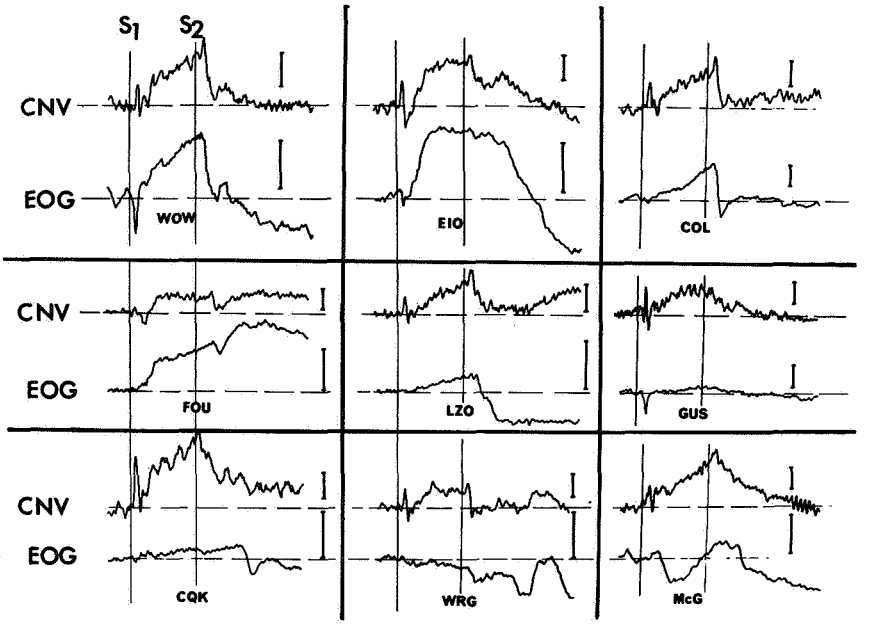

FIGURE 4–28.—Simultaneous recordings of the CNV and the deflection in the vertical EOG, caused by synchronous involuntary eye movements. Calibrations are 20 μV for the CNV and 100 μV for the EOG (negative up).

vertex. Each subject made upward and downward eye rotations of specified angles, and the EOG deflections were measured along with the EAP, which could be algebraically separated from the concurrent tCNV by a subtraction method, described fully in Hillyard and Galambos (in press).

The amplitude of the EAP induced at the vertex (in microvolts) is plotted in figure 4–29 as a function of the potential shift recorded across the eyes during eye rotations of different sizes. This relationship was linear in all subjects, and the parameters of the lines of best-fit are given for the vertex-mastoid channel. The solid circles represent EAPs that were induced simultaneously in a frontal electrode, placed 4 cm anterior to the vertex. In the frontal electrode, which was closer to the eyes, a greater proportion of artifact was induced per unit of eyeball rotation. By taking such calibration curves and applying them to CNVs that were recorded in the S_1–S_2-lever pressing situation, the appropriate amount of EAP at the vertex could be calculated. By such procedures, it was found that 23 percent of the CNV was composed of negative EAP in the average subject, because of a net tendency to move the eyes downward in synchrony with the CNV.

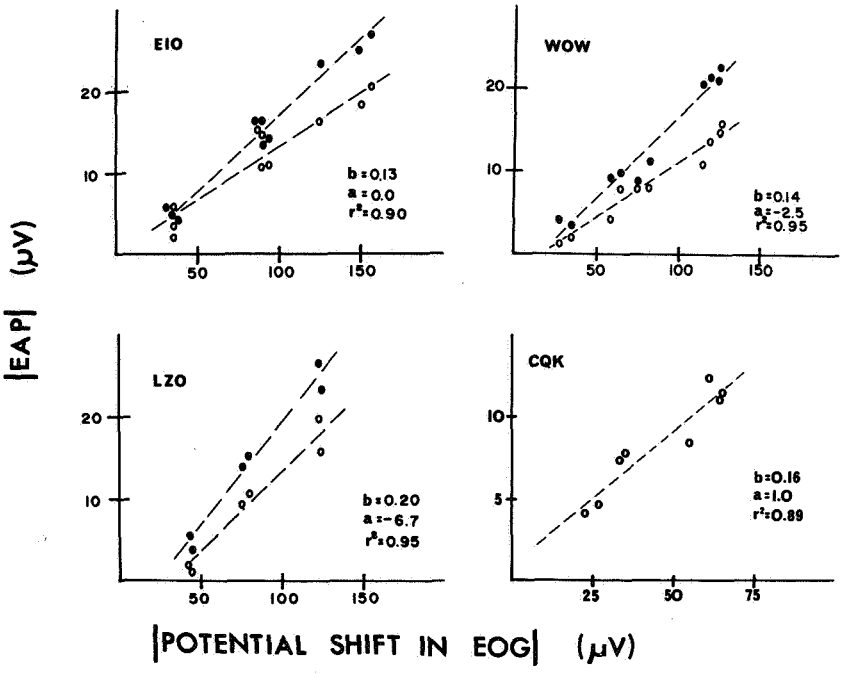

FIGURE 4–29.—Linear increase in eye-movement artifact (EAP) with increasing potential shift in the EOG, both induced by voluntary eye rotations. Parameters of best-fit lines: b=slope, a=intercept, r^2=Pearson correlation coefficient, squared. Solid circles: frontal-mastoid. Open circles: vertex-mastoid.

Within a given subject, however, there was considerable variability from trial to trial in the magnitude of the eye rotation (fig. 4–30). At times, the involuntary eye movements were downward, thus incrementing the tCNV; however, on other sets of trials, the EAPs were absent or even positive, thus partially cancelling out the tCNV. Eye movements introduced a tremendous amount of variability into the CNV, even under constant conditions. It is therefore possible that experimental manipulations, such as a change in the stimuli or task conditions, could produce change in the CNV, either by affecting oculomotor mechanisms (and the EAP) or by altering the tCNV.

Figure 4–31 gives a graphic illustration of how the eye artifact can affect what is recorded from the vertex. For each subject, three blocks of 12 trials are shown, selected and summed on the basis of the size of the concurrent EOG deflection. In the set of trials labelled A, the eye was rotated downward in subject McG; in B the eyes didn't rotate much, and in C the eyes rotated upwards, producing negative, zero, and positive EAPs, respectively. Notice the reduction in the CNV caused by positive EAP and its enhancement by negative EAP.

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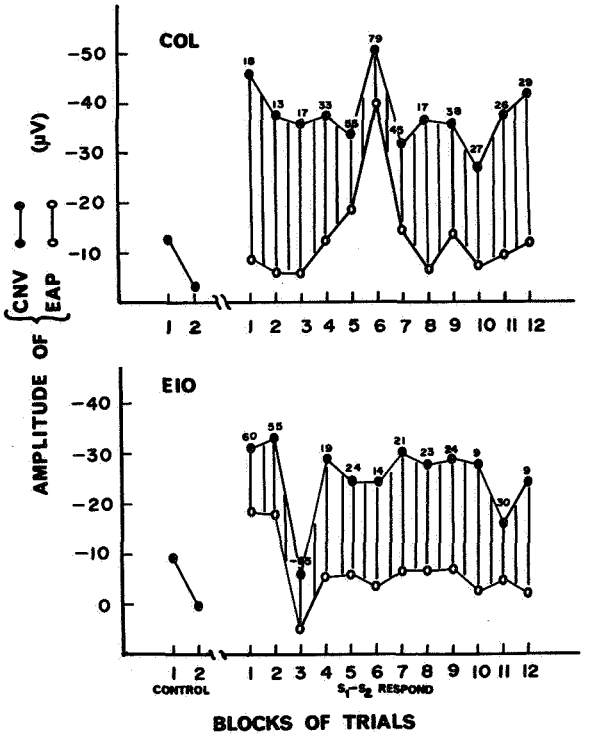

FIGURE 4–30.—Spontaneous variability to the CNV, broken down into EAP and tCNV (hatched area) components. Number above each point is the percentage of CNV comprised of EAP, or simply "percentage artifact".

The story is the same for subject EIO; CNV and EOG from three blocks of 12 trials are shown, and the CNV was progressively diminished as EAPs became more positive. In the frontal electrode, the EAP was larger than at the vertex for a given amount of eye rotation, while the tCNVs were smaller by about 25 percent.

These relationships are shown graphically in figure 4–32. In each subject, 96 trials were subdivided into blocks of 12 on the basis of the EOG deflections. The CNV amplitudes recorded from the vertex were a linear function of the eyeball rotation, which was indexed by the transorbital EOG.

One way to eliminate ocular artifacts was to perform the CNV experiments with the eyes fixated on a point. Typical CNVs recorded from four subjects with the eyes fixed are shown in figure 4–33; since the eyes did not move, these potential shifts represent only the tCNV component. In WOW and EIO, there was a small "twitch" in the EOG

after the click (S_1), which could have contaminated the click-evoked potential, but not the tCNV. Eye blinks frequently occurred after the lever press, causing large deflections in the EOG because of upward rotation of the ocular dipole. The resultant EAP caused the CNV to "cut off" more sharply than it would have if no blinks occurred.

The amplitudes of the tCNV that were recorded directly with the eyes fixated were equal to those of tCNV produced with the eyes closed and free to rotate, calculated by subtraction of the appropriate amounts of EAP. This equality substantiates the validity and accuracy with which the CNVs were partitioned into additive tCNV and EAP components.

Further studies were made of the relationship of the CNV and tCNV to the reaction time (RT) of the lever press (Hillyard, in press). Previously, it had been shown that an inverse relation between large CNV and short RT occurred in the context of acquisition of the CNV (Hillyard and Galambos, 1967; Walter, 1965a); that is, on the first few trials, before the subject had learned the S_1–S_2 association, the CNVs were small, and RTs were long. With practice, the CNV grew larger while RT decreased, thus producing a significant negative correlation over acquisition trials.

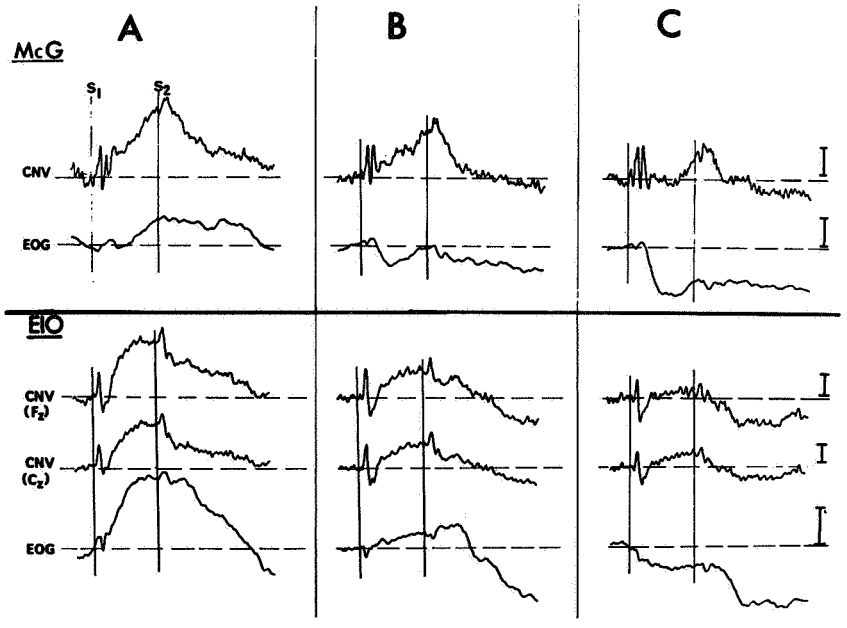

FIGURE 4–31.—Correlation of CNV amplitude with ocular potential shifts. Calibrations: CNV=20 μV, EOG=100 μV (negative up).

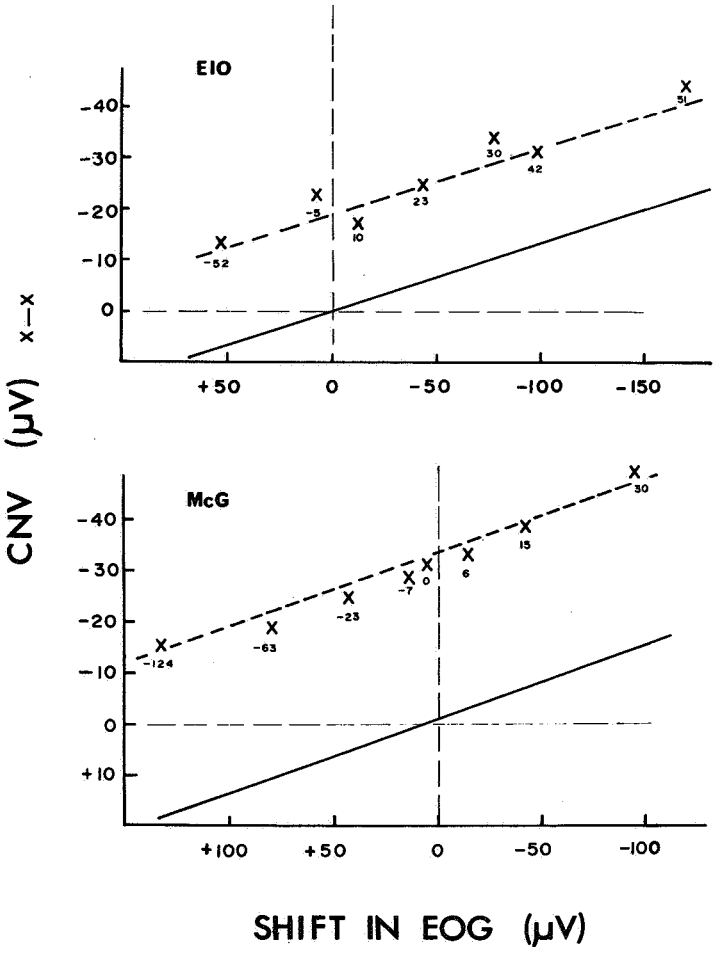

FIGURE 4–32.—Linear increase in CNV as a function of EOG deflections spontaneously produced. Solid line gives predicted value of EAP for given amount of EOG deflection.

I was interested in the trial-to-trial relationships between CNV and RT, within a long series of trials in which there was no net trend of increasing CNV or decreasing RT. A total of 96 trials was subdivided into blocks of 12 each on the basis of RT. The tape-recorded CNVs were summed together on each block as shown in figure 4–34.

The uppermost tracing is the averaged CNV from the 12 trials with the fastest RT, ranging from 104 to 148 msec. The second tracing is from the 12 trials with the next fastest RT, and so on. For this particular subject, CNVs were significantly smaller when RTs were longer, with RT fluctuating spontaneously on a trial-to-trial basis.

Eye movements were very small in this subject, and the tracings contain only tCNV. A second procedure was to consider 15 pairs of immediately adjacent trials, one of which had a fast RT while the other had a much slower RT, and sum the two sets of CNV separately. The tCNV was significantly larger on the trials with the faster RT ($-26.9\ \mu V$ versus $-13.2\ \mu V$), even though the two kinds of trials occurred within seconds of each other. There seems to be a moment-to-moment fluctuation of a response-governing process, resembling concentration or attention, which is reflected in the amplitude of the tCNV. In many subjects, the tCNV amplitude could serve as a predictor of the RT of the ensuing motor response.

This inverse relationship between tCNV and RT is plotted in five subjects in figure 4–35. The CNV were averaged in blocks of 12 trials, and the mean tCNV is plotted against the median RT (msec) of the 12 trials. In each case, there was a statistically significant negative correlation. This analysis was made on ten subjects, but only in these five did a significant correlation emerge between tCNV and RT. I have no good explanation why some subjects did not display the correlation, but they did tend to have RTs that were somewhat faster and more narrowly distributed, and/or tCNVs that were smaller and less variable.

DR. WALTER: Could I ask a question on this figure? The line con-

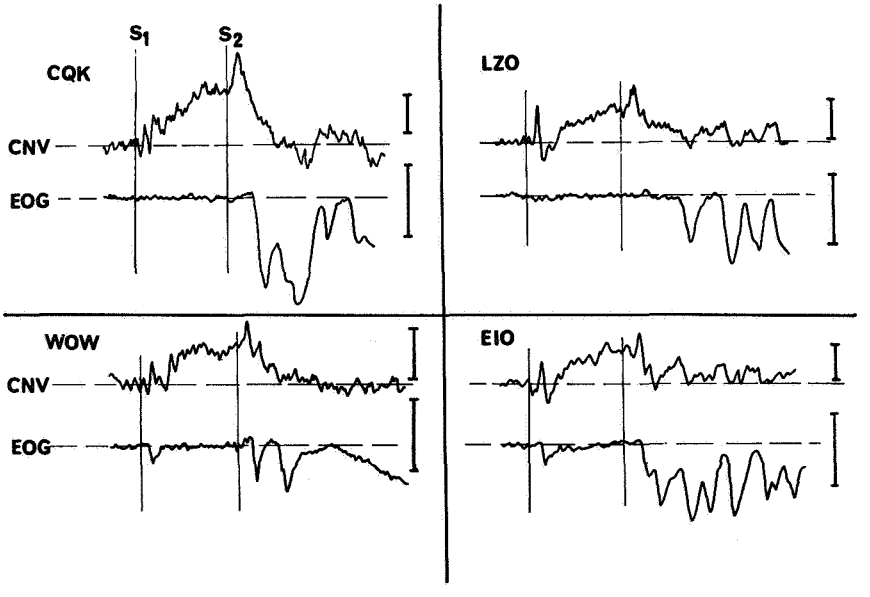

FIGURE 4–33.—CNVs recorded with eyes fixated. EOG deflections and EAP are negligible. Calibrations: CNV=20μV, EOG=100 μV.

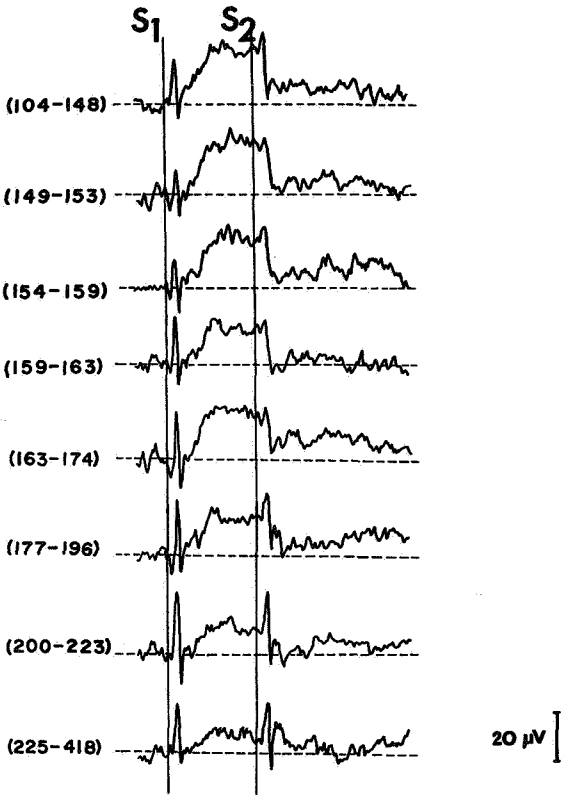

FIGURE 4–34.—Correlation between spontaneous variability in RT and the amplitude of CNV preceding the motor response. Each tracing is the average of CNV from 12 trials, having the range of RT shown at left in msec (negative up).

necting the x does not really imply anything about sequence. Is that just so you can find all the x?

DR. HILLYARD: Yes; RT and CNV of different magnitudes were distributed evenly throughout the series of trials. Therefore, the speed of RT was independent of sequential position.

DR. CALLAWAY: I want to ask Dr. Vaughan a question concerning that figure. Do you think that if you had averaged backwards from the response that this would have disappeared?

DR. VAUGHAN: I would like to ask Dr. Hillyard if he did that.

DR. HILLYARD: As I understand your argument, it is that there is greater variability in RTs that are longer, and hence the peak latencies of CNV associated with longer RTs would be more dispersed in time relative to the triggered epoch of computer averaging. Thus, CNV

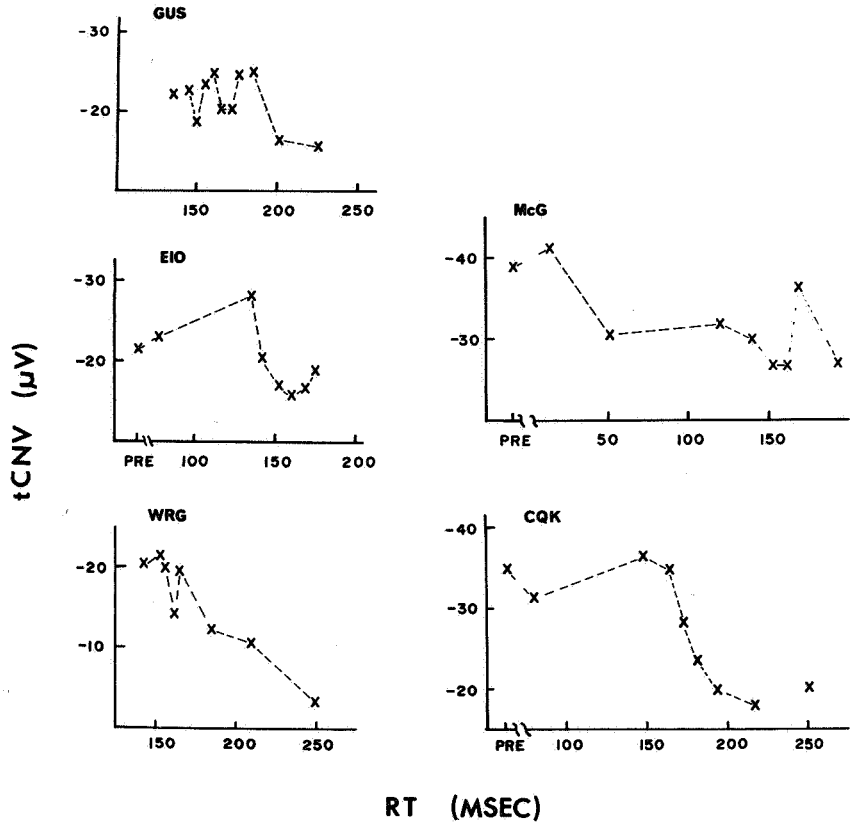

FIGURE 4–35.—Various forms of the relationship between increasing RT and decreasing tCNV in five different subjects. "Pre" indicates trials on which erroneous, premature lever presses were made before the onset of S.

of variable latency would not sum to their full amplitude because of reduced time-locking of the response with the averaging epoch.

DR. VAUGHAN: This is true. It may not be the whole story. It may be that there is in addition, of course, a true relationship between speed and the CNV.

DR. HILLYARD: I don't believe that that criticism applies to these data, because the CNV were summed in blocks having relatively constant response latencies (RT); this is equivalent to summing with the lever press used as the time-locked reference point. Furthermore, the CNV waveforms shown in figure 4–34 had reached plateau amplitudes well before S_2 arrived, and a plateau is not reduced in amplitude upon averaging by small desynchronizations of time-locking. Also, the difference in magnitude between "fast" and "slow" CNV was so great that a small failure of time-locking could not have accounted for it.

DR. LINDSLEY: In the first records that you showed us, what was the subject instructed to do with his eyes? Were his eyes closed, was he in the dark, or what? You had him fixating, and there was no oculogram during the first part, during the S_1–S_2 interval. What was he doing when there was correspondence between the oculogram and the CNV?

DR. HILLYARD: The only instructions given were to press the lever as fast as he could.

DR. LINDSLEY: What were the eyes doing? Were the eyes closed, or were they fixating something?

DR. HILLYARD: The eyes were closed. Systematic involuntary eye movements only occur when the eyes are closed, and the large correlation between the CNV and the EOG deflection is seen only then. If the eyes are open but not fixated, there will be irregular eye movements that are not closely synchronized with the CNV, but nonetheless can contribute artifact to it.

DR. COHEN: When you determined eye movement effects on the vertex, what were the instructions to the subject to determine the eye artifact on the vertex?

DR. HILLYARD: I had them make small square-waves of eyeball rotation; the eyes were rotated downward at S_1 and upward at S_2. This produced a square-wave deflection in the EOG, with its amplitude and polarity dependent upon the direction and extent of the eye movement. A square-wave of EAP was concurrently induced in the vertex-mastoid montage, at a reduced level of amplitude, of course.

DR. COHEN: That sounded very similar to one of my records (fig. 4–13) where the instruction was to move the eyes, and this produced a true CNV.

DR. HILLYARD: That is right.

DR. COHEN: So it may be very possible that some of your eye movement effect at the vertex is true CNV, in addition to possible ocular movements.

DR. HILLYARD: That is correct; the total potential shift induced at the vertex by voluntary eye movements is a composite of EAP and tCNV. The magnitude of the EAP depends upon the size of eye movement and is completely independent from the tCNV, which is increased when eye movements are made with greater speed and vigor. The details of the separation of the potential shifts during eye movements into the EAP and the tCNV are somewhat complicated (Hillyard and Galambos, in press), and I didn't want to go into that here.

CHAPTER 5

Data Analysis Techniques in Average Evoked Potential Research

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INTRODUCTION

THE PURPOSE of most studies of the average evoked potential (AEP) is to determine the extent to which the complex waveform of the AEP varies with the parameters of the stimulation, the state of the subject, and the recording site. Data analysis techniques in AEP research should, therefore, provide for reliable, objective, and easy-to-use methods for measuring and specifying differences between any two AEP. Statistical analysis provides us with a body of tools whose purpose is to allow the investigator to evaluate and judge differences of this nature. However, there are two major difficulties in applying classical statistical analysis to AEP data, namely, the fact that the AEP is a multidimensional observation and that more often than not the format in which the data are available is that of the graphic output of an averaging device.

The multidimensionality of the AEP makes it insufficient to state that two AEPs are "different"; this statement must always be supplemented by a more detailed specification of the difference. Thus, two AEPs might have identical waveshapes but different amplitudes; the difference might be limited to a small segment of the AEP, or the two AEPs might be virtually identical except for a major difference in one or more components. The differences might be caused by changes in the general waveform, or they might be caused by shifts in the latency of specific components. For these reasons, general statements that two AEP waveforms are different are relatively devoid of meaning.

Clearly, AEP analysis requires more than a simple technique for judging the significance of differences. What is required is a body of techniques that enables the source of the differences between any two AEP to be specified. Further, on occasion, the experimental hypothesis might predict very specific differences, and it should be possible to test such a specific hypothesis. There are, of course, statistical techniques designed specifically to handle such multidimensional data; however, their application and use in this field are quite rare. To a large extent, the meager use of statistical analysis in the AEP field results from the predominant role that the special-purpose averaging computer plays in our research.

Using a "CAT" type computer, the investigator has access only to the AEP waveform obtained as a culmination of the averaging process. This immediately eliminates the possibility of applying any analysis that evaluates differences in terms of the variability in the data, which, after all, is what statistical analysis is all about. Furthermore, only the analog output of the computer is easily available as an X–Y plot of the AEP. Most averagers do provide a digital output; however, the conversion of this output to computer-compatible format is a fairly complex procedure requiring rather expensive equipment. Thus, any numerical representation of the AEP waveform that is required for statistical analysis of the data must be obtained by direct measurement from the X–Y plots.

TECHNIQUES BASED ON X–Y PLOTS

For these reasons, the two data analysis techniques used most often in AEP research are (1) visual inspection of the AEP records in an attempt to detect similarities and differences and (2) the measurement of peak-to-peak amplitudes and the latencies of various evoked response components. The definition of the components (namely, the decision concerning which specific amplitudes should be measured) is usually determined by visual inspection of the X–Y plots. However, after the measurements are made, the obtained values serve to represent the evoked response, and subsequent analysis assumes that these are the primary data.

In many cases when the experimental questions are simple and the results are sufficiently unambiguous, examination of two AEPs suffices as evidence of their similarity or difference. When two AEPs coincide perfectly or when a large discrepancy between them is immediately apparent, there is little need of recourse to statistical analysis. In fact, a display of part of the AEP data for perusal by the reader is desirable in all publications, if only in the interest of facilitating interlaboratory comparisons.

There are, however, considerable and obvious drawbacks to the use

of visual inspection in AEP research. The conclusions drawn from such an inspection are subjective, and as the questions raised in AEP experiments become more complex, agreement on whether differences are "large" will become more difficult to achieve. Furthermore, there is a limit to the number of simultaneous visual comparisons that can be made at any time. Thus, only a small portion of the data collected in a study is actually used in the analysis presented in the published reports. Statements that the "data for other subjects are essentially similar to those shown" abound in the literature.

Another major drawback of visual inspection as an analysis technique is its failure to provide detailed information on the nature of the differences between the AEP. It is in the provision of information about specific differences that the second method mentioned earlier—the determination of amplitudes and latencies for different AEP components—is useful. This approach is particularly helpful in cases where the hypothesis can be stated specifically in terms of expected changes in one or two components. Much use of such measures was made, for example, in attempts to determine the functional dependence of AEP latencies on stimulus intensity and other stimulus parameters (e.g., Devoe et al., 1968). Clearly, the degree to which this is a useful method depends on the reliability and objectivity with which the evoked response component can be defined. The definition and identification of components by visual inspection is discussed in detail by Goff in chapter 3, and I shall not dwell on this matter.

Even if we assume that the definition of the components is flawless, there are grounds on which this approach is unsatisfactory. A not too trivial objection is the fact that applying this technique requires that the experimenter derive from the graphic output of the averager information that is, in fact, available to him in the computer before the plots are made. Thus, if the information could be made available directly from a computer, much labor would be saved. What is more important is the need to devise analysis techniques that provide a basis for the evaluation of AEP differences with respect to the intersubject and intrasubject variability, as well as with respect to the intersession variability in the data. The raw data required for such an analysis must be available in a form that is amenable to numerical manipulation. Ideally, the "single trial" data should be available in a manageable form. By "single trial data" I mean the segment of the EEG record that immediately follows the stimulus. I shall assume in the following discussion that such segments are always of the same length and that when digitized they are always digitized at the same rate. Such data are conveniently obtained with a small general-purpose digital computer. These devices, when equipped with an analog-to-digital converter, can perform as a powerful averager, when the single-

trial data are digitized and brought into core storage. In addition, it is relatively easy to store the single-trial data on magnetic tape for subsequent retrieval for the purpose of statistical analysis. In view of the fact that the cost of general-purpose computers is currently undergoing a major decline, while the cost of special-purpose averagers has not changed substantially in the last 5 years, it is to be expected that an increasing number of laboratories will be equipped to obtain the data in forms that would allow a very detailed analysis of AEP data matrices. In the remainder of this report, I shall review some of the problems encountered in applying statistical analysis to such matrices and describe briefly some of the techniques that have been proposed to date.

THE AEP AS A MULTIVARIATE OBSERVATION

The body of statistical techniques appropriate for use with AEP data is known as multivariate statistical analysis (MVA) (Anderson, 1958; Seal, 1964; Rulon et al., 1967). Multivariate analysis is applied to multivariate observations. An observation is multivariate when, for each of the observed objects, measurements are made on a number of different variables. Thus, for example, a student's scores on a number of different tests are a multivariate observation on his performance. Multivariate techniques are applied when a proper understanding or utilization of the data requires an understanding of the interrelationships between the variables, in particular when a considerable degree of interaction can be expected. When no such interaction exists, it is, in fact, appropriate and easier to study each variable separately.

The AEP can be considered as a multivariate observation if we consider the successive time points at which measurements are made on the AEP as different variables. Consider a typical AEP experiment in which n different stimuli are presented to a subject. For each presentation of the stimulus, a series of voltage measurements are made between a pair of electrodes. The measurements are made at m equally spaced points in time (time points), with time measured from the onset of the stimulus. Thus, with each stimulus presentation, an ordered series of numbers can be associated—$x(111) \cdots x(ijt) \cdots x(npm)$, where $i=1, n$ represents the n stimuli, $j=1, p$ represents the p presentations of the stimulus, $t=1$, and m represents the m time points. We can consider the m time points as m different variables, each variable defined as the voltage (between a pair of electrodes, etc.) recorded $m \cdot Dt$ msec following stimulus onset (where Dt is the interval in msec between two time points).

Thus, each EEG segment associated with a stimulus presentation is a multivariate observation, and appropriate statistical techniques

devised for these observations can be used. The catch, of course, is in the word "appropriate." As in all statistical techniques, numerous assumptions are made about the data before an analysis is applied. Furthermore, the technique must be selected for use with consideration of the experimental questions involved and with a hope that the conclusions will be interpretable in terms of the goals of the study.

It is helpful in understanding multivariate statistical analysis to consider its geometrical interpretation. Any ordered series of numbers—a vector—can be considered a point in a multidimensional space. Each variable (time point, in our case) represents one dimension in the space, and the measurement obtained for a given observation on this variable is the coordinate of the point representing this observation on that dimension. The location of a point in this space is thus specified by its set of coordinates on all the dimensions of the space. The notion of a multidimensional space is a natural extension of the familiar two-dimensional space, which is defined by two axes X and Y, and in which a point is located by a vector (x, y) specifying the coordinates of the points on each axis. It is impossible to describe graphically spaces of more than three dimensions, but the logical extension of the concept of "space" to a space of any number of dimensions is quite natural (Rao, 1965).

Given such a space, any set of single-trial records, or any set of AEP, is represented by a swarm of points in the space. The AEP is, in fact, the centroid of the swarm of points representing the set of single-trial records on which it is based. The problems of AEP analysis can be framed in terms of the geometry of multidimensional spaces, as questions about the relationships between points in this space. Thus the distances between points, the angles between any two vectors, the degree to which various swarms of points are differently dispersed in the space can be used, when appropriate, as measures of the similarity and difference between AEP. Each such application will require some specific assumptions about the distribution of points in the space and on the relationships between the various dimensions.

It is possible to develop some useful applications of MVA in this field by using some of the assumptions common to all AEP research, and on which the very use of the AEP as an estimate of the cortical evoked response depends. The assumptions are very simple. For each vector X with elements $x(ijt)$ defined earlier, we assume that each element can be described as

$$x(ijt) = s(it) + n(ijt).$$

In this model, $s(it)$ is a constant, independent of the replication index and depending on i, the stimulus index, and t, the time-point index. The term $n(ijt)$ is considered as representing samples of a random

variable, samples for nearby values of t being possibly correlated (hence a random process in t). The random process is assumed to have zero mean and a variance that does not depend on t. These assumptions imply that the mean and variance of the n process are independent at the time point t; also, since $s(it)$ is not a function of j, s and n are independent and hence uncorrelated at any lag.

Of course, all this jargon amounts to a restatement of our common assumption that each single-trial record is a sum of the evoked response to the stimulus and ongoing EEG activity that is unaffected by the presentation of the stimulus. It is this assumption that leads us to hope that when the data are run through the averaging mill the ongoing activity will "average out."

An additional assumption that is helpful in applying the analysis techniques, although not required as a basis for the averaging process, is that n is a normally distributed random process. If we are willing to accept this assumption, then the data in AEP experiments not only are multivariate observations, but also have the characteristic that they are multivariate observations with a multinormal distribution. Most MVA techniques easily available for use to date have been devised to deal with multinormal observations (Anderson, 1958; Morrison, 1967).

I have discussed elsewhere (Donchin, 1966) the degree to which these assumptions are tenable. All are to a large or small extent violated by the data. There are good reasons to doubt the independence of the evoked response from the ongoing activity, to question the constancy of the variance along the time points, to doubt the constancy of the evoked response from trial to trial, as well as to question the degree to which the data are indeed normally distributed about the derived average. There is, at the same time, evidence indicating that the deviation of the data from the assumption is not necessarily great enough to invalidate the application of these techniques. Essentially, the issue is not that of the absoluteness of the propriety of the assumptions so much as the degree of robustness of the statistical analysis to deviations from the assumptions of the magnitude observed. It is noteworthy that so far no significant modification in any of the statements that have been made about average evoked potentials had to be modified for reasons relating to deviations from the classical model of the evoked response data. For example, it is easy to show that the variance is not constant from one time point to another; however, no evidence available to date demonstrates that this fact led to erroneous conclusions about any two AEP.

ON REDUCING DIMENSIONALITY AND IDENTIFYING COMPONENTS

When the data define points in a multidimensional space, it is al-

ways tempting to try to reduce the dimensionality of the space. In essence, whenever the peak-to-peak amplitude of an AEP component is measured and the data are then characterized in terms of this amplitude, steps for a reduction of dimensionality have been taken. The single number, peak-to-peak amplitude replaces a set of, say, 100 numbers that were previously used to characterize that component. Thus the data were transformed from a 100-dimensional space to a 1-dimensional space. At the root of the operation is the conviction that all the information contained in the 100 measurements that originally represented the component is represented adequately by the amplitude measure. This requires one to ignore the speed with which the amplitude is reached, small "shoulders" that ride on the component, and other bits and pieces of information that might be of some use. But it appears reasonable to avoid the distraction of small details if it can be shown that the major differences between AEP that are related to the experimental questions are described sufficiently by the amplitudes, latencies, or some other characteristic of the component.

The intuitive reduction in dimensionality described has a natural counterpart within the framework of the multidimensional model. The reduction in dimensionality is performed in this context by linear combinations of the dimensions that give a description of the data without losing any of the information. There are many different ways in which such linear combinations can be determined—and for different tasks, different ones are appropriate.

The notion of reducing dimensionality by a linear combination of the dimensions is basic to the familiar operation of defining regression lines. Suppose a variable y is measured for different values of a second variable x. Each observation is then characterized by the vector (x, y) as a point in a two-dimensional space. However, if all the points fall on, or very close to, a straight line in that space, it is possible to describe the data in a one-dimensional space—a line whose equation $ay+bx+c=0$ is a linear combination of the two dimensions of the space. Thus, by forming a linear combination in the two-dimensional space, we have reduced it to one dimension.

These concepts can, of course, be expanded to any number of dimensions. Three-dimensional space can be reduced, the data permitting, to two- or one-dimensional spaces, and multidimensional spaces with n dimensions can be reduced to m dimensional spaces ($m<n$) with the considerable reduction and economy of presentation of the data that comes with such a reduction.

There is an infinite number of ways to reduce the number of dimensions in an evoked potential data matrix. Each depends on the criteria that the linear combinations must satisfy. For example, in reducing a two-dimensional plane to a line by regression analysis, we

require that the line be such that the mean square deviation between the line and the data be minimal; the least-squares line is thus obtained. However, if we desire a line that minimizes the absolute error or satisfies some other criterion, a different line will be obtained. None of the different lines is better or worse except to the degree to which it satisfies the requirements imposed when we set out to compute it. It is important to remember this fact because the apparent arbitrariness of the results of MVA derives from the fact that different questions require examination of the data from different vantage points.

In trying to reduce the dimensionability of a space, it is possible to start with a selected set of orthogonal functions and to fit such a set to the data. This approach has been taken by Freeman, who fits a set of damped sinusoids to the data that he records in an extensive investigation of the electrophysiology of the prepyriform cortex of the cat (Freeman, 1962a, b, c; 1964; 1968a, b). Essentially, Freeman shows that the prepyriform AEP can be regarded as the sum of noise plus two dampened sinusoids, each having an equation characterized by a number of parameters; the AEP are analyzed in terms of the empirical values determined for the parameters from the data. In the series of papers cited, Freeman puts these parameters to use, in evaluation of predictions from a model for the AEP-generating process, as well as for an evaluation of the effects of stimulus intensity, habituation, and other variables on the AEP.

Another approach, principal component analysis (PC), is unlike Freeman's approach in two ways; PC does not assume any special form (such as damped sinusoids) for the components, and it produces orthogonal axes in the reduced space. Its application to AEP data has been described in detail by John et al. (1964), Ruchkin et al. (1964), and Donchin (1966). Raviv and Streeter (1965), in a somewhat inaccessible report, have also discussed its application to AEP data. Their report is particularly interesting in that it presents, in detail, the mathematical background of the application of PC analysis to these data. In fact, by pointing out the identity of PC analysis to the Karhumen-Loeve expansion, they bridge the gap between the classical spectral representation of the data and PC analysis. Karhumen-Loeve analysis ". . . may be thought of as a generalized spectral representation of a random process. In this generalized representation, the components are not limited to the family of sinusoids but instead are chosen on the basis of economical approximation" (Raviv and Streeter, 1965, p. 8).

The "economies" involved in PC analysis can be defined as follows: the dimensions on which the data are described are so selected that the first dimension accounts for the maximum possible variance in the data; additional components are selected to account for additional

portions of the residual variance, with the restriction that all the dimensions be orthogonal. It is possible to conceive of the dimensions obtained under this procedure as good estimates of the AEP components commonly determined by visual inspection. Some examples of this application have been provided by Donchin (1966), Duffy and Lombroso (1968), and Glaser and Sutter (personal communication).

Another approach to the reduction in the dimensionality of the data has been taken by Lehman and Fender (1968). These investigators approximate each AEP waveform by means of a set of Gaussian curves (the well-known bell-shaped normal distribution). The details of their technique have not been described in the paper cited. In essence, it involves an iterative procedure in which Gaussian curves are fitted to the data following these criteria: (1) The first Gaussian will be fitted so that its mean will be aligned with the biggest peak-to-peak amplitude in the AEP. (2) The goodness-of-fit criteria for the Gaussian is derived from the variances around the AEP. (3) Each successive Gaussian is then fitted to provide for some of the variance left after the earlier Gaussians were fitted. The AEP waveform is then described by the set of parameters representing the Gaussian curves (the mean and the standard deviation of each Gaussian). The technique has the virtue that it conforms to the intuitive approach used in measuring evoked potential characteristics. It thus places the measurement of amplitudes and latencies on a more solid basis as well as allowing for an essential automation of this procedure, making it less vulnerable to biased judgments.

There is a common difficulty to all of these techniques that derives from the fact that some independent variables affect the AEP by producing a shift in the latency of the various components. Consider a series of AEP that have an identical waveshape of an identical amplitude, but each successive AEP being shifted by 20 to 50 msec along the time scale. When the time points are used as the variables in a PC analysis, or when any series of orthogonal functions is fitted to the data, it must account, in terms of AEP shape, for a certain percentage of the variance that is caused by the shifts in latency (and thus are unrelated to the waveshape). The outcome in this case would be to increase the number of dimensions required to describe the data. Thus when there is a strong possibility that the latency of the AEP is changed by the experimental variables, a spurious increase in the number of dimensions is to be expected. There is, at present, no solution to this particular problem. Ruchkin (personal communication) has suggested that a thesis by Bennett (1965) provides a means for determining the proper number of dimensions, but it does not provide for a means for estimating the dimensions. It should be noted that the latency shifts affect the interpretation of AEP components even when the com-

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ponents are derived by visual inspection. Thus it is quite easy to confuse the appearance of "late" components that are related to changes in the task of the subject as the experimental conditions are changed with "earlier" components that have been shifted in latency as a function of other changes in stimulus parameters (Donchin, 1968).

It is important to note that all of the attempts to reduce the dimensionality of the multidimensional space defined by the time points over which the AEP is measured concur that such a reduction is eminently possible. The consensus of all the studies cited earlier is that it is possible to obtain an adequate description of the AEP by using three to six dimensions. The agreement on the small number of dimensions is quite remarkable. It also has important implications for evoked potential research in general. In effect, it confirms the intuitive judgment used when the 100 to 400 measurements on that many time points are reduced to a small number of peak-to-peak amplitudes. It also points out the inadequacy of using analysis techniques that assume that all the measurements that constitute an AEP should be given equal weight in evaluating differences between AEP. This is particularly true for an often used measure of similarity between two AEP—the product moment correlation coefficient (Donchin and Lindsley, 1965; Callaway et al., 1965; Dustman and Beck, 1965).

Although the correlation coefficient has a certain intuitive appeal, it has two major drawbacks, namely, that it does not provide information on the source of the differences between AEP and that its interpretation depends on the assumption that all the dimensions on which the AEP was originally measured are independent.

The application of the correlation coefficient to AEP analysis views the AEP not as a measure of n different variables but as a set of n repeated measures on one variable; a second AEP is represented as another set of repeated measures, and the correlation between all the pairs of measurements at corresponding points is obtained. However, correlations usefully can be interpreted if the paired measurements used for their computation are a set of independent measures. But this, as the various component analyses demonstrate clearly, is an inappropriate assumption for the data. In fact, the various measures on successive time points are highly dependent. Thus correlations assumed to be based on several hundred degrees of freedom are, in fact, based on five or six degrees of freedom.

ANALYSIS OF SINGLE-TRIAL DATA

The application of any of the techniques described previously essentially supplements or replaces analysis techniques that are based on the analysis of the graphic output of the averager. Thus, they must prove their value in demonstrating an advantage over the classical techniques.

There are, however, a number of important experimental questions that can be resolved only by the application of multivariate statistical analysis. An excellent case in point is questions that require information on the relationship between the AEP and the single-trial record. It is well known that it is difficult, if not impossible, to determine the shape of evoked response in the single-trial record. This, of course, is the reason for averaging in the first place. The evoked response is swamped by the "noise" in the ongoing EEG; thus the detection of evoked responses and the determination of their waveform require averaging. In other words, there is so little information on the evoked response in each record that we must use an ensemble of records, and, by combining data from this ensemble, we can determine the shape and characteristics of the evoked response. However, the need to use an ensemble to get sufficient information on the detailed waveshape of the AEP should not obscure the fact that in each single-trial record there is a certain amount of information about the evoked response. It is possible that, on occasion, experimental questions arise for which this small amount of information is sufficient for an answer. This is particularly true when the information obtained from the ensemble of single-trial records is available. As an example, consider the following question. Suppose it has been established that there is clear-cut difference between the AEP obtained under two experimental conditions. This was established by obtaining two ensembles of single-trial records, recording the average, and determining by some of the methods discussed earlier that the two AEP are different.

Suppose we are now presented with a single record. We are told that while it is known that it was recorded in one of the two experimental conditions, it is not known in which of the two it was recorded. It is possible to determine the experimental condition by measuring the similarity between the two AEP typical of the condition and the single-trial record. This is a typical classification problem that has received much attention from statisticians (Kendall, 1957; Rao, 1965; Morrison, 1967; Rulon et al., 1967). Note also that classification requires less information than waveshape description. When one is asked to classify signals according to their source, it is assumed that information is available about the classes into which the signals are to be classified. Furthermore, there is no uncertainty about the presence of the signal in the cases to be classified. Detection of the presence of signals, particularly when their waveshape is not known, requires considerably more information. I am dwelling on this point because it is sometimes suggested that the single-trial record is noisy and therefore, there is no way of gaining any significant information from it. The confusion derives from the amount of information required for different decisions (Donchin, 1969).

DISCRIMINANT ANALYSIS IN AEP RESEARCH

The problem of measuring the deviation of an individual observation from a mean of a group is usually solved by means of the standard score. A standard score is a measure of the deviation of the observation from the mean, expressed in units of variability. The following is required for a study of individual observations: (1) a proper estimate of the group mean, (2) a measure of the "distance" between the group mean and the individual, and (3) a measure of variability in the group in whose units the distance can be expressed. Furthermore, if probability statements are sought about the observations, tenable assumptions about the distribution of the data must be made.

The multidimensional model described earlier provides a framework within which these desiderata can be obtained. Distance in the multidimensional space can be measured by the Euclidean distance which is equivalent to the Manalanobis D^2 (Rao, 1965). The determinant of the variance-covariance matrix can be used as a measure of the variability in the space. It is essentially a measure of the volume in the space encompassed by the swarm of points representing the ensemble. Thus a multivariate standard score can be determined for each single-trial record with respect to each AEP. With the usual assumptions, the probability can be determined that a given single-trial record will be obtained for any experimental condition that is characterized by a given ensemble with its AEP and dispersion in the space. The record then will be classified as belonging to that ensemble for which the smallest standard score was computed.

The computations required for obtaining these distance measures, as well as for the calculation of the associated probabilities, are performed as part of the computations required in developing a discriminant function. Discriminant Analysis is a classification technique that uses the data obtained from members of different groups whose group membership is known to derive criteria for the classification of observations whose group membership is doubtful. The classification is achieved by partitioning the multidimensional space in which the observations are located into a number of mutually exclusive regions. Each region is identified with one of the classification groups. The classification of newly observed points then depends on the region of space into which they fall. Like principal component analysis, discriminant analysis consists of the projection of points in multidimensional space onto a smaller dimensional space. The criterion for developing this projection is different in the two cases. While principal component analysis attempts to erect an orthogonal space to account for the smallest number of dimensions for the variance within the observed groups, discriminant analysis erects a space that attempts

to account for the variance between the groups. Raviv and Streeter (1965) have discussed in detail the similarities and differences between the two techniques as applied to AEP data, and Walter et al. (1967) have discussed the application of discriminant analysis to EEG data.

A useful refinement of discriminant analysis is the stepwise approach to its computation, which, in a sense, combines the advantages of both principal component analysis and discriminant analysis (Ralston and Wilf, 1960; Dixon, 1968). Stepwise analysis, in this case, provides for a reduction in the number of variables (time points) that are actually used for the analysis before the determination of the best way to perform the discrimination. Briefly, stepwise analysis proceeds as follows. A variable is selected that provides for the best possible discrimination between the two groups. After all the information correlated with this variable is removed, a second variable is selected; a discriminant function is then determined for the space defined by these two variables. The second variable is added only if its addition provides an improvement over the discrimination when based on one variable only. Additional variables are added similarly, the process terminating when no additional improvement in the classification procedure can be obtained with further inclusion of variables. (In the BMD 07M Program, the process is terminated when none of the F values computed for the unused variables exceeds a specified value). The outcome of this procedure is a discriminant function (a classification rule) that utilizes the smallest number of variables that are required to provide the best possible discrimination.

If principal component analysis and discriminant analysis are applied to the data, the variables that are found necessary for obtaining a good classification are those corresponding to the components identified by principal component analysis. Thus, for example, Donchin and Cohen (1967) found that the discrimination between AEP recorded to task-relevant and task-irrelevant stimuli is based essentially on time points at 300 msec, as well as on time points at 144, 48, 288, and 136 msec, with most of the discrimination based on the 300-msec time point. Figure 5–1 is a plot of the principal components obtained for the same data; and the component accounting for most of the variance indeed peaks at 300 msec. Such a relationship between the two analysis techniques implies that the major source of variance in the data is the "between-group" variance.

A useful application of discriminant analysis techniques to AEP data can be seen in the following example. Callaway (1966) has predicted that schizophrenic patients manifesting a certain syndrome will tend to persist in perceiving the difference between two tones—a 600-Hz and a 1000-Hz tone—longer than would normal subjects. He predicted that this difference in the ability to ignore

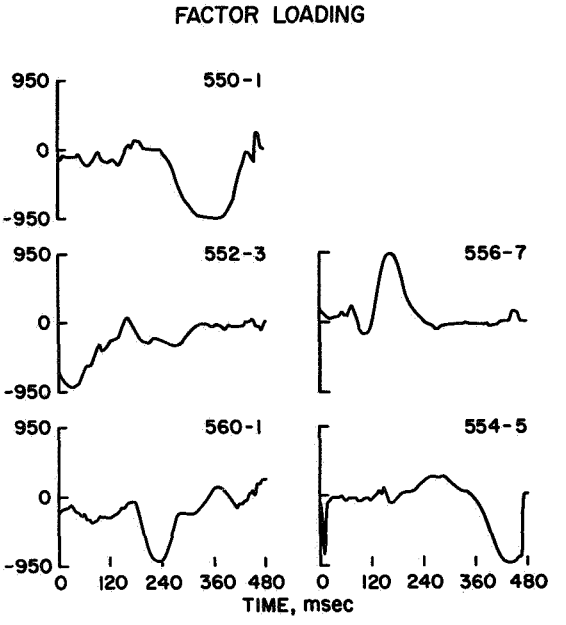


FIGURE 5–1.—Principal components of evoked-response data matrix. Data were obtained in a study of task-relevance and evoked responses. The major contribution to the variance is by the component labeled 560–1; successively smaller contributions are by the components labeled 552–3, 550–1, 554–5, 556–7.

trivial differences would lead to the following finding—the differences in the AEP to the two tones will be greater for the appropriate group of schizophrenic subjects than for an appropriate group of normal subjects.[1] To test this hypothesis, each of 20 subjects was presented with a randomly mixed series of the two tones and an equally long series of 1000-Hz tones. Evoked responses were obtained in the case of the two tones for each tone. When only one tone was presented, AEP were computed for two groups of 1000-Hz stimuli selected at random. Figure 5–2 presents the data for 4 out of the 40 sessions.[2] Two sessions at which the same tone was presented and two sessions at which only one tone was presented are shown. Summarizing these results by visual inspection of the records is quite difficult. Clearly, 600- and 1000-Hz tones evoked rather similar AEP in the subjects. There

[1] See Callaway's review (chapter 8) for a more detailed description of the rationale of his work.

[2] The data are presented here for illustrative purposes only. A detailed report of the study and its analysis are in preparation.

is no clear indication that the differences in the case of the two AEP representing the presentation of an identical stimulus (one-tone trials) are less pronounced than the differences apparent for AEP elicited by different stimuli (two-tone trials). It is apparent that the records obtained from the two patients show more AEP-to-AEP differences than the data obtained from the normal subjects. However, to say that these data present solid evidence for any contention whatsoever would be difficult indeed.

If the correlation coefficients between the two curves are computed, we obtain the following:

Subject 6 (Norm. 2-tone)	0.98
Subject 7 (Norm. 1-tone)	0.98
Subject 8 (Pat. 1-tone)	0.93
Subject 9 (Pat. 2-tone)	0.88

The correlations obtained for the patients are somewhat lower than those obtained for the normal subjects. However, there is no orderly way in which the one-tone/two-tone distinction is represented

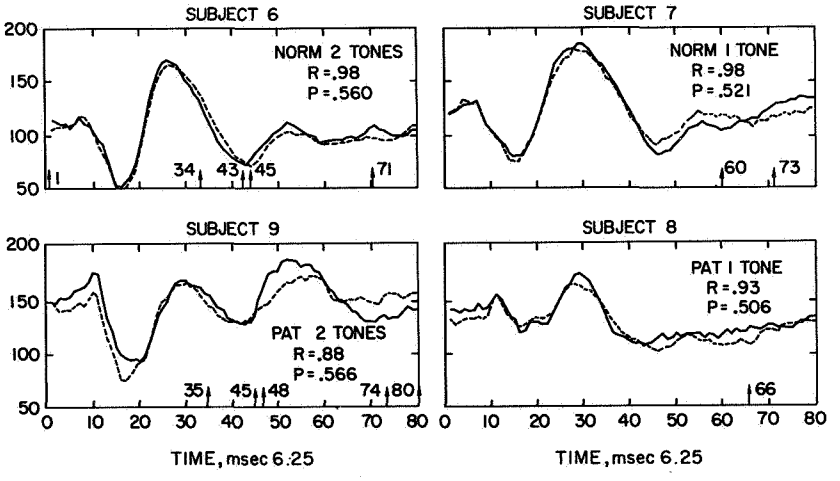


FIGURE 5–2.—Average evoked responses obtained in the two-tone discrimination study. For two-tone sessions, the dashed line represents an evoked response to a 600-Hz tone, and the solid line an evoked response to a 1000-Hz tone. For one-tone sessions, the two lines represent two evoked responses to the same (1000-Hz) tone. Subjects were either "normal" (Norm.) or "schizophrenic" (Pat.). The numbers labeled R are the product moment correlations between the two evoked responses. The numbers labeled P are the mean probability of correct classification for the single trial data. The arrows on the abscissa represent the variables selected by the discriminant analysis program for use with the data. The abscissa represents 80 time points, the interpoint distance being 6.25 msec (negative up).

by the correlations. Furthermore, the differences between the coefficients are not impressive, and it is somewhat difficult to determine which evoked response components are associated with the difference. In fact, the data presented for subjects 8 and 9 suggest that the correlation is affected by events at the later part of the displayed AEP.

When discriminant analysis is applied to the data, a number of interesting details begin to emerge. For the purpose of this analysis, the data are divided in two groups—two ensembles of 140 single records each representing, for each session, data used in the computation of the two AEP. By applying the discriminant analysis program (BMD 07M in Dixon, 1965), we determine two things: (1) The variables required to produce the best possible discriminant function that would allow a decision concerning which of the two tones was presented, and (2) for each of the single-trial records, an estimate of the probability that it was elicited by either of the tones. The probability is derived essentially from a multivariate standard score and the assumption that we are dealing with two multinormal populations (having identical variance-covariance matrices).

On the abscissa of each curve presented in figure 5–2, I have indicated the variables used to provide a proper discrimination. For the curves for the one-tone sessions (that is, where the two curves represent replications of the "same" AEP), discriminant analysis suggests

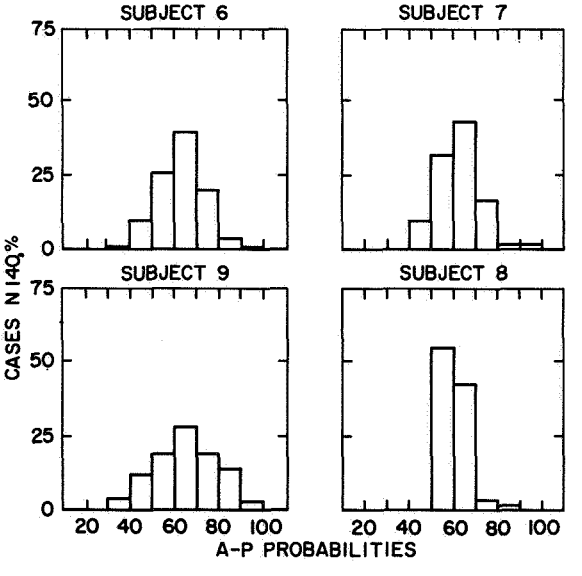


FIGURE 5–3.—Distribution of the probability of correct classification for the single-trial data obtained with the 1000-Hz tones. See text for details.

a very poor discrimination. Only one or two variables are selected. In both cases the variables selected are at a very late segment of the AEP.

On the other hand, five or six variables are selected for comparisons between the AEP representing two different tones. The variables selected in this case represent time points ranging from the 30th to the 45th variable (180 to 280 msec). Thus, on the basis of these analyses and similar ones done for the other subjects, it can be said that a discriminant is developed from the two-tone trials, but is not developed for the one-tone trials, suggesting that there are significant differences between the AEP elicited by the two tones and that these differences are associated mainly with the time points between 180 to 280 msec.

A further look at the data is possible if we consider the distribution of the a-posteriori (A–P) probabilities shown in figure 5–3. Each of the single-trial records is assigned an A–P probability for each of the groups used in the classification. Thus, for the data discussed here, each single-trial record is assigned two A–P probabilities. The A–P probability assigned to record j for group k is the probability that a record such as j would be obtained by a process of random sampling if the population sampled is characterized by a mean such as the AEP for group k, and a variance-covariance matrix characterizing group k. When the two groups used in the classification are clealy distinct (the means are well separated in the n-space, and the dispersions are relatively small), the A–P probabilities would be high. Most of the records identified (a priori) as belonging to group k will be assigned high A–P probalities for group k, and small A–P probabilities for the other groups.

When the groups are not clearly distinct, the A–P probabilities would tend to have values in the neighborhood of 0.50, indicating that the classification is difficult and that any observation is as likely to belong to group k as to any other group. Thus, the A–P probabilities might be used as normalized measures of the distance between a given single-trial record and a given AEP. In addition, the distribution of A–P probabilities for all records of group k provides information on the distinctness of the single-trial groups obtained in the experiment. When the AEP are clearly different, the distributions would have a negative skew, with most probabilities ranging over 0.75. On the other hand, when there is a small difference between the two (or more) AEP, the probabilities would be close to 0.50.

The mean of the probability distribution histogram and its variance, although distorted by the skew, can serve as indicators of the degree of separation between the two swarms of points in the multidimensional space that represent the two ensembles. Thus, for example, when two subjects with considerably different AEP waveforms are compared,

the mean probabilities range from 0.68 to 0.90, and the standard deviations are of the order of 0.30, for the data presented in figure 5–3, the two histograms representing one-tone trials, the histogram is concentrated between 0.50 and 0.60, and the mean probabilities are 0.50 and 0.52. In the case of the two-tone data, the distributions are more skewed, and the mean probabilities are 0.54 and 0.56. In general, we find that for 19 of the 20 subjects of this study, the probability associated with the two-tone trials is higher than that associated with the one-tone trials. This differentiation between the two experimental conditions is reinforced by the fact that in the case of the one-tone data, the probability is based on just one or two variables from the later segments of the EEG.

It is beyond the scope of this report to discuss the substantive implications of these results. It has been my purpose here to demonstrate the fact that examining closely the data and using multivariate statistical techniques can provide information on the structure of the data that is not easily available by the usual means by which these data are analyzed. While the analysis can provide more information, it cannot assure that any deeper insights will be obtained from the data. There are at present no insight-enhancing techniques that can be covered by this review.

Several other techniques have been proposed for the analysis of single-trial data. One which has potentially wide usefulness has been described by Ruchkin (1968), who has proposed a method for detecting inhomogeneities in a long series of single-trial records. Essentially, his technique is an extension of the work by Burns and Melzack (1966); see also Burns et al., 1967, who have suggested that it follows from the classical assumptions used in evoked potential research, which were enumerated earlier, that the cumulative sum of amplitudes at any time point is a linear function of the trial number. A sharp break in this line implies that the evoked response has changed in value at the breakpoint. A graphic analog of this technique has been described by Tepas and Armington (1962), who suggested that a repeated plot on a contracted time scale of the successive evoked responses would indicate whether the AEP is growing linearly with the trials.

Ruchkin's contribution has been to provide a statistic (PRECUM) that allows a determination of the time points along an AEP at which such breakpoints might be observed. The statistic is an estimate at each time point of the deviations between the predicted and the observed cumulative curves. With the use of PRECUM, time points along the AEP at which inhomogeneities occur are determined, and a detailed study at the cumulative curve at these points in the manner suggested by Burns and Melzak can be undertaken. In his report of this technique, Ruchkin provides a number of examples concerning the useful-

ness of this statistic as well as a computing algorithm. It must be remembered when PRECUM is applied that it is appropriate only for detecting serially occurring inhomogeneities in the single-trial progression. Thus, if two single-trial samples representing two different AEP are mixed at random, PRECUM will indicate no inhomogeneities in the data.

Other approaches (e.g., Palmer et al., 1966; Woody, 1967) to the analysis of single-trial data have been suggested. Galbraith (1967) has proposed an ingenious technique for selecting single trials for analysis as a function of the "coupling" between different brain structures. In all cases, the analysis requires access to the raw data of the AEP study in the form of digitized single-trial records. There is little doubt that no single method would provide a panacea for all the problems that arise in evoked potential research. However, it is also clear that the limits imposed by the special-purpose averaging device should not be as confining as they have been in the past.

It has been my purpose in this review to indicate some of the possible applications of statistical analysis to AEP research, going beyond the measurements of features of the X–Y plot. Whether such applications will become prevalent depends essentially on the degree to which it can be shown that their use is not only statistically elegant but also that it yields a return unavailable by other methods. It is thus incumbent on those of us who are interested in the analysis of AEP not to be content with a suggestion of proper and available techniques but, to demonstrate their use in actual studies.

DISCUSSION

DR. WALTER: I too think discriminant analysis is a good thing, and both Donchin and I have been using a program that should be acknowledged because not all discriminant analyses are identical. It is acknowledged in his paper, but I wanted to reiterate that this is all based on the BMD 07M program, which is based on statistical theory developed by many statisticians (Rao, Mahalanobis, Anderson, and others); however, the actual success in putting the various options together really results from the cooperative effort of Dixon, Jennrich, and Sampson at the Health Sciences Computing Facility at UCLA (Dixon, 1968).

If you are comparing two numbers, you can subtract them and observe the sign of the difference; if you are comparing samples from two stochastic variables whose distributions overlap noticeably, you must use a more sophisticated technique; we have seen a few examples of that. However, when comparing realizations of two triggered stochastic processes whose distributions overlap noticeably, you must use techniques such as discriminant analysis.

I want to present another example in which the differences between evoked potentials, or evoked current records, in two different situations are such that you cannot determine whether they are different by visual inspection.

Figure 5–4 is taken from a study that is just being finished by Mr. Martin Gardiner. A brief report on this project is contained in the supplement to this volume as an example of a study in which discriminant analysis techniques have been very helpful. I wish to describe some of the details of an application of the calculations provided by the discriminant analysis program that have not been described by Dr. Donchin, and which Mr. Gardiner has found to be very useful in his study. In the example shown here, the AEP are compared for tone bursts of two slightly different loudnesses, as recorded during a task in which the subjects were attempting to determine each time a stimulus was received, which of the two possible loudnesses was presented. The potentials evoked by loud and soft tones are shown in solid and dashed lines, respectively.

Surely the curves differ; but by how much? We didn't plot the variances around these averages; however, if we had, it would have been obvious that there was immense overlap. Therefore, the question is, again, how trustworthy are the differences shown?

The BMD 07M program computes, among many other things, F ratios for the probability that the difference between means at each time-point could have arisen by chance (F_0 in our figure); under the assumption that the whole world is joint-Gaussian distributed, these F ratios can be converted into probabilities. In one way, those are not very important; however, they show how significant the differences would be if the world were so distributed.

One feature worth noting is that the highest peak in the F_0 function (whose great height may perhaps in part be a sampling fluctuation) occurs at a delay—I should not say "latency" since I have tried to convince everyone to use some other word—which is rather long (about 400 msec) in terms of some of the evoked potential components that we have heard about today. However, an additional apparent feature of the F_0 curve (that is, the plot of the F ratios as a function of delay after stimulus) is its appearance of periodicity. Periodicity is in one sense an indisputable description of this F_0 curve, but these differences are independently distributed. We know this, because, after evaluating the F_0, the program selects the delay showing the greatest F, and "says", in effect, "If I had to build a discriminant function with just one time point, I would choose this one." Then it performs a regression of all of the data on the value at this delay time so that each evoked current record is compensated for whatever can be predicted by linear regression on the basis of the

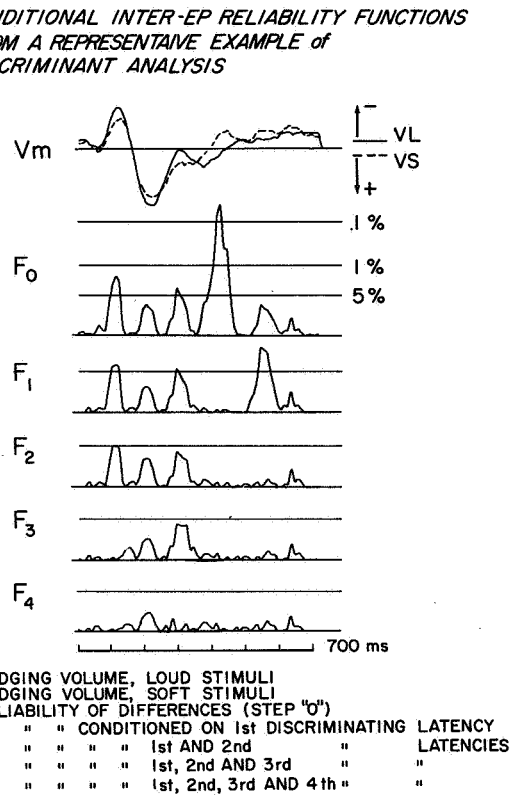


FIGURE 5–4.—F Tests from a two-group discriminant analysis in an evoked potential study (from Gardiner, 1969). Vm: Average evoked potentials recorded with a vertex-mastoid derivation. Each trace shows evoked potentials for 710 msec following stimulus onset. Negativity is indicated by an upward deflection. VL, VS: Two evoked potentials under comparison. F_0: F statistic is calculated at 10-msec intervals, commencing with stimulus presentation, and then a smooth curve is drawn connecting the outcomes from these calculations. Confidence levels are for F for normal distribution; F1, . . ., F4. conditional F, showing that VL vs VS differences at nearby latencies (within "mountains" of the F_0 function) are correlated, but that at separated latencies are relatively uncorrelated (see text).

value observed at this particular delay; the F ratios then are recomputed with a slight adjustment in the degrees of freedom. The major observation about the F_1 curve is that there is relatively little change in the improbabilities that are attributed to each of these events except

near the selected delay, where everything is reduced. Thus, everything in the F_0 curve in the peak around 400 msec does covary with the values at the selected delay time.

In the next step, the program selects the delay with the maximal F_1 point and says, in effect "If I had to make a discriminant function based on just two delays after stimulus, I would choose this one and this one," and proceeds to do that, to perform a regression of all of the remaining voltages on the best linear combination of those two, and to compute on the basis of the residuals after that regression, what is the improbability of the remaining numbers. It does this through five steps, which seem to have exhausted most of the significant differences between these distributions. However, I repeat that although these differences appear periodically as a function of delay, they are not attributable to a single coefficient on some oscillating stochastic process, which is the single correlate of the contrast in responses. The differences are distributed independently in the unaveraged EEG sample records—or very close to independently distributed—so there really are five different things occurring. These five things, which are not linearly dependent on one another, differentiate these two curves from each other. These findings show an aspect of the outputs of the discriminant analysis program, which in some cases can provide interesting information that one would not have guessed either from the curves themselves or from the F ratios without regression.

The next figure (fig. 5–5) shows a control result against one effect that we have heard much discussion about today: whether the movement, in this case writing down "L" or "H", has a discriminating effect on the AEP. Clearly it will have some effect, but will it be an effect that artifactually affects the differentiation between AEP which the program is attempting? Mr. Gardiner averaged back from the response, then subtracted from each individual EEG segment the average motor potential, synchronized to the time of response in that segment; this is what "Before Subtraction" and "After Subtraction" refer to. These before and after curves do look slightly changed, but discriminant analysis shows that the F_0 curves are relatively little affected, and the set of delays selected is essentially unaffected too.

Mr. Gardiner has also shown that some of the manipulations that we have been discussing today, such as establishment of a baseline, although they change some apparent relationships between AEP waveforms, do not change the delays at which discrimination is established by the program. Thus, if we have a definite question to answer, and a method that responds well to that question, we may be able to avoid some of the worries that occur in descriptive statistics, when we don't know what question the description is supposed to help us decide.

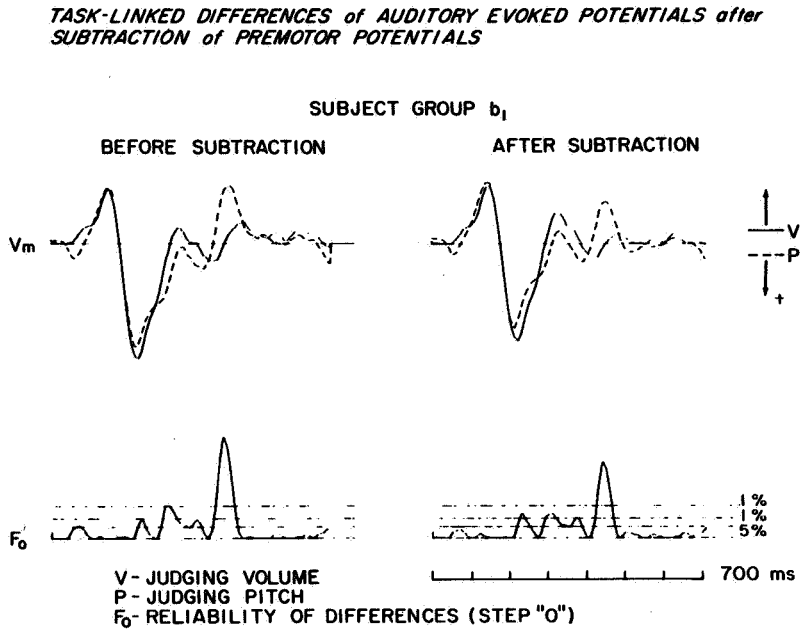
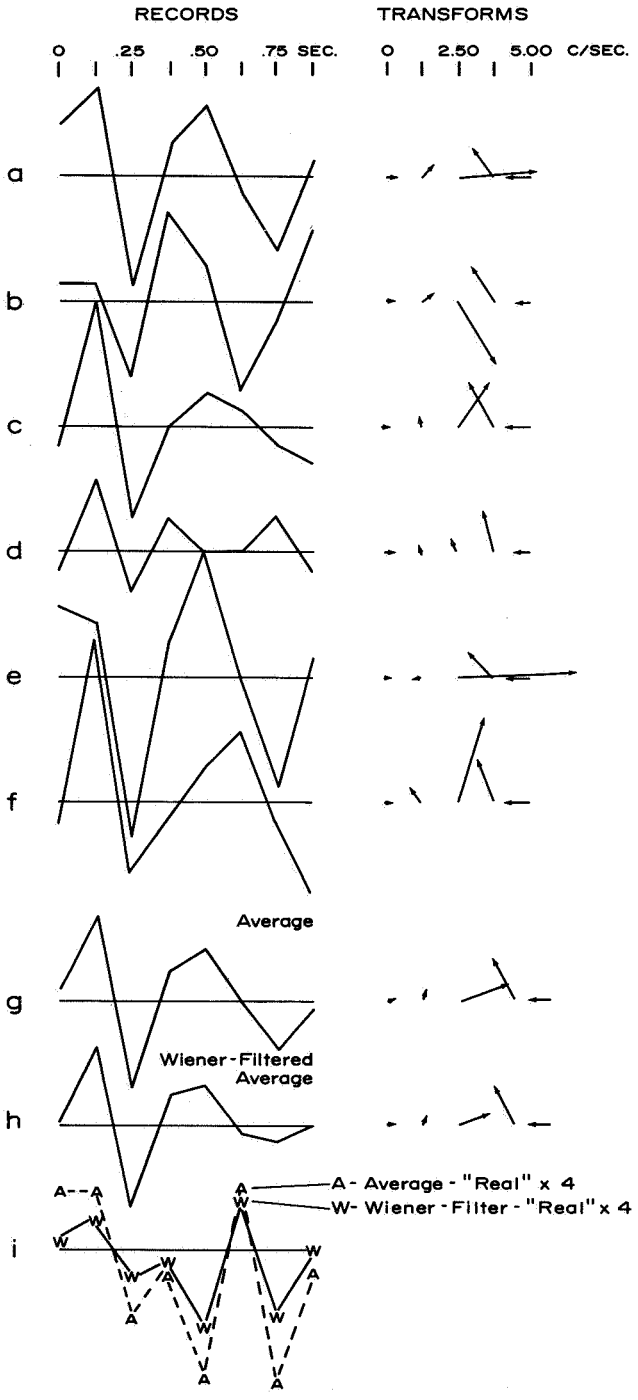


FIGURE 5–5.—Control showing effect of subtraction of premotor potentials on an evoked potential comparison (from Gardiner, 1969). Vm: Average evoked potentials recorded with vertex-mastoid derivation. b1: Source of data. For discussion of data, see Supplement A to these proceedings. V, P: Two evoked potentials under comparison F_0: Initial F calculated by discriminant analysis, as described in the caption to the preceding figure. Before subtracting, after subtraction: Analyses made before and after adjustment for effects of premotor potentials have essentially the same outcome.

Now I would like to make one more quite disconnected comment about data analysis methods for evoked response studies; I base it on figure 5–6, which concerns a totally different topic. This is a "pretend" average response experiment, and this figure illustrates a new analysis method. Here, I have just six stimuli, six responses, and eight times of digitizing because I had to do all of these calculations by hand to begin with, in order to develop the theory. The objective is to assist those individuals who would like to increase the sensitivity or the selectivity of evoked response extraction, over what can be done by straight averaging. The general approach is to use Wiener's technique for separating signal from noise where you know what "signal" is and what "noise" is, or at least where you know the spectrum of the signal and the spectrum of the noise. Then if there are frequency bands at which the signal is very weak and the noise is very strong, you might as well suppress them. They are only contributing irrelevant variance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A--A
i
A - Average - "Real" x 4
W- Wiener - Filter - "Real" x 4

to your recordings and averaging. On the other hand, if there is a frequency band where the stimulus is strong and the noise is weak, you should let that pass and give it essentially unit weight.

The implementation of that idea, then, requires you to take the Fourier transform of each response. Those of you who know my previous work could have predicted that if I was going to do anything for evoked responses, it would involve the frequency domain, and this is how it enters. The Fourier transform of each response is not actually used by itself but should be converted into a spectrum for each response, in spite of the fact that each response is nonstationary. Nonstationarity and nonGaussian amplitude distribution is not important in this case.

If you average the spectrum of each of the responses, you will get an average spectrum, which will be different from the spectrum of the average. These operations do not commute, because making a spectrum is a quadratic operation and hence involves a nonlinearity. The basic point is that the spectrum of the average has a

FIGURE 5–6.—Illustrative improvement of average response calculation. a–f: Six "records" assumed to have been recorded as successive responses to be averaged; the interval between observation times for each record is 0.1 sec, and there are 8 observations per record. To the right, the six transforms (discrete Fourier transforms) corresponding to the records; the vectors at 0 and 5.00 Hz are always horizontal, by the definition of the transform; vectors at other frequencies each have a real component, ϕ_r, and an imaginary component, ϕ_i, as defined in the text. The spectrum of each response could be thought of as resulting from rotating each of these vectors into both a horizontal and a vertical position (so as to define two edges of a square region), and then creating a new function of frequency having heights proportional to the areas of the squares so delineated. A spectrum at this resolution is sometimes called a periodogram. g: The average of records a, b, . .f. To the right the transform of the average, which is equal to the (vector) average of the transforms. The spectrum of this average could be represented as above, by rotating these vectors, but the result would not be equal to the average of the spectra because the algebraic representation of area is nonlinear. h: The average resulting from filtering. The average transform shown in g is multiplied by the ratio of the spectrum of the average to the average of the spectra, and the result inversely transformed (see text). i: The errors of the two averages, g and h, as estimates of the "real response"; the vertical scale is multiplied by 4 for easier visualization. Note that the error of the Wiener-filtered average is less than that of the usual average at all times but one and is often considerably less.

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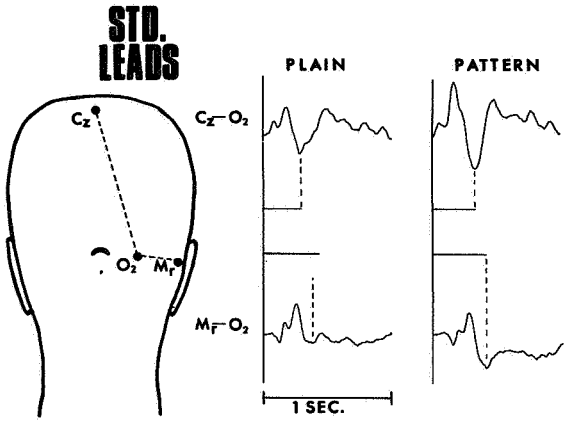

FIGURE 5–7.—Standard electrode configurations C_z–O_2 and M_T–O_2 are shown with the simultaneously recorded VER to plain and patterned light. Note that the latency to component showing the most change (dotted line) is a function of electrode placement. Note, also, that the change in VER produced by pattern is more marked in the C_z–O_2 electrode configuration.

little less of the spectrum of the noise in it than does the average of the spectrum. By algebraic combination of these two, you can make an improved estimate of what the spectrum of the "real response" must have been.

If you then apply a filter to the Fourier transform of the average response, which makes its spectrum like that of the inferred "real response," you can inversely transform that modified Fourier transform and produce what I call a Wiener-filtered average response.

The curve labeled "A" is the error of the ordinary average response in this example, and dashed-line the curve labeled "W" is the error of the Wiener-filtered average response. In this case, at least, it seems justified to state that the effect of what I have called Wiener filtering is to improve the accuracy of the calculated result as an estimate of the time-locked part of these various responses. The process is explained in the EEG Journal (Walter and Brazier, 1969).

Dr. DUFFY: Dr. Lombroso and I have been impressed by the lack of standard scalp electrode placement in evoked potential experimentation. Indeed, much of the confusion and variable results reported in the literature appear to result from the erroneous assumption that the VER waveshape is constant, and that electrode placement is of secondary importance. Figure 5–7 shows that not only are waveshapes different for different electrode positions, but also that when experi-

mental conditions are altered, the change that occurs in the VER may be a function of the electrode montage. As a solution to this problem Clynes (1965) has described a technique of electrode placement in which the scalp overlying the occipital cortex was surrounded with a circular array of four bipolar electrode pairs. Such an array is illustrated in figure 5–8. Under column headed CAT 1000, one sees four simultaneously derived evoked potentials. Inspections reveal that these four evoked responses appear different from one another and point up again the importance of electrode orientation in obtaining the VER with bipolar electrodes. Nonetheless, there appeared to be VER components with representation in each curve. For example, there is one with maximum value at about 185 milliseconds and another at 270 milliseconds. It is to be noted that component 1 appears to be represented maximally at 136°, and component 2 at 90°. This suggests that the electrical fields of 1 and 2 traverse the rosette array at different angles; this, in turn, suggests that the dipoles that produced 1 and 2 were of different orientation with respect to the rosette. In other words, 1 and 2 are separated not only in time, but also by the different spatial orientation of the dipoles that generated them. Despite the dissimilarity in these four VERs, one has the impression that they may all be linear algebraic combinations of two or more basic components. (In this case, components would be defined by electric field orientation.) In a sense these four curves may be considered analogous to a set of simultaneous algebraic equations. Carrying the analogy a step further, a factor analysis was applied to these four

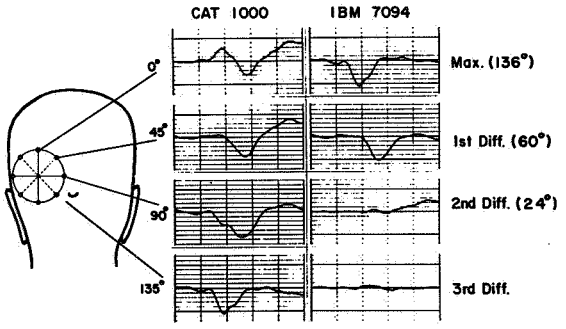

FIGURE 5–8.—A rosette of four bipolar pairs is shown applied to the left occipital area with grid 1 as black and grid 2 as open circles. Under "CAT 1000" are the four VER representing input to the factor analysis program; under IBM 7094 are the output components. In either case, each curve is 500 msec long, and each major vertical dimension represents 10 μV.

VERs and the resultant, "independent component," displayed under the column IBM 7094. A separate printout shows, by virtue of trigonometry, that the Max. (largest) component has an orientation of 136°, the 1st Diff. (next largest) at 60°, 2nd Diff. at 24° and that the 3rd Diff. curve is not significant. Note that Max. is identical to 1 and the first Diff. is component 2. This "factor analysis," which is based on spatial field orientation rather than position along the time axis, may be considered a form of data reduction permitting one to examine one, two, or three "pure" curves rather than four mixtures.

The major application of this technique in our laboratory has been in the field of color vision. As you know, color may be defined by a point in the three-dimensional space of red, green, and blue. I am sure you are also familiar with the apparent paradox demonstrated many times by Dr. Land, where he appears able to create all colors by a combination of two colors and a series of shapes. The paradox is simply stated as "How can one take two-space information and transmute it into three-space?" Now Dr. Lettvin of MIT has postulated that there must be, therefore, an interconvertibility of line, shape, and color. In other words, shape, movement, or orientation of lines may be interconvertible with third-axis color information. He postulates that this occurs at the ganglion cell level where a given ganglion cell might respond to stimulation of the retina by color or by shape. The application of this, then, to the study of color evoked response is that, if one limits himself to stimulation with small spots of color, he is really asking "How does color influence the evoked response to a spot?" rather than "What is the evoked response to color?" As an answer to this, Dr. Klaus Herberg and I constructed a large plastic shield which we have termed the *farbenvelt* onto which color is projected, containing no shape whatsoever. Our results seem to indicate that, contrary to many reports in the literature, there is very little or no difference in the VER to different colors when shape is entirely removed. If one applies factor analysis to the VERs, one finds that the only significant difference is the slight angular rotation of one component about the rosette axis. It would be difficult to appreciate this subtle change of electric field orientation if one were to view a single bipolar array. The rosette factor analysis technique lends itself to average power measurement because the outputs of the factoring analyses are independent components whose individual power (expressed as the integral of the voltage squared) may be summed as the first approximation to a response magnitude.

DR. LIFSHITZ: It seems to me that expressions of evoked potential data in terms of the extrapolated electric field at a single point may be a dangerous oversimplification. We are not dealing with simple dipole

generators in a homogeneous medium; therefore, the fields we are dealing with are not symmetrical about sources and sinks. If we think of an evoked potential presented as the electrical field on the surface of the scalp in the manner of Rémond (1964) and if we make a voltage into spatial (as height in a gravitational field) transformation, then we can think of the variations in voltage over the scalp, at a particular instant in time, as being topographical, as are the mountains and valleys of a topographical map. The largest positive potential would be equivalent to the highest mountain peak, and the largest negative potential the deepest valley. Looking at the entire evoked potential following a stimulus then can be considered analogous to looking at a map across geological time. A stimulus results in a mountain range rearing up in a particular area, and then perhaps sinking back, and then maybe a mountain range or a valley appearing in another area.

If we take a set of electrodes, such as the rosette array, or a crossed bipolar array, we can try to determine at a particular point, and at a particular instant in time, what is the direction of the maximum slope and how steep the slope is at that point. The slope direction and steepness are the analog of the electric field vector. This vector presumably will point toward the mountain peak, and those portions of evoked potentials that have a mountain peak in the same location presumably have some functional relationship. In order to determine the direction of slope and steepness at a point on a surface, it is required to determine a plane. Three points are sufficient to determine a plane. We can get three points from two leads having a common electrode. We don't need an array of eight electrodes or four bipolar pairs. Indeed bipolar pairs of electrodes without common links may result in an error of interpretation since it would not be known if an electrode pair lies at a significantly different potential level than another pair; the differential amplifiers discard this information. Extrapolation of electric field vectors from such pairs of electrodes could lead to erroneous results.

As the spacing between electrodes gets wide, we will include territorial irregularities between our measuring points; thus, it becomes meaningless to say "which way is up." There is no specific up. Averaging "redundant" information from different electrode locations does not solve the problem; it results rather in a type of territorial smoothing, taking into account only two points, which may markedly distort the real terrain. If we make the rosette larger, and use more than four bipolar pairs, all that could be defined would be the terrain on the perimeter of a circle on which the electrodes lie. Even using all the information from all electrode pairs would not enable us to decide precisely the electric vector in the center of the circle. No matter which way we averaged, if the electrodes were on the rim of a crater, we would remain ignorant of a hole in the center, which could as well be a

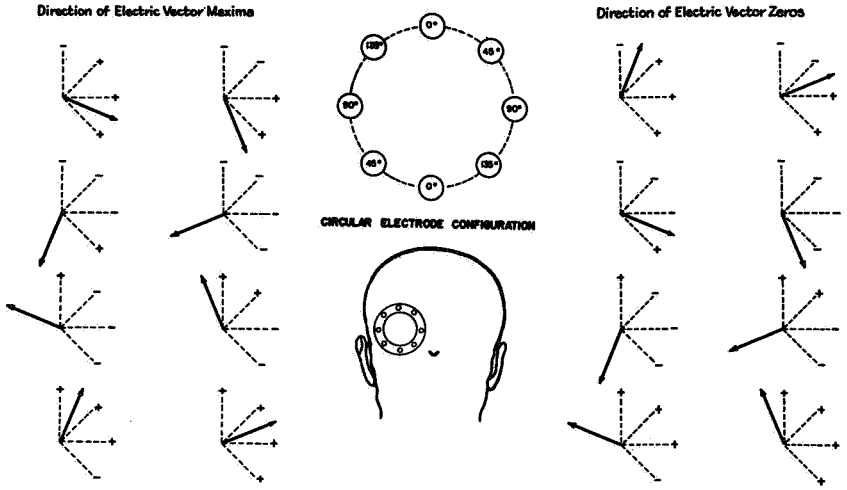

FIGURE 5-9.—Circular array of eight electrodes (rosette) to measure spatial evoked potential. Measurements are taken simultaneously between opposite pairs of electrodes, resulting in four traces. These are spatial deviations of electric vector at center point of electrode circle. On the left and right is a schematic representation for estimating direction of nulling of electric vector from peak polarities in four traces, 0, 45, 90, and 135 degrees, respectively. Note that if the peak is the same sign in all four traces, the direction of zero lies in adjacent octant, i.e., between 135 and 180 degrees, or between 0 and —45 degrees. Vector direction of zero is taken to be the angle at which change from negative to positive occurs. Electric vector maxima are +90 degrees displaced from electric vector zero. In searching for spatial origins of components, the rosette is displaced in line of electric vector maxima until no peak is obtained for the new rosette position. Then the source lies directly under the rosette (see also: Clynes, M.; Kohn, M.: Electroenceph. Clin. Neurophysiol. Suppl. 26. pp. 82–96, 1967).

mountain peak. However, if we bring the electrodes close together so that they span a small region (which is easier with three electrodes than eight), then we can determine "up" for a specific point with greater accuracy. We can also note that, unless we have simple mountains, as for example cones, the direction of up (or the maximum rate of voltage change) may not be in the direction of the peak.

DR. CLYNES: Regarding Donchin's and Walter's use of discriminant analysis, it is important to distinguish between the changes in the "noise" and the changes of the "signal." With two sets of average curves, differences may be caused by either the variability of the noise, or the actual variability of the response itself. There should be a statistical way to differentiate between these. It is not enough to say that there are two averages and that they are different. More than two are required to make some sort of separation between them. That the

two averages are not the same is not enough to ascertain if the difference was caused by noise variability or by the signal variability in the two subjects.

I would also like to know if Dr. Walter considered the effects of a slow baseline drift on the discrimination? I should also discuss another matter that was raised, namely, the technique of the rosette analysis. This technique aims to measure the spatial differentiation of the electric vector in contradistinction to the measurement of voltage differences (fig. 5–9). We are trying to find the vector E and its spatial differentiation at the various instants of time. If there are components that are independent in space, then they would tend to zero and maximize at different angles from each other. Now, the theoretical size of the electrode circle should be infinitely small. The smaller it is, the less activity comes from directly underneath and inside the circle, and the more from outside. (Of course, the total amplitude of voltage recorded is also reduced in proportion to the diameter of the circle.) In practice, this is not possible; thus, one must limit himself to some kind of compromise between spatial resolution and sensitivity. On the other hand, even a large rosette is of some benefit—one can use it right around the top of the head, and a 6-inch diameter is still of interest.

We have developed a technique of making this rosette-electric-vector measurement three-dimensional by extending the rosette at right angles to the scalp. If one takes a substance that has a conductivity comparable to that of the brain, or better of a substance of somewhat smaller conductivity, he can build, as it were, an "extension" of the head with this conductive substance and then put electrodes in this substance in addition to the eight placed parallel to the scalp. One then can measure potential differences and components at right angles to the scalp. It is advisable in interpreting this to be careful to account for the skull geometry as far as possible. The extension should be larger than the area investigated so that edge effects are minimized.

Regarding the color effect, I quite agree that the color effect is dependent upon the visual angle; we found this several years ago in our color studies. There are relative inhibitions of various areas, and these inhibitions differ for different colors. For example, with green, the effect of changing the area is very different than with red. Also, if one has a large undifferentiated visual field of red covering the entire visual field, the red color actually tends to disappear after a while; if one places a half pingpong ball directly in front of the eye, the red sensation is maintained for only a short time, and the field will look dark. But this does not occur with a green field.

DR. RUCHKIN: I would like to add some comments concerning the use of discriminant analysis. We have used a similar procedure to analyze sequences of evoked responses recorded from animals during

conditioning experiments. In some cases, there was reason to believe that the sequence of evoked responses was not homogeneous, but that there were several categories of evoked response waveshape. However, we did not have sufficient information for specifying a discriminant procedure. For such cases, we have tried a cluster analysis technique, similar to that of M. Okajima et al. (1963) and G. H. Ball (1965), in an attempt to identify the category of each evoked potential and to obtain the average evoked potential waveshape for each category. The procedure consisted of averaging reasonably similar evoked potentials while avoiding combinations of markedly dissimilar waveforms. Various similarity measures were tried, including the mean square difference between two waves and the average student's t for two waves. The procedure was iterative, "bootstrap," in form. The evoked potentials were processed sequentially, and the final result could depend upon the order in which they were processed. The waveshapes of the resulting averages were reasonably independent of the order of processing, but the categorization of the individual evoked potentials to some extent depended upon the sequence.

I also would like to comment on the question of significance of differences raised by Dr. Clynes. We routinely compute student's t for all time points when comparing average evoked potentials. In cases where there are no known reasons to expect significant differences and visual inspection has suggested that the averages were similar, we have found that t's of the order of two to three often occur. In cases where significant differences are to be expected, very large t's of the order of 5 to 15, often occur. The t's of the order of two to three for apparently similar waveform pairs may partly be due to chance and in part due to random phenomena that are not accounted for by the simple signal-plus-noise model. The apparently spurious significance is likely to occur when a large number of evoked potentials is used.

We deal with this problem by computing t's for two pairs of waveforms. One is a control pair, where both averages are expected to be the same. The second is an experimental pair, where it is hypothesized that there is a difference. If the second pair has larger and consistently significant t's, then the hypothesis is accepted.

DR. BROUGHTON: The problem of noise, or the degree of participation of incompletely cancelled background activity in the evoked potential is, of course, very serious. Many applications of the summation technique for evoked potential extraction involve very considerable differences of background activity; for example: (1) evoked potentials during normal relaxed wakefulness and arousal, which occur during states of relatively synchronized and desynchronized background activity; (2) evoked potentials changes during shift from wakefulness to slow wave sleep, in which the amount of random back-

ground activity (noise) to be cancelled increases markedly; and (3) also during stimulating and during epileptic discharges. In all such studies, the "biological noise" changes perhaps as markedly as does the cerebral reactivity, and both determine the signal-to-noise ratio, or the evoked potential. But the participation of the former is seldom considered and the potential changes are interpreted only in terms of altered cerebral reactivity.

We can ask ourselves to what extent background activity has been cancelled in our usual evoked potential recordings, given the relatively small N used. And, if the residual noise is significant, how often do we try to reduce it substantially by delivering the much greater number of stimuli usually needed, that is, squaring N each time we wish only to double the signal-to-noise ratio?

Dr. John Woods and I have been very interested in this problem of noise (Woods and Broughton, 1968; Woods, 1968). We have found, for instance, that summing background activity without stimulation does not give a reliable index of noise in the response, as appears to be accepted by many. This is because the stimulus produces both a discrete evoked response and also modifies ongoing background activity. The latter has caused us to seriously question the validity of all "excitability cycles" in which the S_1–S_2 interval is less than the duration of the response to S_1 (R_1) and in which subtraction of R_2 has been performed. Therefore, examining the cyclic variations at 10 Hz in Dr. Walter's discriminant analysis curves of average evoked potentials recorded at the vertex led me to ask whether this was not simply caused by more background alpha rhythm being present during one recording situation than the other.

I also would like to ask Dr. Walter if there is some way of assessing incompletely cancelled rhythmic background activity or noise in the response by analyzing a fairly prolonged prestimulus epoch and then further analyzing the poststimulus epoch selecting out whatever activity remains in phase with the preceding rhythmic activity, alpha rhythm, or other. This obviously would depend greatly upon the temporal stability of the rhythm as is indicated, for example, by autocorrelation. But it could be a useful approach.

DR. ANLIKER: When Dr. Walter spoke of measurements of variability in n-dimensional space, I was reminded of a story I heard somewhere about Gertrude Stein and Alice B. Toklas. It seems that these two had many discussions concerning the possibility of life after death, and they agreed that the one who died first would attempt, on the threshold of death, to signal whether there was anything "over there." Later, as Miss Stein was dying, her friend asked, "Well, what is the answer?" The dying woman's last words, according to this story, were "What is the question?"

In applying variability analyses of a high order of complexity, we frequently encounter a similar problem, namely, that we are seeking answers without defining questions. There is no guarantee that a mathematical transform that is useful in enhancing the signal-to-noise ratio in one application will not have an adverse effect in another application; without a careful matching of the mathematical instrument to the analytical problem, the transform is more likely to degrade the signal than to enhance it, and to render the simple complex rather than vice versa. The use of complex analyses frequently reveals some tantalizing order in the data; yet on further analysis, this "order" is finally recognized as nothing more than 60-Hz artifact, "ringing" of electronic filters, or something obvious to more direct inspection, such as the alpha rhythm. On the basis of the material presented, I would say that we have not excluded this possibility here.

In Dr. Walter's presentation of his discriminant function analysis, it appeared to me that there was a striking tendency on the part of the discriminant function to generate a characteristic peak at about twice the periodicity of the data being analyzed. In other words, if you take a sine wave of some arbitrary frequency and superimpose another wave of the same frequency upon it, the probability density for the discriminant function is high at every half-period. Looking at his analysis, I had the distinct impression that there was a regular rhythm present, possibly alpha, such that the activity peaks missing in the first pass tended to appear in the second or third pass; even the blank spaces were regular and consistent with an order based on alpha rhythm. If it is merely alpha activity that is being detected, the discriminant function analysis is not of much interest since there are more efficient methods for the extraction of such rhythms. How can we be sure that what we have seen is not alpha activity?

Another problem I should like to mention concerns the use of the Wiener filter concept in Dr. Walter's model. It is my understanding that the use of the Wiener filter requires the assumption that the process studied is stationary. However, the processes under investigation here are notoriously nonstationary. It seems doubtful to me that the present model will prove very useful on anything other than very limited time series. The Kalman filter, by contrast, does not require the assumption of stationarity and might be more suitable for this type of model (see review by Sorensen, 1966).

DR. CALLAWAY: I want to comment about Ruchkin's suggestion to use a *t*-test. Dr. Ruchkin has been one of the pioneers in showing us how to look for variability rather than consistency; and sometimes variability is what we are interested in. However, I would like to object to the use of the *t*-test as a measure of consistency. The *t*-test is extremely sensitive to background activity. The probability of finding a high *t*

if you are looking through a series for a maximum t is often a function of the point density distribution of the sample and may have little or nothing to do with the significance of the differences between the means.

DR. WALTER: The question of stationarity is a bugaboo that should have been exploded long ago. It is true that stationarity is a very convenient assumption in the context of justification, and in the context of giving a theoretical explanation of how and why, and to what extent a method works under idealized conditions; but the mild violation, or even strong violation, of that assumption or restriction does not make a method totally inapplicable in the context of measurement or application. It only makes it somewhat less sensitive, somewhat less specific, and requiring more of controls and test analyses; it means that we should not rely heavily on tables of distribution and tables of significance; but it does not destroy the utility of the technique.

I think the best example for that viewpoint was given by Dr. Tukey about a year ago in a small conference. He pointed out that the pH meter was invented by somebody who just wanted to measure something and found that it varied mostly with hydrogen ion concentration; then the theoreticians became involved and said, "yes, but you have to be very careful. You can't really compare pH if there is anything else in the solution, and you have to apply it only to very slightly polluted water." Nevertheless, soil scientists insert the instrument into wet dirt and get some measurements that are useful to them, provided that they include enough controls, comparisons, and analyses to justify the scientific value of what they do. Similarly, the readings of pH meters inserted into human serum are useful, given enough controls.

Now, blank spaces between periodic phenomena are of course periodic, and I said yes, the F_0 curve is periodic. However, I said furthermore that because the program proceeds by successively regressing, performing a regression analysis of all of the data on the voltage values at each of the selected delays, the fact that only the high F-values in the immediate vicinity of the point selected were reduced to negligible values made it necessarily the case that the mountains were independently distributed (at least to the extent that the world is joint-Gaussian distributed; they certainly are uncorrelated). Therefore, it could not be an alpha wave in the ordinary sense.

Suppose that the stimulus triggered an alpha wave, or an alpha-like wave, with more or less the same phase each time but with somewhat variable amplitude. Indeed, if this amplitude were correlated with the discrimination we asked the program to perform, we would get the F_0 curve under contention. However—and this is what I don't seem to have communicated—you would not get the next F curve.

Instead, you would get an F_1 curve essentially equal to zero at every delay. Putting this in statistical terms, the differences between the AEP, at the various delays that gave peaks in the F_0 curve, would be completely correlated with each other.

Dr. Broughton suggested the same thing about the alpha, which I hope is answered by this idea of serial regression; he also suggested analyzing before the stimulus, and in some way predicting what would have happened had the stimulus not come. I think this is a good idea for some purposes. "Filtering predictors" (see Wiener: *Extrapolation and Interpolation*) can be run a certain distance into the future so as to predict what would have happened had you not given the stimulus. But one unfortunate feature of such a calculation is that the questions that are most interesting—concerning "ringing," for example—are at a delay which is so great that I think the filtering predictors would have fallen dead by then and given as much unpredicted variance as if you had used no predictor at all. So, unfortunately, that is probably not the solution to the "ringing" problem.

Neither do I think that my suggestion of "Wiener filtering" will solve that problem because the "ringing" is so close to the free-running alpha frequency. I have another idea that I plan to work up for next year, which might solve that problem.

To Dr. Ruchkin, speaking just in a friendly way, I would say that cluster analysis indeed is a step beyond discriminant analysis. I would say that it is a step off the ice and into the water, after which it is difficult to find your bootstraps again. One of the good features, I felt, of discriminant analysis as contrasted with cluster analysis or factor analysis is that, in spite of all of the distributional assumptions that are used in the discriminant analysis program and used in the derivation of the method, you get a distribution-free test out of the program. It says, "Well, I think the best combination of the variables I selected is this combination, so now I will try it on the real data and see how well I do." Although this has other drawbacks and is not perfect, still it gets around many of the difficulties that you might otherwise feel about questions such as, "Is the value at delay 100 milliseconds joint-Gaussian distributed with the value at delay 220 milliseconds?", and things of that kind.

I think that Dr. Clynes' depth electrodes in jelly are just marvelous. I wish I had thought of it. I think that is a splendid idea because if you match the impedance of the local tissue reasonably well, it gives you the opportunity of having a transcortical orientation without going to the neurosurgeon. I think everybody should do it. What material do you use? Salt water?

Dr. Clynes: Electrode jelly can be mixed with inert substances in proper proportions. You must vary it; it depends on how much hair

the subject has. It probably would be better to use a bald subject.

DR. WALTER: I see. Well, we selected our subjects on many different bases, but that is a new one. To answer another question, certainly the discriminant analysis method contributes nothing to the question of discriminating noise variability from variability of the "real response," and I didn't claim that it does. However, I think you missed one point, possibly because of the way the figures were drawn, showing an average and not showing the variance around that average. In fact, the discriminant analysis program uses both of those parameters in considering each delay and concerning both of the groups of unaveraged EEG samples being contrasted, so that the variability both within each group, and between the two groups, is definitely included.

Just one final comment about Dr. Duffy's and Dr. Lombroso's method. I think that it is excellent to try to reduce the rosette data to something such as principal components, but there is a problem in principal components also. Suppose that you have just two times when you are measuring, so that you have only a two-dimensional space. Suppose that in one analysis, your principal components are oriented at $\pm 45°$ to the measurement axes; they imply an ellipse, say the concentration ellipse at density half the peak. Suppose also that in a second analysis, the principal components are oriented at 10° and 100°, almost parallel to the measurement axes. In spite of this completely different orientation, the second-analysis vectors can very easily have lengths such that the implied ellipse passes through the end points of the first-analysis vectors. That finding could then be interpreted by rotation of the factor axes (not the rosette, which is in real space), as having been produced by a different combination of the same generators. Unfortunately, principal components provide only an apparent objectivity.

DR. DONCHIN: Let me add one point with respect to the use of discriminant analysis. As I said, when two AEPs are compared by this program, we are informed eventually which time-points were those at which a useful discrimination between the two AEPs was made. These time-points, as illustrated, for example, in figure 5–2, are identical with the peaks of the F curves that Walter and Gardiner use. There is an interesting manner in which the validity of this technique can be confirmed. If you subject the same set of data that was analyzed by discriminant analysis to principal component analysis, a small number of components will emerge as accounting for a large percentage of the variance. These components are loaded most heavily at some narrow range of time points. The interesting point is that very often the time ranges at which the principal components are identified

correspond nicely with the variables that were identified by discriminant analysis. This is not a computational artifact; it reflects the fact that the discriminant analysis is not looking only at the background activity but at substantive differences between the evoked responses.

DR. WALTER: This is wrong. In figure 5–4 it might turn out as you suggest, but if you made a principal-component analysis of most of the sets of data that Gardiner used you will find a principal component centered at peaks of the AEP; however, you also will find that the significant time points for the discriminant analysis are somewhere in between these peaks. I am not certain—since we have not done it—but I feel rather sure from looking at a visual analysis that the times of greater differentiation are often on the shoulders of the peaks that emerge from principal component analysis.

DR. DONCHIN: I am not suggesting that there is a correspondence at the peak of the AEP components. I have said that there is a correspondence between the time ranges that are contributing to the principal components and those time-points that were identified by discriminant analysis. If you take the total epoch of the AEP and subdivide it both by way of the principal component technique and by discriminant analysis, then the two subdivisions are often in good agreement. In both cases, we have reduced the dimensionality of the data, using a different criterion for developing the new space in each case. The principal component technique is an attempt to account for the total variance in the space, and discriminant analysis is essentially an attempt to account for the between-group variance. There is no inherent need for the two techniques to yield identical structures. This would only happen when the between-group variance accounts for a major proportion of the total variance. This is why I feel that the empirical agreement between the two techniques adds substance to the application of discriminant analysis of AEP data.

CHAPTER 6

The Specification of Psychological Variables in an Average Evoked Potential Experiment[1]

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INTRODUCTION

ON THE FACE OF IT, the assigned topic of this paper is puzzling. Why should the specification of psychological variables in an evoked potential experiment be in any way different from their role in a GSR experiment, in a learning experiment, or in any kind of experiment that involves behavior? In seeking reasons for special concern with the treatment of psychological variables in evoked potential research, three important issues emerge:

(1) Implications for experimental design of what I have called the triangular experimental paradigm

(2) Implications for experimental design arising from temporal and spatial averaging

(3) Problems in construct definition

THE TRIANGULAR EXPERIMENTAL PARADIGM

In evoked potential experiments in awake humans, one is always dealing, intentionally or unintentionally, with three classes of vari-

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ables—physical or stimulus events, physiological events, and psychological events. One can conceive their relationship diagrammatically by permitting each class of variables to occupy one corner of a triangle. The relationship between stimuli and psychological events has been the traditional domain of psychology; between stimuli and physiological events, the traditional domain of physiology; and between physiological events and behavioral events, the traditional domain of physiological psychology. Of course, these divisions have never been rigid, and there have always been classes of experiments in all three fields in which investigators have attempted to cope with all three corners of the triangle at the same time. However, it has been relatively easier to stay limited to two of these domains at a time than is now possible in evoked potential research with awake humans. Animals can be anesthetized for physiological research, thus eliminating any concurrent overt behavior of the animal. Even in awake animals, experimenters often ignore the fact that "something may be going on in the animal's head." Behaviorists, as an article of faith, have maintained that it is perfectly valid to obtain relationships between stimuli and psychological events without reference to any physiology. In evoked potential research in awake humans, I think it is always desirable to cope with all three classes of variables in the same experiment. I emphasize in the same experiment because it is not quite the same thing to deal with these variables two at a time. For example, a number of reports have now appeared comparing the relationship between stimulus intensity and sensory magnitude and between stimulus intensity and some aspect of the average evoked potential. In most cases, the psychophysical experiment and the evoked potential experiment are done in separate sessions, although usually on the same subjects.

Problems Posed by Psychophysical Findings

However, there are significant limitations in this approach. These limitations are implied in the results of some psychophysical experiments by Kietzman and Sutton (1967). In most psychophysical experiments, one tells the subject what to observe; e.g., "tell me when you see two flashes rather than one flash." However, in some psychophysical procedures, one simply asks the subject to report which of several stimuli is the different one. In our experiment, three of the four stimuli within a trial were a single pulse of light, and one was a double pulse of light. Under these conditions, even when the subject is operating at a 90 percent level of accuracy, when we ask the subject to report how the stimulus which he has correctly identified as different appears to be different, we found that less than one-third of the trials elicited a report of flick or twoness for the double-pulse stimulus. A somewhat

larger proportion of trials elicited a report that the two-pulse stimulus was of longer duration, and the balance of the trials elicited reports of "color difference" and a variety of other percepts.

As can be seen from such data, the human organism, even under highly controlled conditions, cannot be made to follow a strict isomorphism between stimulus and psychological event.[2] The identical stimulus configuration seems to be compatible with several quite different percepts. A variety of internal states evidently enters into the determination of the percept. The question that arises for evoked potential research is twofold: (1) Can this source of variation be ignored with impunity in evoked potential experiments; i.e., can one legitimately average across trials where such perceptual variation is present, and (2) Is it possible that evoked potential research may be an important tool for elucidating or reducing this source of variance? For example, if one were to average on trials in which the report of the subject was "longer" separately from when the report of the subject was "flick," would these averages be reliably different? Would the average obtained in connection with reports of "longer" in some way be related to what one obtains when one actually manipulates stimulus duration? At this point, I can only suggest that our psychophysical work indicates that it would be highly desirable to examine all three corners of the triangle in the same set of trials. Otherwise, there is the serious risk of averaging across quite different perceptual states as well as losing the opportunity to isolate some very important sources of variance.

There are no available examples which show that the kinds of psychophysical attributes that I have been describing might affect evoked potential wave forms.[3] However, the finding by Haider (1967) that, in a discrimination situation, stimuli that were correctly identified yielded different average waveforms from identical stimuli that were not correctly identified shows that care to separate trials along some psychological dimension might be rewarding.

Importance of Sorting on the Behavioral Response

At a somewhat different level of psychological complexity from the

[2] It is for reasons of this kind that it would be seriously misleading to consider evoked potential experiments as having one independent variable, the physical stimulus, and two dependent variables, behavior and physiology. In fact, these are problems that in other contexts have raised major philosophical storms, e.g., mind-body dualism, isomorphism, etc.

[3] Bartlett and White (1965) did use a temporal forced-choice psychophysical method in connection with the study of evoked potential correlates of two-pulse stimuli. However, evoked potential and psychophysical data were obtained in different sessions. Further, in the psychophysical sessions, they instructed the subject to judge which stimulus was brightest, ignoring the possible presence of other cues.

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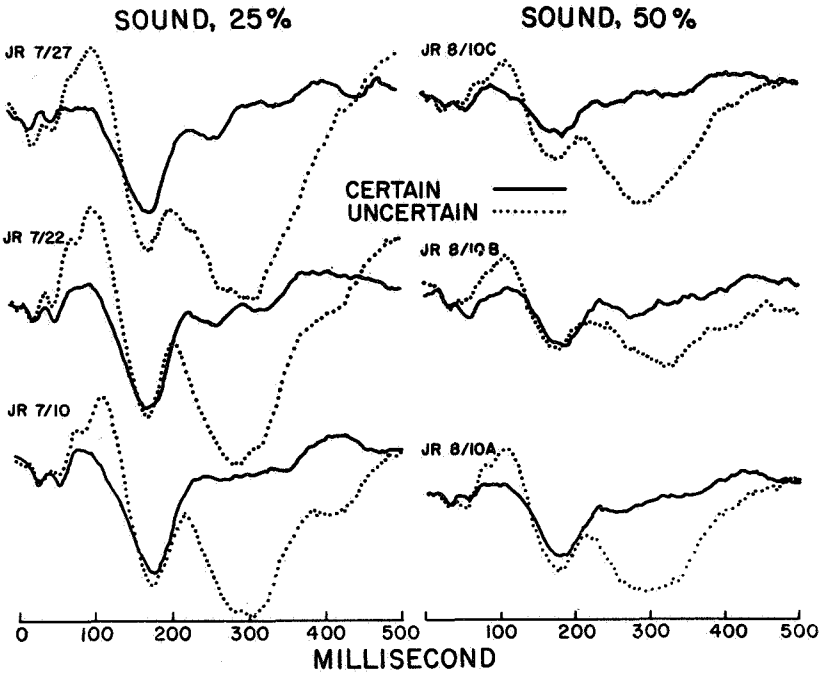

FIGURE 6–1.—Average evoked response for certain (solid lines) and uncertain (dashed lines) clicks for one subject. On the left, clicks had a 25 percent probability of occurrence; on the right, clicks had a 50 percent probability of occurrence. Pairs of waveforms on the left were obtained on different days extending over a period of 17 days. On the right, pairs of waveforms were obtained in different experiments on the same day. Electrodes are vertex to earlobe.

psychophysical report, Patricia Tueting of our laboratory recently has produced a rather striking illustration of the importance of taking the psychological dimension into account (Tueting, 1968). In our 1965 study of the effect of uncertainty on the evoked response waveform (Sutton et al., 1965a), we originally noted that the P_3 component of the vertex potential was much larger when the subject was uncertain with respect to the identity of the stimulus to be presented than when he knew in advance which stimulus was to be presented. Figure 6–1 shows some of the data from that study; P_3 is the component that reaches peak amplitude in the vicinity of 300 milliseconds. We also noted that when we varied the relative probability of occurrence of two stimuli, P_3 was larger for the stimulus with a lower probability of occurrence. This was a qualitative finding, and Dr. Tueting recently undertook a systematic, quantitative investigation of the relationship of stimulus probability to P_3 amplitude. In the first experiment (I),

she used low-pass and high-pass clicks as her two stimuli, and these were presented in different experimental conditions in the following proportions:

(1) 20% low; 80% high
(2) 40% low; 60% high
(3) 60% low; 40% high
(4) 80% low; 20% high

The subject was told the a priori probabilities to be used in a given block of trials, but he did not know which stimulus would occur in any trial. He made a verbal guess that was confirmed or disconfirmed by the occurrence of the high or low click.

The findings were essentially the same for the high and low clicks. For simplicity of exposition, I will limit the presentation to one of the two stimuli. In figure 6–2, we have plotted the amplitude of P_3 of the average evoked response to low clicks on the ordinate as a function of the probability of occurrence of low clicks.[4] The data are averaged across four subjects. A monotonic function is obtained; the lower the probability of occurrence of low clicks, the larger is the amplitude of P_3.

Tueting also explored a more general question that was derived from an information theory approach (Hyman, 1953). In a second experiment (II) with the same subjects, she varied, not the relative frequency of the two stimuli, but rather the sequential dependency. In this design, the two stimuli occur in a 50:50 proportion, but the probability that one stimulus will follow the other or itself is varied.[5] Again she used four sets of probabilities:

(1) 20% alternation; 80% repetition
(2) 40% alternation; 60% repetition
(3) 60% alternation; 40% repetition
(4) 80% alternation; 20% repetition

Thus in condition 1, 20 percent alternation means that low clicks follow high clicks (and high clicks follow low clicks) in 20 percent of the

[4] It should be noted that we are dealing separately with the probability of low and high stimuli and not the average uncertainty of the condition. This is often referred to as the surprisal value of the event (see Attneave, 1959). For example, the 20 percent low—80 percent high condition has the same average uncertainty as the 80 percent low—20 percent high condition. Here we are concerned with evoked responses to low clicks when low clicks had a 20 percent probability of occurrence as being different from evoked responses to low clicks when low clicks had an 80 percent probability of occurrence.

[5] In Experiment I, the only constraint on randomness present in the experiment is that the two stimuli occur in the stated proportions. This, however, necessarily means that a stimulus that occurs more often will more often enter into repeated sequences. In Experiment II, the experimenter manipulates only the proportion of repetitions or alternations. When this is the only constraint on randomness, the resulting relative frequency for low and high clicks is 50:50 on the average.

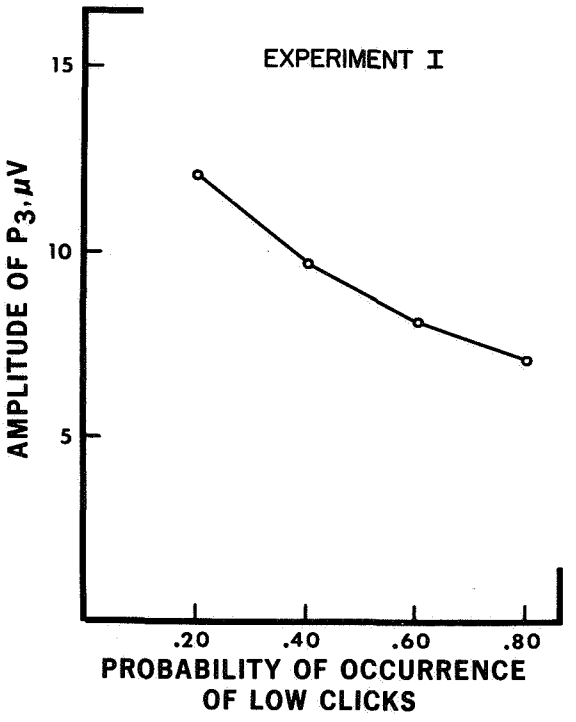

FIGURE 6–2.—Amplitude of the P_3 component of the average evoked response to low clicks as a function of a priori probability of occurrence of low clicks. P_3 is measured from baseline at stimulus onset to peak positivity in the vicinity of 300 milliseconds. Data are averaged for four subjects.

sequences, whereas 80 percent repetition means that low clicks follow low clicks (and high clicks follow high clicks) in 80 percent of the sequences. As in Experiment I, the subject was informed of the a priori probability structure of each block before its presentation. This procedure yields two classes of data—evoked potentials to alternated stimuli and evoked potentials to repeated stimuli. As in Experiment I, only the responses to low clicks are considered, and curve IIa of figure 6–3 is obtained for the P_3 component of the average evoked response to low clicks that followed high clicks; curve IIb is obtained for the P_3 component of the average evoked response to low clicks that followed low clicks. These are average data for four subjects. The curve labeled I is the Experiment I data from Figure 6–2. The logic of the comparison is that if the quantitative probability (and not the procedure by which the probability is generated) determines P_3 ampli-

tude, then all three curves should be identical. It can be seen in Figure 6–3 that while curves I and IIa are fairly similar, curve IIb (evoked responses to repeated stimuli) deviates markedly.

So far we have not considered the fact that we have an additional class of data available in the experiment, namely the subject's guess. In figures 6–2 and 6–3, we have averaged across stimuli, some of which confirm and some of which do not confirm the subject's guess. To include information on the subject's guess, the two categories of stimuli are separated. We obtained one evoked potential average for stimuli associated with correct guesses and a separate evoked potential average for stimuli associated with incorrect guesses; P_3 measurements from these separate averages can no longer be plotted against a priori probability as determined by the experimenter. We calculate instead two joint probability terms that represent the probability of guessing low

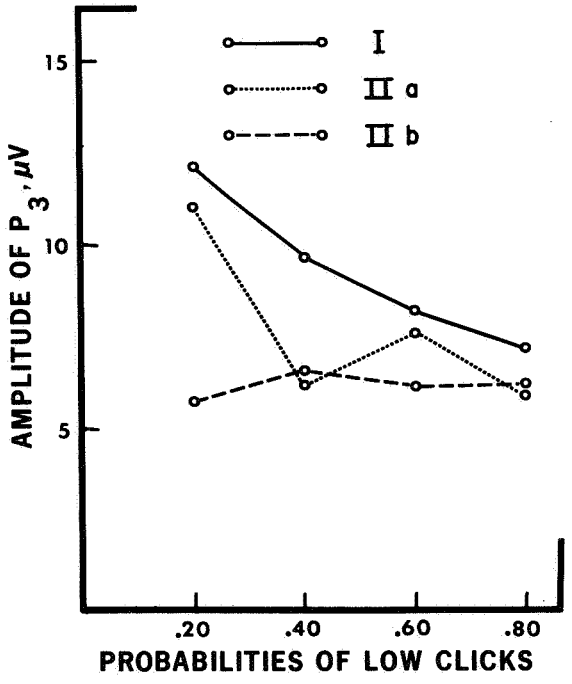

FIGURE 6–3.—Amplitude of the P_3 component of the average evoked response to low clicks as a function of the a priori probability of low clicks. For curve I, the abscissa is the probability of occurrence of low clicks. For curve IIa, the abscissa is the probability that low clicks follow high clicks. For curve IIb, the abscissa is the probability that low clicks follow low clicks. Data are averaged for four subjects.

when the stimulus was, in fact, low ("hits"), and the probability of guessing high when the stimulus was, in fact, low ("misses").[6] In Figure 6–4, we have plotted the obtained hit probability for low clicks on the abscissa and the P_3 amplitude obtained for those trials on the ordinate for both Experiments I and II. It can be seen that now the prediction of essential similarity of all three curves is confirmed, and therefore it may be inferred that it is the quantitative aspect of probability (and not the mode of probability manipulation) that determines P_3 amplitude. Further, the probability measurement that fulfills this statement is based on the interaction between the experimenter-generated stimulus probabilities and the response (guessing) probabilities of the subject, i.e., the probability of hits.

Similar operations with the trials associated with wrong guesses ("misses") yielded the data shown in figure 6–5. These curves are somewhat different from the curves obtained for the "hits," and the similarity among the three curves for the "misses" (fig. 6–5) is less clear-cut than the similarity of the three curves for the "hits" (fig. 6–4). Evidently, the inference that only the quantitative aspects of probability determine P_3 amplitude must be modified to include the qualitative dimension of the correctness or incorrectness of the subject's guess. It might be inferred that any differences between the two sets of curves reflect differences in value that being right and wrong have for the subject.

However, returning to the more general point of this section, these data demonstrate that it is highly desirable to include information on the subject's response when considering the relationship between stimulus conditions and the evoked potential.

The Threshold Problem

Still other issues arise when one attempts to relate, at a quantitative level, behavioral to electrophysiological data. The attempt to compare absolute thresholds from behavioral and physiological data provides a good example of this class of problems. Several investigators have reported that the two thresholds are in reasonably good agreement, i.e., approximately the same stimulus intensity is needed for the subject to say reliably "I see" as is needed to elicit an average evoked potential that can be detected above the noise level. Recently, however, Libet et al. (1967) have reported that the evoked response threshold

[6] These are obtained joint probabilities as opposed to the theoretical or expected joint probabilities. For example, the expected hit probability for low clicks may be calculated for Experiment I data by multiplying the probability of occurrence of low clicks by the probability of guessing low clicks. Actually, it turns out for all our data that the obtained joint probabilities and the expected joint probabilities are very close, i.e., none of our subjects had extrasensory perception.

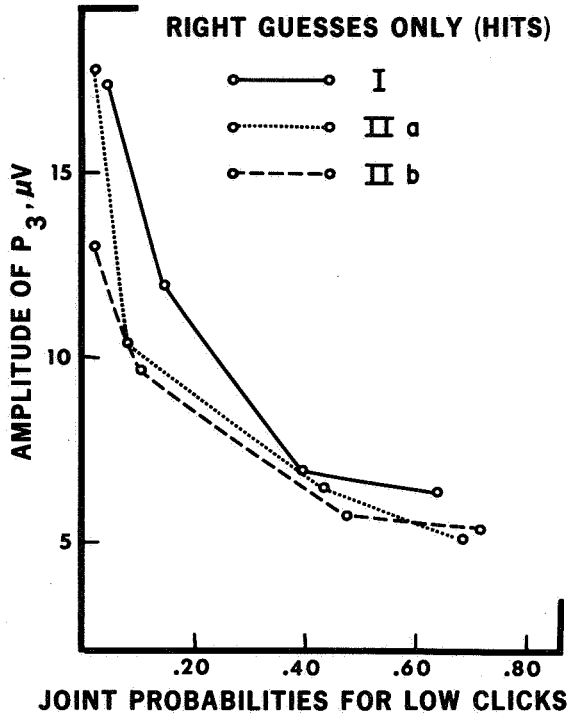

FIGURE 6-4.—Amplitude of the P_3 component of the average evoked response to low clicks as a function of the "hit" probability for low clicks. For curve I, the abscissa is the joint probability that the subject guessed low click and the stimulus was low click. For curve IIa, the abscissa is the joint probability that the subject guessed low click and the stimulus was low click preceded by high click. For curve IIb, the abscissa is the joint probability that the subject guessed low click and the stimulus was low click preceded by low click. Data are averaged for four subjects.

is more sensitive than the behavioral threshold, i.e., average evoked responses could be detected reliably at stimulus levels that were clearly below the behavioral threshold. They suggested that this greater sensitivity was caused by the fact that their electrodes were subdural, and further, that the discrepancy between the two thresholds might be related to the question of subliminal perception.

I cannot say whether these inferences are true, but I would like to suggest that there are methodological problems that prevent making such statements from the data presented. The first of these problems

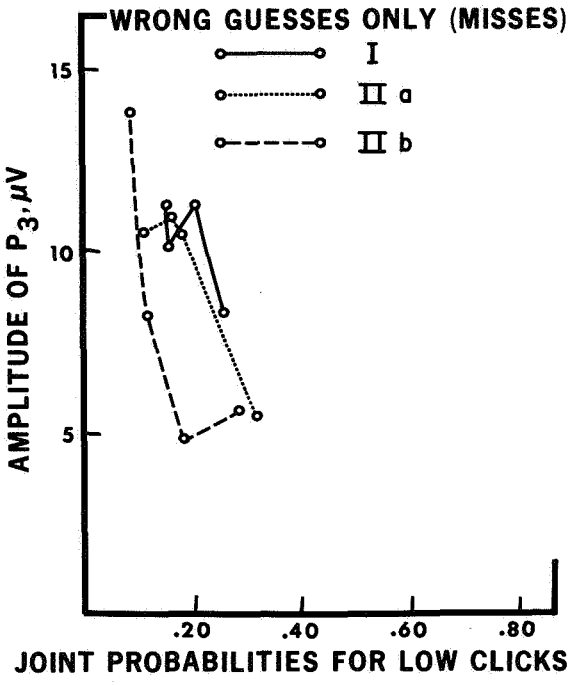

FIGURE 6–5.—Amplitude of the P_3 component of the average evoked response to low clicks as a function of the "miss" probability for low clicks. For curve I, the abscissa is the joint probability that the subject guessed high click and the stimulus was low click. For curve IIa, the abscissa is the joint probability that the subject guessed high click and the stimulus was low click preceded by high click. For curve IIb, the abscissa is the joint probability that the subject guessed high click and the stimulus was low click preceded by low click. Data are averaged for four subjects.

relates to the fact that the subject's behavioral response in each trial is a binary measure—that there was, or was not, a stimulus (in Libet's experiment, the subject was also permitted an uncertain category which, they note, was rarely used). In contrast, what enters into the average evoked potential is a graded or quantitative measure. One might suggest that it would be surprising if two such mathematically different estimates of the threshold, a binary and a graded quantity, yielded the same values for the threshold.[7] This would be logically

[7] For a discussion of binary versus graded judgments, see pp. 38–46 of the chapter by Swets, Tanner, and Birdsall in Swets (1964).

equivalent to saying that a two-valued nominal scale (yes–no) carries as much information as what is probably an interval scale (voltage measurement in the evoked potential).

A proper comparison of the electrophysiological and psychophysical thresholds would require logically comparable operations. As an example, one might permit the subject to use a wide range of ratings on each trial in order to allow him to scale his level of certainty. An average of these ratings might yield a statistic that might be logically comparable to a measure of amplitude in the average evoked potential. Or, alternatively, one could retain the binary psychophysical operation but for the electrophysiological data, require a computer or the experimenter to make a yes-no decision on each individual evoked potential waveform. Whether this latter procedure would yield comparable thresholds would depend in part on whether the same criterion was used by both the subject and experimenter. Of course, both procedures would require that psychophysical and physiological measurements be made on the identical set of trials.

The issue of criterion is quite complex, and it is my belief that it is an important factor contributing to the findings of Libet et al. Several years ago Gad Hakerem of our laboratory compared the psychophysical visual threshold and the pupillary response threshold in the same sets of trials (unpublished data). Just as in Libet's experiments, he compared thresholds obtained with a yes-no verbal report of the subject with the average pupillary response. He found that while indeed in some subjects the pupillary threshold was more sensitive than the visual threshold, in other subjects the visual threshold was more sensitive, and in still other subjects the two thresholds were equally sensitive. We suspected at the time that we were dealing with criterion differences among subjects. Conservative subjects, who hesitated to report seeing the light unless they were sure, might be the subjects for whom the pupillary threshold (which is presumably unaffected by the criterion) was more sensitive. On the other hand, it was possible that the subjects who operated with a looser criterion were the ones who gave a more sensitive, or equal, psychophysical threshold. Unfortunately, we were at the time somewhat naive with respect to detection theory, and we did not generate the behavioral data in a form to permit calculation of d', which would have been distinct from the influence of the criterion variable. Such a measure might have given less intersubject variability when compared with some appropriate measure of the pupillary response.

In the Libet et al. study, there is evidence that the psychophysical procedures were such as to establish a very high criterion in all subjects. This is the direction that would be required for greater sensitivity for the physiological measure. They "required that the subject

report a distinct subjective feeling or awareness of the sensation" (Libet et al., 1964, p. 549). That these instructions operated to establish a uniformly high criterion is supported by their report that very few false positive responses were obtained. The nub of the matter lies in Libet's use of words such as "awareness" (in the 1964 article) and and "conscious sensation" (in the 1967 article). The measurement of threshold is by its nature an uncertain situation, a boundary between sensing and not sensing, with which psychologists have normally coped by using statistical definitions. These definitions have nevertheless produced reproducible values for the psychophysical threshold. Libet in effect requires his subjects to be certain—to produce high thresholds. Unless one is prepared to assume that the usual psychophysical threshold does not involve cortical activity, it is reasonably predictable that evoked potential activity will be detected at stimulus intensities below those needed for Libet's psychophysical threshold.

If the conditions for the two sets of measurements could be made more comparable both as to the scaling operation and as to the handling of the criterion problem, then it would be quite interesting to know whether there would be a residue of greater sensitivity for the evoked potential. The problem, however, may be more complicated since it is not inconceivable that certain aspects of the physiological response might also be affected by the criterion variable. An aspect of such interaction is related to the problem of construct definition which is discussed in the last section of this paper. However, one brief example may be given here. As indicated earlier, we have shown that the presence of uncertainty with respect to which stimulus will be presented markedly affects the evoked response waveform. Donchin (1968) has interpreted the findings of an experiment ostensibly aimed at evoked potential correlates of psychophysical judgment as primarily reflecting the role of uncertainty rather than the role of the stimulus differences that the subject was discriminating.

IMPLICATIONS ARISING FROM TEMPORAL AND SPATIAL AVERAGING

Signs versus Codes

In order to obtain a readable signal from scalp, investigators in this field have used averaging techniques. When the signal is particularly small or variable, they often increase the number of trials. While it is certainly true that the average cannot extract something that is not present in the individual trials (the opposite is not necessarily true), we cannot take for granted that this means the information is available *to the brain* in a usable form. We tend to assume that averaging is imposed on us by our conditions of measurement but that the brain itself can read its own messages, untroubled by the noise and variability that appear at our electrodes. While it is true that the brain is probably

not troubled by the contaminations that arise in getting from cortex to scalp, not all the noise, and certainly not all the variability, arise from this source. Goldstein et al. (1959), for example, have shown when recording directly from the cortex in cats, the upper limit of evoked potential resolution is, under optimal conditions, approximately 50 clicks per second. However, by use of averaging, this upper limit can be raised to approximately 200 clicks per second. However, the question remains; the computer can find a signal buried in cortical noise, but to what extent can the brain do so? Normally, one would want to use a behavioral criterion to define the functional limit. If the results of stimulation can be manifested in behavior, then it follows that the brain can find the signal in its own noise unless, of course, the signal we are observing is not the relevant one for the brain. Uttal (1967) has suggested a terminological distinction that is relevant here. He suggests that if there is evidence that what we are recording is information that is used by the nervous system (e.g., not lost at some subsequent synapse) and affects behavior, use the term code, but for physiological correlates that do not meet these criteria, use the term sign.

When we pose problems in the form of "is the evoked potential threshold more sensitive than the behavioral threshold," we have cast ourselves loose from the behavioral anchor. Even if the experiment is done with the most careful methodology, we are left with the problem of whether the greater sensitivity of the evoked potential is the result of what can be extracted with an external computer or whether in fact the brain also has some means of utilizing this information.

This last issue of proving the relevance of physiological correlates is of course by no means unique to human evoked potential research; it is shared by the whole field of physiological psychology. In animal work in the last 15 years, the problem has not been one of finding physiological correlates, but one of finding too many. To take one example, correlates of binaural interaction of stimuli at the two ears turn up at several levels of the nervous system as well as in at least two different ways at the cortex. It is this kind of problem, rather than the issue of methodological purity, that has emphasized the need to limit oneself to the term physiological correlates rather than the more desirable term of the physiological basis of behavior. In animal work, the fundamental way out has classically been via ablation techniques. Despite the extreme care necessary in interpretation, properly used ablation procedures form an important adjunct to electrophysiological data on the path toward the establishment of necessary and sufficient status for physiological correlates. In the human evoked potential area, the barrier of the meninges, skull, and scalp has so far prevented us from facing too soon an embarrassment of riches. But our problems ultimately remain the same: how to establish necessary and

sufficient status for a finding—and here, without even the mixed blessing of availability of ablation techniques.

Davis and Onishi (1968) have recently pointed out that, despite the fact that the amplitude of the vertex potential increases with stimulus intensity, a number of other properties of the vertex potential such as its relatively long recovery time make it a poor candidate as a correlate of the loudness function. In Uttal's terminology, the growth of amplitude of the vertex potential with loudness is a sign rather than a code.

It should be clear that "signs" are neither unimportant nor uninteresting. It now appears probable that evoked potential techniques will find significant diagnostic and other medical applications. Furthermore, we should before long be able to use our evoked potential data "in reverse." For example, as we establish more firmly the evoked potential correlates of attention, we should be able to look at a particular set of data and infer that the subject was or was not paying attention. Further possible applications of evoked potential data may arise in using evoked potential findings to sharpen up the behavioral level of analysis. For example, it should be possible ultimately to use evoked potential data to decide whether two experimental operations, which in terms of existing behavioral classifications should be equivalent, are in fact equivalent.

Randomization of Experimental Conditions

Still another implication of averaging is the need to accumulate a sufficient number of trials under sufficiently equivalent conditions to permit meaningful combination. Very few investigators are content with as few as six trials in the average; some have used as many as 500, and the mode is somewhere between 25 and 100. It has already been established adequately that even—or perhaps particularly—with simple stimuli such as flashes of light, profound changes in amplitude occur over successive trials within a block and across blocks of trials. We have even obtained a decrement in amplitude of evoked potentials over 4 successive days of testing under identical experimental conditions (Tueting, 1968). Some of these effects are related to habituation and dishabituation; others may involve issues such as fatigue, boredom, or attentional drift. One way to study the habituation process has been used recently by Ritter et al. (1968). Rather than averaging responses within a block of trials, they averaged all first responses across blocks, all second responses, etc.

The one fundamental way to cope with the problem of averaging over constant conditions is to interdigitate or to randomize stimuli whose evoked potentials are to be compared (Diamond, 1964). It

would seem to me logical a priori that this randomization procedure be carried to its limit wherever possible, i.e., the randomization of stimuli by trial. That this is not yet common practice is, I assume, the result of equipment limitations. Of course, there are specific experimental designs that by their nature do not permit randomization of experimental conditions by trials (for example, when the variable under investigation is the relative proportion of two stimuli in a block of trials). Here departures from perfect randomness are used intentionally by the experimenter to create sets or expectancies. But the point is that incomplete randomization of experimental conditions may create sets that are not intended by the experimenter.

A recent finding, which I suspect is related to the question of randomization, is reported by Buchsbaum and Silverman (1968). They found that certain subjects give an inverse relationship between evoked potential amplitude and stimulus intensity. The different intensities were presented in short blocks of trials. This finding is reminiscent of the report (Jarl, 1957) that it is more difficult to obtain a monotonic relationship between stimulus intensity and reaction time when stimuli are not randomized by trial. Evidently, if stimuli are all of the same intensity within a block, this permits subjects to establish arbitrary sets—e.g., to find low intensity blocks challenging and high intensity blocks an opportunity to relax effort. Randomizing stimuli by trial eliminates such factors and permits a monotonic relationship to emerge between reaction time and stimulus intensity. Of course, in the case of the Buchsbaum and Silverman study, they were looking for differences among subjects, and I do not think they were interested in eliminating set as a variable. One suspects that their intersubject differences would have been enhanced if they had used even longer blocks than they did. However, their finding emphasizes the importance of randomizing conditions by trial for experiments where one is trying to avoid intersubject differences of this kind.

Näätänen (1967) has recently pointed out that alternating, rather than randomizing relevant and irrelevant stimuli, as has been done by Satterfield (1965) and by Chapman and Bragdon (1964), militates against the crucial nature of these experiments for the question of selective attention. It can be argued that alternating the stimuli permits the subject to enter a cycle of alternating excitability. In other words, it is not the relevance or meaningfulness of the stimuli that affects evoked potential amplitude but rather is the subject's cyclical alternation of readiness prior to the stimuli. While I do not agree with Näätänen's conclusions with respect to selective attention, his criticism of the nonrandom presentation of conditions is cogent.

Constancy of Stimulus Meaning

Another aspect of the problem of repetition of stimuli necessitated by averaging may emerge as investigators become more venturesome and begin to consider evoked potential correlates of the meaning of semantic stimuli. While this kind of discussion is premature, in the sense that there is not as yet a body of studies to evaluate, a number of investigators have begun to consider research into the possibility of evoked potential correlates of meanings of words (e.g., John et al., 1967). In dealing with meaningful stimuli, the problem of accumulating many trials becomes more serious. The phenomenon of verbal satiation is well established—though it is as yet little more than the formal name for the rather common observation that the surest way to destroy the meaning of a word is to repeat it; e.g., dog, dog, dog, dog, dog, etc. If investigators are to undertake seriously the study of evoked potential correlates of semantic meaning, adequate experimental designs must be evolved that guarantee that the stimulus is meaningful in each trial, and preferably that the same stimulus always has the same meaning.[8]

Another issue in guaranteeing identical meaning with each repetition is a fairly subtle one, and I am not aware of any psychological literature on the problem. However, meaning is not so much a single thing as it is an envelope of variation. The specific meaning is usually given by the context. The word dog may conjure up something fearful, or friendly, or the image of a particular breed, or the spelling D–O–G, or an organism that imposes problems in a city apartment, etc.

Implications of Spatial Averaging

There is one property of the average evoked potential that must be considered when one attempts a quantitative examination of the relationship between shape or amplitude of the average evoked potential and psychological variables. This is, the fact, that what we are recording from scalp (and to some extent also from cortex, although perhaps less so) may represent a summed average of a variety of processes (Cooper, et al., 1965). Since what we record is only whether the sum of such processes is positive or negative with respect to some reference, the problem of disentangling the relationship between shapes, latencies, or amplitudes of components and some physical or psychological variable is discouraging. We and others have sometimes used difference waveforms between two experimental conditions in order to obtain a better estimate of some process (Sutton et al., 1965b), but this can be used only in limited situations since latency of similar compo-

[8] The evoked potential correlates of verbal satiation itself might make an interesting study.

nents often varies with experimental conditions. Variance in latency would result in a different waveform that might be highly deceptive.

This is not the place to comment on the physiological implications of these limitations of recording from scalp. Instead, I would like to note that what this means in terms of experimental design is that behavioral aspects must be simple, and great care must be exercised to study correlates of behavioral variables parametrically, and, as much as possible, one at a time. Factorial design of experiments involving several variables affecting the same set of trials, as a result of recording from scalp, may yield data that are difficult if not impossible to interpret. While correlates might be obtained under such conditions, since only if processes are exactly opposite in polarity and amplitude will they completely cancel out, lack of separation of factors influencing the waveform would confound seriously any quantitative properties of the evoked potential waveform.

PROBLEMS IN CONSTRUCT DEFINITION

We are participating in a relatively new area of research that has stirred the imagination of workers in several fields. The reason for this interest is rarely made explicit, but I think it lies in the fact that, despite the limitations resulting from averaging and the difficulties of physiological and anatomical interpretation, many of us consider that we are involved in a breakthrough. Evoked potentials are not just another physiological measure like the galvanic skin response, or pupillography, or heart rate, but something much more exciting—a direct reflection of time-locked activity of the brain associated with specific conscious processes in awake human subjects. In the terminology used earlier, the interest in part arises from the possibility that we may be dealing with codes rather than signs—or at the very least, signs of the activity of the central nervous system rather than of peripheral processess. This is not altered by the fact that many of the findings might be duplicated with other physiological indicators. For example, in our own laboratory (unpublished data) we had no trouble finding differences between pupillary responses to certain and uncertain stimuli.[9] One might, however, expect a wider range of psychological variables to be reflected in the evoked potential. I doubt, for example, that one would expect to find heart-rate correlates of visual form, unless perhaps they were visual forms associated with a particular kind of reinforcement history.

It is perhaps because of this sense of bright horizons, that one detects a tendency for investigators to behave like explorers with an

[9] But the pupillary effects have a much longer latency than P_3 of the evoked potential, suggesting that the pupillary effects are secondary.

uncharted continent to explore. A partial list of psychological terms for which evoked potential correlates have been reported is:

anxiety
arousal, activation, and interest
conation
conditioning and learning
contingency
correctness vs incorrectness of detection
difficulty of discrimination
distraction
endogeneous stimuli
excitement
expectancy, set, and readiness
habituation
intention to respond
meaningfulness
motivation
novelty
orienting
positive and negative effect
segmental set
selective attention
significance
suggestion and hypnosis
symbolic or semantic value
task relevance
uncertainty, predictability, and information
vigilance and altertness
visual recognition

In the studies in which these terms have appeared, many of the experimental procedures used and the potentials described overlap. The terms themselves also have a great deal of overlap in meaning. It is difficult to believe that all of these findings involve genuinely different potentials. If they are not different, one must then ask with how many are we dealing, and where different experimental operations yield similar changes in waveform, what is the common denominator? The problem posed by a plethora of cross-cutting, poorly defined concepts is not a trivial one. First, they make claim to a level of generality from which one can only retreat. Second, they make a poor foundation for moving forward since progress will depend less on the broadness of the claims and more on the precise control and specification of experimental operations and on the precision of reasoning involved in attempts at construct validation.

It is always risky to attempt a sociology of knowledge, but it is worth commenting on the reasons that such a situation has arisen. Many of us enter the laboratory with the mood of "why not?" Why not attempt to see if evoked potential waveforms correlate with some particular complex psychological phenomenon? This kind of sentiment is allied with the fact that in a pioneering field there is a strong urge to be the first to colonize a new area. Such a sentiment can easily lead to the relaxing of criteria for making scientific statements.

It is easier for this purpose to direct criticisms against oneself. In one paper (Sutton et al., 1967), I made the statement that the evoked potentials (or more specifically the amplitude of P_3) are a function of the "significance" of the stimulus to the organism. Now the state-

ment as made did summarize the fact that the term significance seemed to be the best way of collecting under one umbrella the diversity of behavioral operations that we had found to affect the amplitude of P_3. But more sober reflection, the opportunity for which has been provided by the writing of this paper, made me realize that I did not mean, or at least should not have implied, that any time the stimulus was made more significant by any experimental operation, P_3 amplitude increased. Even at the time the statement was published, there was available Davis' investigation (Davis, 1964) on the effect of a discrimination task on the evoked potentials to click stimuli. He reported that only one of the six subjects showed a positive component at a latency which I would interpret as appropriate to P_3. More recently, we have been working with discrimination tasks in our own laboratory, and although the findings are complicated, they cannot be subordinated with any ease to the general statement that P_3 always increases with increase in stimulus significance.

One attempted solution for this problem of multiple terms is, I think, related to the sentiments that lead to the premature statements in the first place. One has a tendency to prefer his own terms to the terms of others. If the sentiment that I described earlier might be called intellectual imperialism, then what I am describing now might be called intellectual cannibalism. Thus one, without addition of any new data, might attempt to make a case that the experiments that have led to these terms are all really dealing with arousal, attention, degree of mental activity, information, significance, or habituation. It is not that one can dismiss such a possibility a priori; however, I think that it is equally premature to attempt to bend all the findings to fit one concept.

One well known criterion of the usefulness of a theory or a concept is its ease of disproof. If one wants to use one term in preference to another, one must be able a priori to define what would be a negative case. Are there any operations by which stimuli can be made more or less significant, but not different in attention value? Can something be made more meaningful, but not more significant, and vice versa? The design of such controls will require much experimental ingenuity. Furthermore, if discrimination is the operation for determining task relevance, how shall we approach the problem of studying evoked potential correlates of discrimination itself? If the operation of adding two numbers defines meaningfulness, how are we to look for evoked potential correlates of addition?

There really is no simple way out of such a dilemma. Experimenters continually add controls in which they vary some aspect of their procedure while retaining something that still fits under the concept. Extensive activity of this kind is occurring with respect to the CNV.

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I will develop an example of this kind of construct search with respect to the P_3 component of the vertex potential. However, I should first point out that, whatever the role of constructs in leading us to do experiments, when we have accomplished the experiments, it is the experimental operations that are important while the concepts must remain tentative. If the experimental operations are precise enough, the results will hold, whatever we label the finding.

When we first began to work on the relations between stimulus uncertainty and P_3 of the vertex potential, we knew nothing about P_3 nor did we have precise formulations of the uncertainty concept. Initially, we borrowed a loose terminology from information theory to define our experimental operations. This seemed to work very well, and I have shown in the figures the monotonic relationships obtained between uncertainty measures and the amplitude of P_3. When P_3 became for us a well-known phenomenon, we began to reverse our operations. We took P_3 as given, and began to ask what behavioral manipulations—other than the ones with which we began—alter P_3. Degree of monetary payoff for guessing turned out to be one such manipulation. Such results made us think of a concept such as "significance." Also, P_3 was found to be relatively small or even appeared to be nonexistent when there was no uncertainty (fig. 6–1), i.e., when we told the subject before each stimulus which of two stimuli we intended to present. Therefore, at first we did not measure the amplitude of P_3 under this condition. More recently, when we began measuring P_3 in the "certain" condition, we found to our surprise, that even this small P_3 was altered in amplitude by the relative frequency of the two stimuli.

The data are shown in figure 6–6 (data from Tueting, 1968). In order to compare the "uncertain" condition with the "certain" condition, we must omit information on the subject's guess in the "uncertain" condition since there is no guessing in the "certain" condition. In figure 6–6, we show again as the solid curve, the data from figure 6–2 as the "uncertain" condition (I). In addition, the dashed curve shows the data from identical blocks of trials for the same subjects, but in these blocks the subject is told before each stimulus which of the two stimuli will be presented (III). We can see that although the amplitude of P_3 is much smaller for the "certain" condition, this small amplitude is still sensitive to stimulus probability—P_3 is larger for lower stimulus probabilities. We doubt that this is a reflection of a sensory recovery function since the interval between stimuli is quite long, on the order of 6 seconds.

The finding that the "certain" condition also yields a relationship between P_3 and stimulus probability now made information theory, with which we began, inadequate to cope with all of the data since,

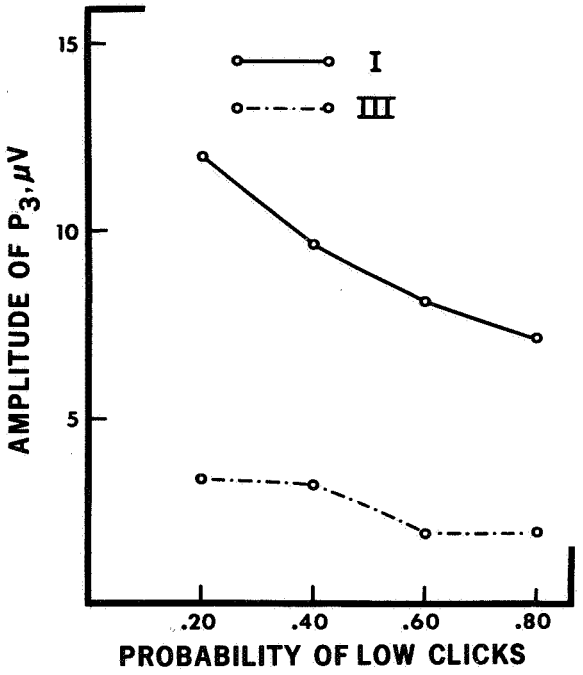

FIGURE 6–6.—Amplitude of the P_3 component of the average evoked response to low click as a function of the a priori probability of occurrence of low clicks. For curve I, the subject guessed before each click whether it would be high or low. For curve III, the subject was told whether the next click would be high or low. Data are averaged for four subjects.

regardless of stimulus probability, the formal information transmitted is zero when the stimulus is completely known in advance.

Reviewing to this point, the term "significance" seems inadequate because, as indicated earlier, we were unable to fit this formulation to some of the experiments in which difficulty of discrimination is manipulated. A generalized arousal concept that might incorporate the monetary payoff data does not fit other of our data that unequivocally show that P_3 amplitude is dependent on the probability of occurrence of a stimulus whose identity is unknown to the subject before its presentation (fig. 6–1). The relevance of this finding is that one cannot, without involving additional factors, use a common condition to explain differences between events. Therefore, a generalized arousal concept cannot be used to explain amplitude effects that are dependent on which of two uncertain stimuli is actually presented. A generalized arousal concept also does not fit Näätänen's

(1967) recent data in which he presented task-relevant and irrelevant stimuli in random order. The task-relevant stimuli clearly gave larger P_3 amplitudes.[10]

What about "task-relevance" as the basic and necessary feature controlling the P_3 component? This fits much of the data but conflicts with a recent experiment by Ritter et al. (1968). They had subjects reading a book during the experiment and presumably "ignoring" tone stimuli presented at fixed intervals. At unpredictable points during a block of trials, the experimenter shifted to a tone of a different frequency. The first of the shifted tones produced a large P_3 despite the fact that all the tones were equally task-irrelevant. Of course there is always the possibility that their subjects did not succeed in following instructions and did not "ignore" the frequency shift. Problems of this type are discussed below, with reference to subject option.

This seems to bring us back full circle to a concept such as uncertainty. But as we have shown earlier, the quantitative relationship obtained between P_3 amplitude and stimulus probability under the "certain" condition substantially weakens our attempted generalization. "Information delivery," which is another term we have used, is merely the inverse of uncertainty and therefore encounters the same difficulties.

We are currently conducting experiments on the relationship between P_3 and the reinforcing properties of the stimulus. However, we doubt that this will lead to a general formulation since again the stimuli in the Ritter, et al., experiment cannot be viewed as reinforcing.

It may turn out that the most useful way of looking at the determinants of the P_3 component is in terms of orienting or dishabituation (Haider et al., 1968). However, it would be necessary to extend the orienting response concept to include the quantitative properties observed for P_3. It is possible that any change of stimulus, even when it is known in advance, may result in a small amount of dishabituation or orienting. It is not unreasonable that the greater the amplitude, the rarer the new or different event. In this framework, our data would be consistent with the notion that under conditions of uncertainty, the whole curve is shifted (amplitude of response is increased), but the same quantitative relations are maintained. The full implications of attempting to view P_3 as a correlate of the orienting response are yet to be explored.

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[10] Actually, Näätänen discounted his own positive data on this point, but inspection of his significance tests and figures supports the above statement. Näätänen was considering the whole waveform and did not particularly focus on P_3 (f_1 in his terminology). As a result, he dismissed a positive finding for P_3 as not consistent with the rest of his data.

Subject Option

The particular class of problems and directions of solution discussed earlier are not unique to human evoked potential research. For many years, we have been involved in research on the problem of finding measurable differences in the performance of hospitalized, mentally ill patients and normal controls. In this area, we encounter a problem that is generally not assumed to arise with trained normal subjects. When we find a difference between patients and normals, let us say in two-pulse resolution, we must consider whether in fact we are dealing with a perceptual difference, or whether the difference between groups results from differences in cooperation, motivation, attention, understanding of the instructions, etc. In coping with this problem, the usual subjective-objective dichotomy does not help—the problem remains equally serious whether the measure is reaction time or a verbal report. I have not found any term in the literature that reflects this problem, and I have coined the term "subject option" to cover it. In our work in psychopathology, we are continuously striving to find experimental strategies to reduce or otherwise control subject option.

Paradoxically the more promising a future we project for evoked potential correlates, the more seriously we will have to be concerned with the problem of subject option. If, for example, factors of set or attention did not influence evoked potential waveforms, then we would not need to be concerned with how the subject approached a task. On the other hand, the more classes of psychological variables there are that affect the evoked potential, the more rigorous our experimental controls must be to reduce the role of subject option. In some of the earlier studies on the correlates of the sensory properties of stimuli, a typical comment was that the later components of the evoked potential were more "labile." More recent work from our own and other laboratories shows that in fact these later components relate systematically to more complex psychological variables. We can therefore assume that the report of lability for these components simply meant that in a study of simple sensory correlates, experimenters did not control more complex psychological aspects of the experimental situation.

For these reasons, it is necessary to avoid experimental designs that rely on instructions to produce complex psychological states, e.g., "to attend to or to ignore the differences between two tones," or "to imagine squares or circles," or "to attend to stimuli delivered to the left hand while ignoring identical stimuli delivered to the right hand," or "to try to perceive the after-image," or "to recognize the

stimulus," or "to think high or to think low CNV." [11] Such designs rely on the understanding, good will, and training of the subject to do something which, at best, is defined only poorly by the instructions. Such designs may have a place in exploratory investigation to decide whether something may be worth chasing down, but they can never establish any finding on a firm basis.

The foregoing discussion should not be interpreted as an argument against the use of instructions. On the contrary, it is not unlikely that limiting subjects to an instruction such as to sit quietly while clicks or light flashes are occurring leads to a great deal of subject option. Most subjects will try to reinterpret such a senseless and boring task and the experiment is at the mercy of the subjects' interpretations. Rather, the argument here is in favor of clear and precisely defined instructions that are easy to follow and that make sense to the subject. It is only in this way that there is a possibility of maintaining a subject in a constant state for the duration of the experiment and of maintaining a relatively constant state across subjects.

There are two generally mutually reinforcing directions now in use in evoked potential research for the reduction of subject option. One is, as much as possible, to assign the variable under investigation to the stimulus. To investigate uncertainty, one does not tell the subject to "be uncertain;" one alters the probability of occurrence of stimuli when the subject must guess what stimulus will be presented. The other direction for controlling subject option is implied by what I have described as the triangular experimental paradigm, that is, to use some appropriate response variable as an indication of what the subject is doing. In the foregoing example, the relative proportion (and perhaps even the sequence) of guesses is such an indicator. In other kinds of situations, one can require a reaction time response or a discrimination by the subject and use the speed or accuracy of response as some indication of variables such as attention or vigilance. It is this kind of paradigm that was used so elegantly by Haider, Spong, and Lindsley (1964). They used accuracy of discrimination to define the level of vigilance that was found to correlate with evoked potential amplitude. Although a number of investigators have used this kind of approach, the actual inclusion of the behavioral data in what is reported seems to be somewhat less common.

I am not suggesting that these problems can be solved with any ease, or that there is one solution for all experiments. As an example, a few years ago we were studying the effect of the size of monetary payoff in a guessing situation on the P_3 component of the vertex potential.

[11] In all fairness, this instruction to produce high or low CNV was used in an experiment (McAdam et al., 1966) to show how one form of what I have called subject option could contaminate results.

Results were fairly straightforward as long as we used different payoffs for different blocks of trials. The P_3 was found to be larger when the subject was guessing for a 10-cent stake than when he was guessing for a 1-cent stake. However, for reasons which need not be developed here, we got into instructions such as "if you guess light and you are right, you win 10¢; however, if you are wrong you lose 1¢; if you guess sound and you are right, you win 1¢; however, if you are wrong, you lose 10¢." We were dismayed when in these situations the orderly relationship between payoff and amplitude of P_3 broke down. Often the higher stake did yield a larger amplitude P_3, but sometimes it reversed. When we queried our subjects, we found that they would say things like "although I did not much care whether I won a penny, I was relieved that I did not lose a dime." Evidently, our instructions created multiple options for the subject. He could treat the same event in terms of winning a penny or in terms of not losing a dime. Thus what was for our experiment a single event, was for the subject an event that could have two different meanings—which we did not control. We abandoned this experiment, not because we did not believe our evoked potential data, but because we did not know how to exercise adequate control over the psychological situation.

SUMMARY

In this paper I have made the underlying assumption that, for the time being, we should proceed in human evoked potential research as if horizons are limitless. However, even if this be the case, it cannot be realized without systematic and precise attention to all three domains of variables that enter into the evoked potential experiment—namely the stimulus, the physiology, and the behavior. In this paper, I have limited myself to the problems of specification and definition of one of these three domains—the psychological or behavioral domain. I have outlined some problems in the psychological domain that are particularly relevant to evoked potential experiments that have been done, or problems that are potentially serious in areas which some of us have begun to research.

In the first section, I have emphasized the importance for evoked potential research to obtain data in all three domains in the same set of trials. I have given an example of how this approach assisted in the interpretation of our uncertainty experiments. I have also discussed an example of the problems that arise when one attempts to make quantitative comparisons between psychological and physiological data.

In the second section, I have pointed out some of the problems that arise from the need to repeat stimuli required by the averaging method.

This requirement has ramifications which (1) affect the ultimate interpretation of evoked potential data, (2) necessitate randomization of experimental conditions in order to avoid contamination because of habituation, fatigue, boredom, attentional drift, or the formation of inadvertent expectations by the subject, and (3) impose serious limitations on experiments concerned with the meaning of stimuli. It is also suggested that the spatial averaging that is a byproduct of recording from scalp makes it highly desirable that the behavioral design of experiments be as simple as possible.

I have also pointed out that the early multiplication of terms and constructs for which evoked potential correlates have been reported must give way to a more systematic attempt to specify and define the relevant constructs. An example of such an endeavor is given for the P_3 component of the evoked potential. Finally, it is pointed out that some of the problems in construct definition arise from imprecise experimental designs that put too much of the construct being investigated into the instructional variable. It is suggested that behavioral indices be utilized more systematically in the attempt to define more precisely the construct under investigation.

DISCUSSION

DR. CHAPMAN: [12] I would first like to compliment Sutton on his very fine paper in which he has touched on most of the major problems connected with this topic. They are quite complex; therefore I won't be able to deal with very many problems in any detail.

He speculated concerning why such a topic was included in the program, and I would like to add my own speculations to his. It seems to me that there may have been two reasons why such a topic was selected. First, I think the point was to reveal that there is a large and varied literature available in psychology, and a great deal of it is quite rigorous in definition and methodology and demanding that the behavioral responses be well defined and measured. This is, of course, one of the major points that Sutton has made. The second reason is that it is important to be concerned about such psychological variables in AEP experiments because these variables really affect the AEP. This is not a trivial sort of question.

I think that there is only one general point in Sutton's paper with which I might take issue, and that is the question about whether simple experiments are to be preferred over factorial designs. I think a case can be made for factorial experiments having more power than simple experiments. Most analyses of AEP components assume that the effects are fixed in time (e.g., multivariate techniques, Donchin,

[12] Supported by Public Health Service Research Grants NB03590 and NB08575 from the National Institute of Neurological Diseases and Blindness

1966) with respect to the stimulus. The basic assumption for obtaining the AEP itself is that the components have fixed latencies. Now, if variable A has a fixed effect by itself (as must be assumed even for the one-variable experiment) and, similarly variable B has its own kind of fixed effect, then a factorial experiment permits one to test whether there is a significant interaction between these effects, in addition to the main effects. If there is a significant interaction, then one can look at the effects of variable A at each level of variable B separately (or vice versa), which is what would have been done in the "simple" design anyway.

Now, I would like to emphasize a simple distinction based on time, referenced to the time at which the stimulus is delivered. There are relative emphases on prestimulus and poststimulus processes in theorizing about AEP experiments with psychological variables. Some experimenters tend to focus on the events that occur before the stimulus is presented, and others tend to focus on the events occurring after the stimulus is presented. This distinction seems to be important because it relates to the general question of the specificity of AEP effects. Can the AEP tell us about the particular poststimulus brain processing or only about the excitability of the brain in being prepared or ready for the stimulus?

Using information theory as a starting point for analyzing psychological effects on the AEP emphasizes operations occurring before the stimulus, such as the relative frequency of stimulus occurrence in the past, and the subject's expressed expectation of a future stimulus. What are those processes occurring after that stimulus is finally given to the subject? Generally, the discussion of poststimulus affairs was restricted to the subject's being right or wrong with possible "different emotional valences."

In contrast to information theory, other starting points such as perception, problem solving, etc. might emphasize the processes occurring after the stimulus is presented, such as discrimination, memory storage and retrieval, comparison of stimuli, etc. I am not saying that one starting point is better than another, but simply that they tend to emphasize different aspects of the problem and that experimental answers generally are limited to the questions that we incorporate into the experimental designs.

If an experimenter extends his design beyond his theoretical starting point, his data often free him from those starting biases. We have seen that situation in Sutton's work when the effects of being right or wrong and the effects of payoff are examined. I started from the poststimulus side, being concerned with the relevance of the stimuli to the subject's task, and found additional effects related to the history of stimulus occurrence. This will be illustrated with data later.

I would like to discuss an important experimental design consideration that leads us again to the distinction between prestimulus and poststimulus processes. Psychologists are usually unable to control directly all the relevant variables; therefore, at the hint of trouble, they randomize. When the stimuli whose responses are to be compared are randomized in the stimulus sequence—not by runs or blocks, but by individual stimuli—the effects of confounding variables such as eye movements, EEG activity, activation level, expectancies, etc. are randomized. This procedure tends to eliminate the differential effects of all processes occurring before the stimulus. It is the possibility of prestimulus differences that has clouded interpretations attempting to relate AEP differences to poststimulus processes.

Randomizing the stimulus order as a solution to this pervasive interpretive problem is a very simple idea. It may be viewed as an extension of the elegantly simple principle of averaging, which has proved powerful enough to extract response out of much larger background "noise." The AEP may be extracted, as we all know, because the unwanted electrical activity is random with respect to the synchronizing stimulus. In a similar manner, many of the effects of confounding variables, both physiological and psychological, can be averaged out by randomizing the stimulus sequence.

A bonus that comes with stimulus randomization is the possibility of assessing whether the stimuli are perceived. We can have the subject indicate what stimulus he saw (and the only way that he can be correct that is better than chance is to have perceived the stimulus). In this way, we can be sure that the stimuli are functional in a behavioral sense. Merely counting the stimuli may not be a sufficiently refined behavioral task unless you are interested merely in the perception that some stimulus has occurred. There is the further danger that even that perception may not be constant if the stimuli are presented at a regular rate.

If one is interested in neural codes—for example, the code for intensity—it may be advantageous to have the subject indicate something about the intensity he perceived. Because the AEP depends on averaging, it is possible that the first few stimuli produce the appropriate code in the AEP, and the rest may produce codes that merely indicate that nothing has changed. Neural habituation and behavioral ennui of subjects are both well known. Are the neural codes active when the behavioral task does not demand it?

I would like to illustrate some of the general points already mentioned and some additional ones with data that I have obtained with Dr. Shelburne and Henry Bragdon at the Walter Reed Army Institute of Research (unpublished experiments). These experiments are based on a relatively simple design (Chapman and Bragdon, 1964; Chapman,

1965; Chapman, 1967; Sheatz and Chapman, in press). We have been studying AEP to meaningful stimuli and have built in the meaningfulness experimentally by making the stimuli relevant to the subject's task. Subjects solved problems on the basis of stimuli, and AEP were obtained to these same stimuli. This is to be contrasted with the probe stimulus or distraction procedure where the AEP are to stimuli whose functional role in the behavior of the subject is uncertain. We used two classes of stimuli, numbers and letters, so that the problems could be based on either class of stimuli. For example, we had the subject tell us which of two numbers on a trial was numerically smaller. This is a very simple task, but it requires that the subject perceive both stimuli and compare them. We also mixed in letter stimuli which were irrelevant to the task. Then in other runs, we switched the relevance and had the subject work the problems on the basis of letters, using the analogous task of alphabetical order.

Basically, four stimuli, two numbers and two letters, were presented at 0.75-second intervals on each trial. The particular numbers and letters were selected at random using 1–6 and A–F. The order of stimulus class was also randomized. We sorted and averaged separately the response to the numbers and to the letters on the two types of trials. For example, in figure 6–7 on the left, the solid lines show the responses to number stimuli when they were relevant to the task. The dotted lines on the left show the responses to the identical physical stimuli on other runs when the numbers were irrelevant (i.e., the letters were used to solve the problems). On the right are shown the responses to the letters that were interdigitated at random with the numbers. There was a difference between the AEP to stimuli when they were relevant and when they were irrelevant. Because the focus of this discussion is on psychological variables, many of the details, including the problem of statistical significance, will be neglected. The eye movement records came from electrooculogram recordings averaged simultaneously with the other responses. The similarity of the eye records when the stimuli were relevant and irrelevant supports the position that differential eye movements are not responsible for the AEP differences that were found. The presence of alpha EEG activity was detected by an electronic scorer (Kropfl, Chapman, and Armington, 1962) and signaled by a fixed voltage step. This scorer output was averaged in the same way as the other responses and thus indicated the percentage of time that alpha EEG was present. This serves as one kind of control for the physiological state of the brain and suggests that the AEP differences found between relevant and irrelevant stimuli were not caused by differences in level of generalized arousal.

Thus, it appears that even when the stimuli are randomized the AEP depend upon whether those stimuli are relevant to the task. I

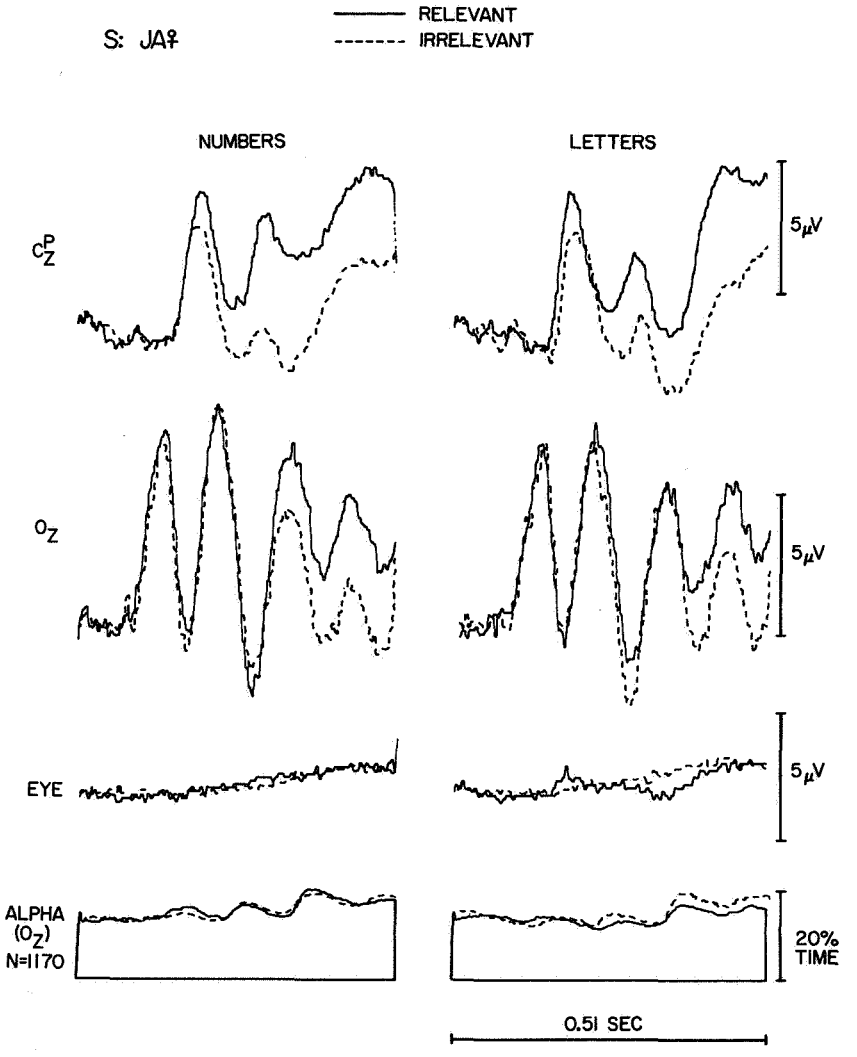

FIGURE 6–7.—AEP to stimuli that were relevant and irrelevant to subject's task. Sequences of numbers and letters, as well as particular numbers and letters, were randomized from trial to trial. In all figures, C_Z^P (electrode between C_Z and P_Z) were monopolar recordings with linked earlobes as references. Eye was bipolar recording with electrodes on external canthis and below one eye; alpha score represents percentage of trials on which O_Z derivation satisfied electronic alpha scorer (Kropfl, Chapman, and Armington, 1962); records, except alpha score, were superimposed at the first part of the record; stimulus was brief strobe flash 30 msec after start of record; computer averages of AEP from a number of runs in a balanced design from a number of sessions (negative down).

would like now to examine this problem in more detail. On each trial, there were two relevant stimuli, and we have pooled their evoked responses in figure 6–7. Since the subject's task was to determine the numerical (or alphabetical) order of the two relevant stimuli, the subject's processing of the two stimuli may be different. For the first relevant stimulus, the subject must perceive it and remember it, store it in memory, if you will. When the second relevant stimulus occurs, he must perceive it, compare it with the memory of the first, and solve the problem. Thus, to simplify, we might refer to the first relevant stimulus as a storage stimulus and the second relevant stimulus as a problem-solving stimulus. We are asking here whether the type of poststimulus processing makes any difference to the AEP.

We have also examined the effect of prestimulus differences based on different expectancies. There are six possible orders of presenting two numbers and two letters, and these six trial types were randomized. However, because of our constraints—each trial contained exactly two number and two letter stimuli—all of the stimuli were not equally random. This illustrates what I think is an important methodological point. When an experimental design involves randomizing, we need to examine in great detail what is randomized and within what constraints. A critical aid is the determination of the actual probabilities of occurrence and the conditional probabilities of the various sequences (or groups) of stimuli.

The data in the following figures indicate that the AEP does depend on these subtleties of experimental design. In figures 6–8 through 6–11, we have sorted the AEP into a number of these categories. At the top of these figures are shown the six possible sequences of two numbers (#) and two letters (L) presented on each trial. The B indicates a blank stimulus (illuminated square patch) that was presented at the beginning and end of each trial. Responses to the blank stimulus will not be shown. The responses shown are to the stimuli circled in each figure.

Figure 6–8 shows the responses to the first stimuli on all trials, which we call Program G. Here we are looking for poststimulus processes since there were no prestimulus differences. On each trial, the stimulus was equally likely to be a number or a letter, and the subject does not know whether to store it or not until he can determine whether it is a number or a letter. If the stimulus belonged to the relevant class, it must be perceived and stored, whereas if it belonged to the irrelevant class, it need only be perceived. Thus, the difference between the AEP shown by solid and dotted lines relate to differences in postperceptual processing.

Figure 6–9 shows the responses to stimuli in the second position (Program H) which are to be stored in memory if they are relevant. The poststimulus processing is the same as in figure 6–8, but there is a

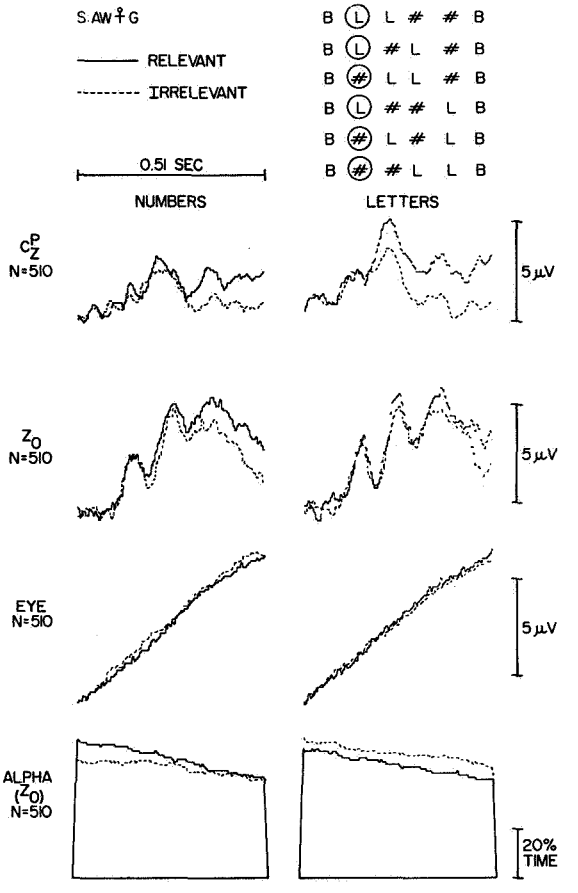

FIGURE 6–8.—AEP to the circled stimuli in the six types of randomized trials using Program G. When relevant, the stimulus information was stored in subject's memory. No prestimulus biases (negative down).

prestimulus difference. There is a prestimulus bias; e.g., if a letter appeared in position 1, then two out of three times, a number will follow. Therefore, although we randomized the sequence in one sense, that is, we made each of the six types of trial equally likely, there are biases within the trials. There are differences between the responses to the stimuli when they were relevant and irrelevant, but with these data alone we wouldn't know whether to attribute the differences to prestimulus or poststimulus psychological variables.

Responses to problem-solving stimuli when there can be no differential expectancies are shown in figure 6–10 (Program J). When these

stimuli were relevant, the subject's task was to compare them with the memory of the first relevant stimulus and indicate numerical or alphabetical order. When these same physical stimuli were irrelevant, the AEP were different, indicating that the postperceptual processing did make a difference. The differences may not be attributed to prestimulus differences since the subject could not anticipate whether a number or letter stimulus would appear and the prior stimuli were balanced in terms of letters and numbers and irrelevant and relevant stimuli.

The same poststimulus processing was required for the problem-solving stimuli shown in figure 6–11 (Program K); however, in addition, there is an important prestimulus difference. Because of the constraint on randomization, the subject can anticipate with certainty whether the stimulus will be relevant. Very large differences between

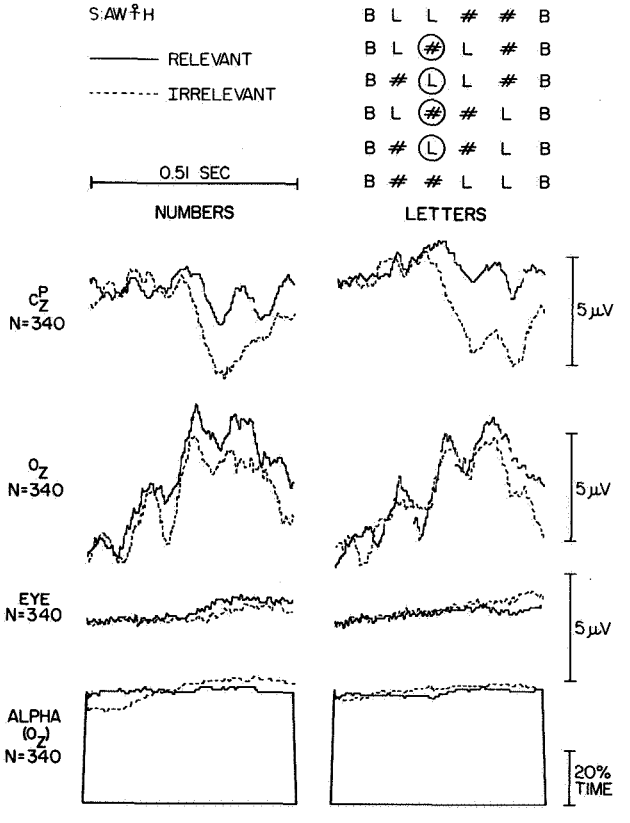

FIGURE 6–9.—AEP to the circled stimuli using Program H. When relevant, the stimulus information was stored in subject's memory. Prestimulus bias (negative down).

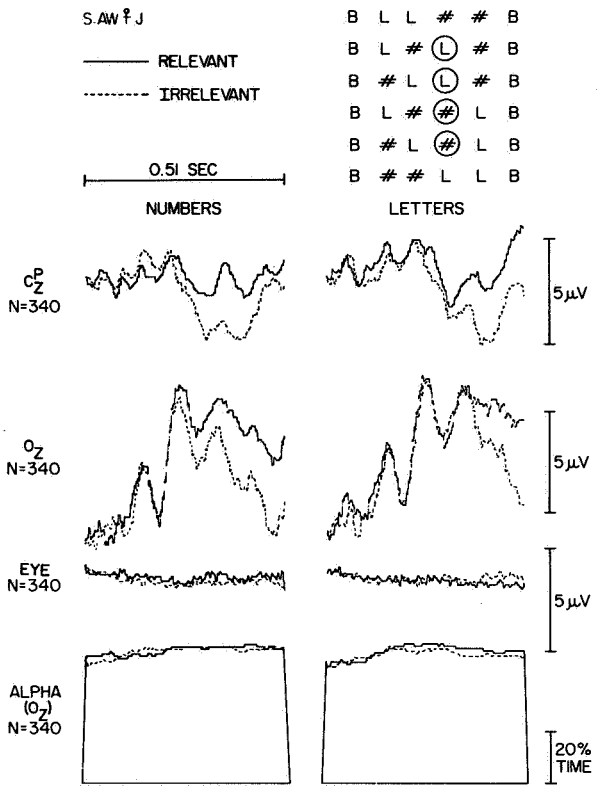

FIGURE 6–10.—AEP to the circled stimuli using Program J. When relevant, the stimulus information was compared with the memory of the earlier relevant stimulus in order to problem-solve. No prestimulus biases (negative down).

the AEP to relevant and irrelevant stimuli were found when both prestimulus and poststimulus variables were operating.

To allow these prestimulus and poststimulus effects on the AEP to be compared more easily, the differences between responses to relevant and irrelevant stimuli are shown in figure 6–12. Programs G and H both involve the poststimulus difference of memory storage, but H has the additional factor of prestimulus bias, which seems to contribute to a larger difference. Similarly, Programs J and K involve the poststimulus difference of memory retrieval and comparison for problem solving; the additional prestimulus variable of prior knowledge in K produced a larger difference. Especially interesting is the difference in AEP effects for the two different, "pure" postperceptual cases shown in G and J.

I would also like to point out that, in one sense, at least, the information available is identical for both relevant and irrelevant stimuli since there were six possible numbers and six possible letters that could have appeared in any of the trial positions. Furthermore, there is more uncertainty for Program J than for K since the subject could not predict whether a letter or number would appear for J, whereas it was known for K. Contrary to what might be expected from Sutton's findings, the more certain condition (K) produced larger differences.

To illustrate the importance of the subject's task further, AEP differences to three different tasks using identical physical stimuli are shown in figure 6–13. Problem 2 is the problem described earlier.

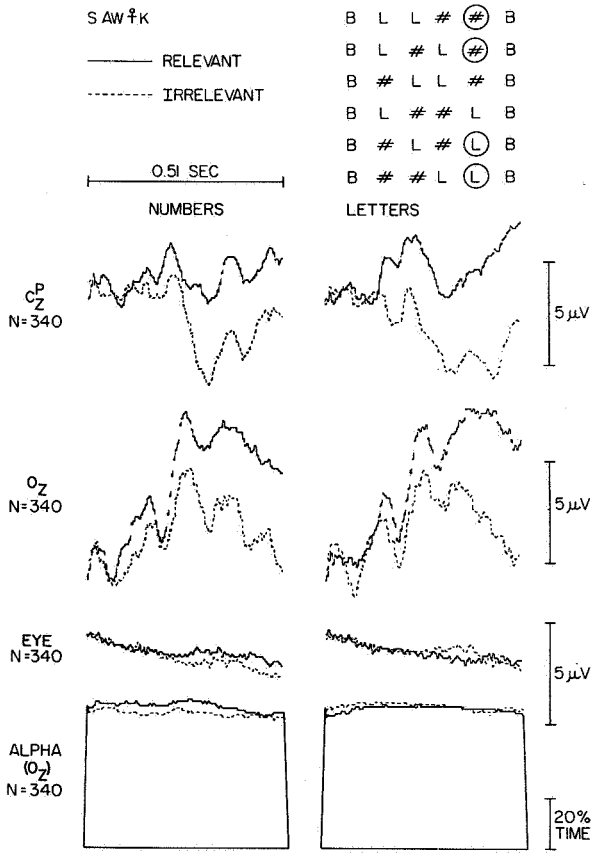

FIGURE 6–11.—AEP to circled stimuli using Program K. When relevant, the stimulus information was compared with the memory of the earlier relevant stimulus in order to problem-solve. Prestimulus biases (negative down).

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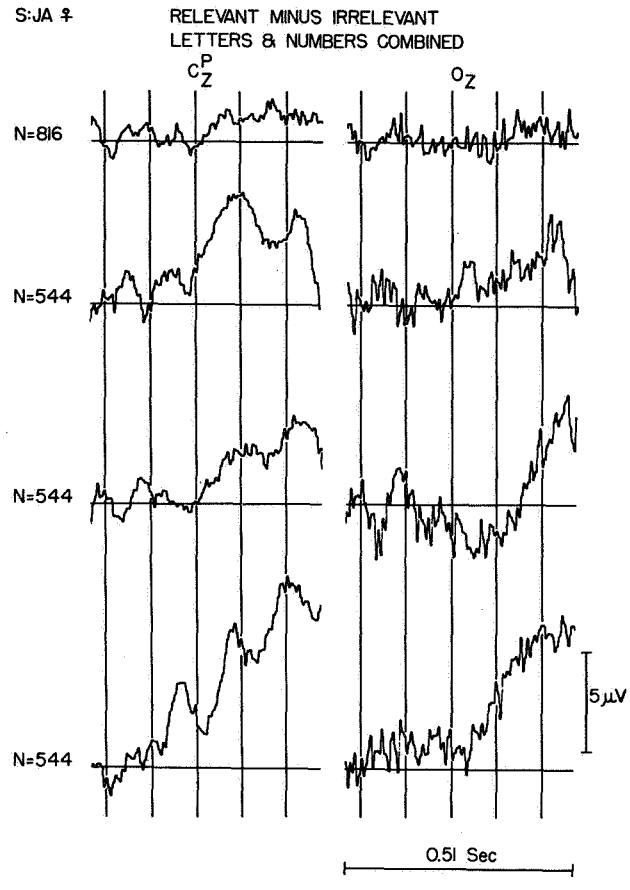

FIGURE 6–12.—Differences between AEP to relevant and irrelevant stimuli at particular positions in trial sequence; see Figures 6–2 through 6–5 for definitions of Programs G, H, J, K (negative down).

For Problem 3, the first number was multiplied by 7 and stored in memory; when the second number appeared, it was added to the stored product, the two digits in the sum were added, and the subject indicated whether the final sum was even or odd. The press-key task was a discriminative reaction-time task in which the subject pressed a key as fast as he could whenever a number appeared. For all three tasks, the physical stimuli and the sorting programs were identical. The AEP differences between the relevant number and irrelevant letters varied markedly with the subject's task.

Finally, I would like to consider some theoretical matters. There is the question of whether a single psychological variable controls the

"psychological" part of AEP or whether more dimensions are involved. For example, can we account for all the psychological effects in the AEP by the amount of information that is delivered, or are some of the effects caused by other variables? Perhaps various kinds of information processing are required, e.g., storage, retrieval, comparison, arithmetic operations, etc. Parsimony dictates that we try to account for all effects with a unidimensional variable if we can. Certainly, "amount of information" would be a good candidate for this approach. We've seen how manipulating the uncertainty, according to the information theory concepts, does systematically alter the AEP. Some complexities in Sutton's data might be covered by information theory without stretching it too much. Even when the subject was told what the next stimulus would be, the AEP was influenced by the history of stimulus probability. This problem might be handled theoretically by considering that information was delivered along two channels: (1) the experimenter telling the subject and (2) pre-

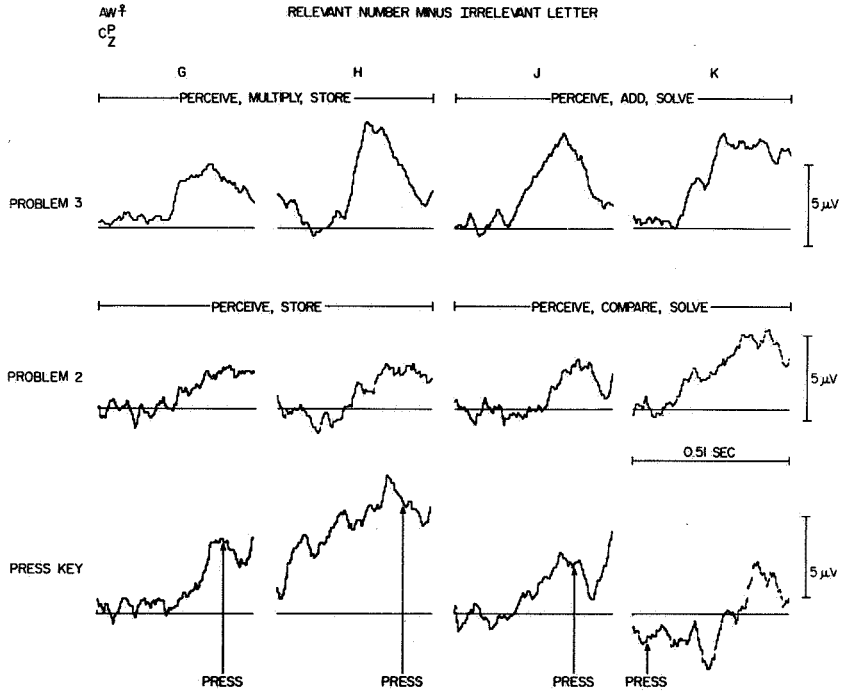

FIGURE 6–13.—Differences between AEP to relevant and irrelevant stimuli at particular positions in trial sequence for three types of tasks. See Figures 6–2 through 6–5 for definitions of Programs G, H, J, K. Median reaction times shown by arrows for press key task (negative down).

senting a set of stimuli with a particular frequency of occurrence. The two channels apparently had unequal efficiency.

What about the data obtained where information theory cannot be applied directly because we don't know the information units? It is tempting to reverse our logic and infer the "amount of information" from the size of the AEP effect. That is, when a stimulus in a certain situation produced a large AEP effect, we would say that a large amount of information was delivered. This approach then gives us a metric for measuring psychological information. This psychological information apparently would be altered not only by the probability of a stimulus occurring, but also by the other characteristics of the situation such as the pay-off associated with that stimulus and the kind of motor responses required. Clearly, this unidimensional approach would be very useful in complex situations that could be handled by this simplifying construct. Equally clear, this approach rests on the unidimensional assumption, which cannot be refuted as long as one permits the amount of psychological information to be influenced by factors outside of those specified by information theory. These other factors, then, are candidates for construct status in their own right and, if they can be manipulated independently, lead to a multidimensional approach. If we want to understand what makes up psychological information, we are forced into some kind of finer distinctions. We might find it useful to consider such classical psychological constructs as perception, memory, motivation, discrimination, etc.

We have discussed using "amount of information" as our unidimensional construct, but we could just as well say the same kinds of things about attention, relevance, significance, etc. We can begin with any of these constructs constrained by operational definitions and show how they modify the AEP. But we soon encounter influences that don't quite fit those initial operational definitions. In our data, for example, the stimuli contributing to Program G seem no more or less task-relevant than those for Program H, and yet foreknowledge or expectancy that the stimulus is likely to be relevant influences the AEP. We have a choice, as we always have in these theoretical matters. If we want to retain our unidimensional approach, we can try to enlarge the defining operations of our construct. In effect, this is reversing the logic, so that the AEP effects are identifying those operations that are the input to the construct. This is what is involved in using the AEP to tell how much attention a stimulus received. This might be extremely useful theoretically when we don't care about finer distinctions. It would seem then, that it doesn't make much difference what we call it; amount of information, amount of relevance, or amount of significance. We would have a rather global

construct, similar to generalized arousal, which for all of its difficulties of definition, still has been useful in guiding our thinking. For example, in studying the effect of psychological variables on the AEP, we take pains to determine if it is just another manifestation of general arousal. We reject the conclusion that all the psychological effects on the AEP are caused by generalized arousal since AEP differences could be related to poststimulus variables alone in cases where prestimulus effects were eliminated by randomization. It seems that the AEP effects, although similar to general arousal, can be much more selective, and hence I would suggest the term "selective arousal," if we want to pursue the unidimensional course. These effects are selective in being short-lived and dependent on particular stimuli within a sensory modality; e.g., effects were found when visual stimuli were only 0.75 second apart and differed only as to whether they were numbers or letters of the same luminance.

If we do not choose to take the unidimensional approach ("selective arousal"), we have the theoretical option of risking a multidimensional approach. For example, we might consider that whether selectively aroused or not, the nervous system processes the stimulus information in various particular ways, and we could attempt to classify these operations in terms of correlations between the task requirements and AEP effects. On the task requirements side, we could entertain such operations as memory storage and retrieval, comparing, adding, etc. On the AEP side, we need to identify the corresponding functional components. It is possible that such an approach could lead us to novel units of processing that transcend the constructs from which we start. This can occur only when we reverse the logic and infer the defining input operations from the response components.

Such a multidimensional approach may not succeed, but we can always return to a global construct such as "selective arousal."

DR. LINDSLEY: Thank you very much, Dr. Chapman, for adding several other parameters for consideration. I would like to use the Chairman's prerogative to make a comment myself, mainly in the interest of broadening the scope of the discussion which I am sure will follow. I will start with Dr. Sutton's point about the probability of occurrence of a particular stimulus event, ranging from 20 to 80 percent. I wonder if he would agree that if we had zero probability or almost zero probability, i.e., if a particular stimulus occurred only once in a series of experiments, it would elicit something comparable to an orienting response. If you had 100 percent probability, it would be comparable to habituation. Thus if you were not concerned with P_3 only, you would observe other components that might be involved.

Another point is one that Dr. Chapman brought out at the very last, namely, the problem of activation or arousal. When we put a

subject in an experimental situation and if he is a naive subject and is in the laboratory for the first time, he is adjusting to a lot of things. If you use practiced subjects, as we often do in visual experiments, their judgments become much more reliable with practice, but they have a different background or basic set as far as the whole experimental situation is concerned.

Additionally, if we are giving subjects something to do, such as "perceive, respond, or compare" tasks, and if we increase the complexity of this task, this in turn is generally conceded to create a higher level of arousal or activation.

This raises the question whether we should only be looking at the evoked potentials during the course of the experiment, or the ongoing spontaneous activity as you indicate before the stimulus and after the stimulus, between trials, and so on, as well as any dc shifts that may occur. We certainly should remember all three of these electrical events that can be recorded.

Another thing has come to our attention when we have presented a click alternating with a flash, once every second. If we directed attention to the clicks, some of the later components of the AEP were enhanced to the clicks and vice versa for the flashes (Spong et al., 1965).

A Finnish student who spent a year in my laboratory, Risto Näätänen (1967), repeated some of these experiments using stimuli that were presented irregularly, and he suggested that his results contradicted our earlier results. I argue that this is a different kind of an experiment. I think that attention means that you can organize the stimuli that are coming to you in some fashion, and if you cannot organize them, you cannot really pay attention to them. In other words, if a person were on an assembly line or if a person were learning to drive a car for the first time, and when there are a variety of stimuli that need to be attended to and the person has not had any experience in organizing these stimuli, I maintain that he cannot pay attention to these things except in a very unsystematic way, and accordingly you will not get the same results.

Just one final comment about attention, perception, storage, problem-solving or thinking. These have been chapter headings for many years in our textbooks on psychology. I wonder, however, whether we can actually separate them, and say they are discrete things. Certainly, if you look up a number in a telephone book and you close the book and go to the telephone and start to dial, it is at this point in the read-out process that we may find that we can't remember the number and have to go and look it up again. You look up a word in the dictionary, and it is the same thing. You get back to your typewriter, and now you are wondering just what that definition was. Certainly, attention, perception, and short-term memory storage are closely related and overlap.

DR. DONCHIN: I have a few brief comments. They are based on data obtained in an experiment described in detail by Smith et al., in press. The subjects were presented in this study with two verbal messages, one to each ear. The messages consisted of a series of random digits read in a slow, even voice. Occasionally, one of the digits was replaced by a letter. The subject's task was to report the occurrence of the letters in one ear or the other. However, the verbal messages were not the only sounds presented over the earphones. A random series of clicks was superimposed in each earphone concurrently with the verbal message. The clicks were also randomly spaced, and a different series was presented into each ear. After the subjects reported the occurrence of letters they were instructed to ignore the verbal messages and to report the occurrence of the clicks. Note that at any time only the stimuli presented in one ear were to be reported. There were thus four experimental conditions in which the subjects were presented with physically identical stimuli, but in which they were given different instructions.

We obtained the AEP to the clicks in all the experimental conditions. As we could distinguish between right ear clicks and left ear clicks, there are eight evoked responses per subject. The eight records for one subject are shown in figure 6–14. On the right are the four AEP obtained when the subject was reporting letters. On the left are AEP obtained when the subject was reporting clicks. Clearly and unequivocally, whenever he was reporting clicks, there was a larger P–300 response than when he was reporting letters.

Can we then say that only clicks which were defined by our instructions as task-relevant, elicit a large evoked response? That we cannot make such a statement is evident from a comparison of the AEP to right and left ear clicks. The size of the AEP elicited by clicks presented to the rejected ear is as large as that presented to the attended-to ear. Clearly we have a case in which clicks which are not task-relevant, and which were not reported by the subject, elicited an AEP as large as those that were reported. Probably, the subject is responding to all clicks as if they were task-relevant, and the decision whether to report the click is made at a stage subsequent to the one in which the amplitude of P300 is determined. We are presented here with a number of difficulties. The difficulties derive from the fact that there are a few subjects whose response patterns are reversed. There are a number of possible strategies with which the subjects can handle the assigned tasks, and it is difficult to predict what strategies they will use. For this reason, it is difficult to rely on the instructions to the subject to provide the definition of the psychological variables. The same set of instructions might be interpreted in different ways by the same subjects on different occasions, or by different subjects on the same

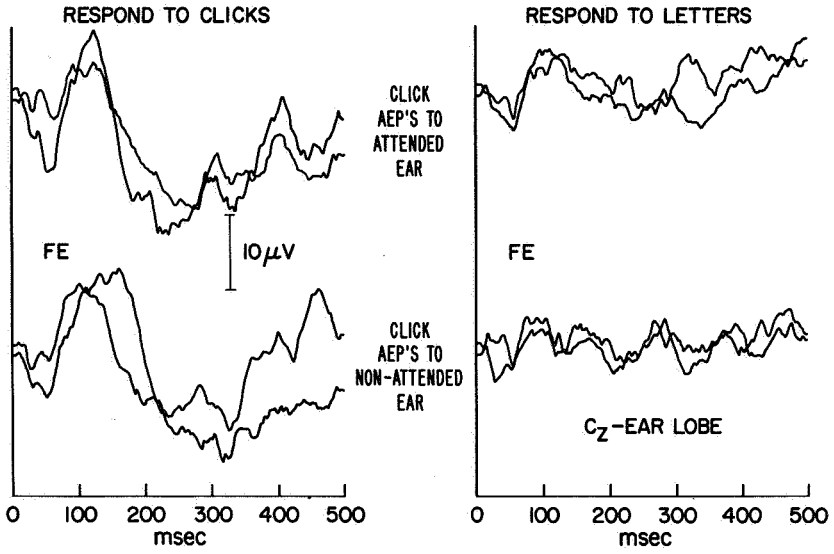

FIGURE 6–14.—Eight average evoked responses elicited by clicks presented either to the right or left ear. Records are from a vertex electrode referred to a linked-ear electrode and negative is up. The four AEP on the left were recorded while the subject was reporting the occurrence of clicks; the four AEP on the right were recorded when the subject was attending to a background speech stimulus. The four AEP in the top row were elicited by clicks presented to the ear the subject was attending to. The four AEP on the bottom row were elicited by clicks presented to the "rejected" ear. Note that when the subject is attending to clicks, all clicks regardless of the ear in which they are presented elicit an AEP with a prominent P300. Whenever the subject is attending to the background speech stimuli the AEP to the clicks is greatly diminished.

occasion. It is also impossible to rely fully on the behavorial measure to assure that the subject was performing as instructed. In the present case, the subjects had a near-perfect record of correct responses, thus indicating that they were able to discriminate the two clicks with relative ease. Yet, the AEP suggests that at some point they were not making this discrimination.

I would also like to comment on the use of stimulus randomization within a block of stimuli. While it is clearly a useful approach in some cases, it should not be forgotten that when the experimental conditions are changed from one trial to the next, a different set of expectancies and contingencies is imposed upon the subject and that he reacts differently than he does when similar stimuli are used in a

single series of stimulations. Fehmi, Smith, and I are now performing a study on the effect of the interstimulus interval (ISI) on the CNV. We are using two types of stimulus presentation schedules. In one, the subjects are presented with a stimulus series in which the ISI is constant within the series. In the other set of conditions, four ISIs are mixed randomly within one stimulus series. The results obtained with the two schedules were quite different. I know that Dr. McAdam has been getting substantially similar results, and I hope he will comment on this later. Thus, in view of the strong effect the stimulus contingencies exercise over the CNV, it might not be proper to randomize stimuli in these studies.

DR. BICKFORD: I think it would be nice if we could manipulate psychological variables as has been suggested by Dr. Sutton and Dr. Chapman without producing related changes in physiologic systems. But, most people when they are given a task, show some associated change in facial expression such as frowning, raising the eyebrows, smiling, etc. As will be seen in figure 6–15, such changes in facial expression by altering tension in cranial muscles underlying our recording electrodes will result in muscle responses to the input stimulus (microreflexes) (Bickford, 1964, 1967, 1968; Bickford et al. 1964b;

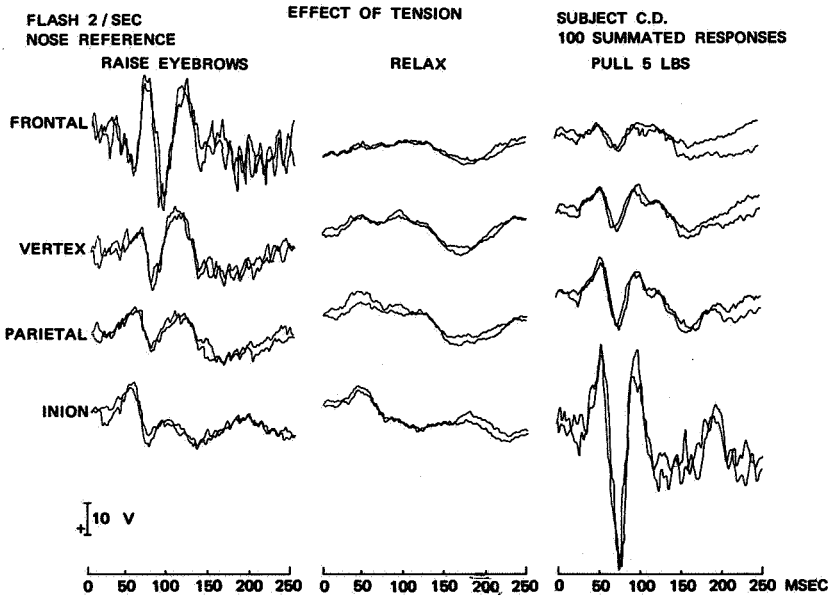

FIGURE 6–15.—Effect of facial muscle tension on photic evoked extracranial potentials (microreflexes). Midline electrode normal subject. The two traces are separate experiments to indicate the variance.

Lee and Bickford, 1968) in normal subjects; these responses are very difficult to distinguish from brain activity. Thus, in the example shown, responses to a photic stimulus in the relaxed state from four electrodes is shown in the center section. When the eyebrows are raised, a new response with a latency comparable to an evoked cortical response appears in the frontal region and to a lesser extent in other electrodes. Because these myogenic responses change amplitude linearly with tension existing in the muscles, they can be shifted around the head as a result of shifting muscle tension, as is shown on the right of the figure where neck and posterior cranial muscles are tensed by having the subject support a weight. Under these circumstances, a large response appears maximally in the occipital regions with latencies of N50, P75, N100. The responses are so large in this subject as to overwhelm the genuine cortical response represented by the center section. While the responses shown in figure 6–15 were produced by a stimulus of intensity 8 (Grass Photo-stimulator P2), we have shown recently that these responses can be obtained down to perceptual threshold although there is some increase in latency at lower flash intensities. Since these responses are present to some extent in the majority of the normal population, they form an important hazard in the interpretation of evoked potential experiments, particularly when the latter involve active subject cooperation in operant situations, etc.

I would like to consider the field distribution of evoked potentials and to introduce a new technique developed by Dr. Harris (Harris, 1967; Harris and Bickford, 1967) in our laboratory, which allows spatial distribution across the head to be computed and displayed automatically. Thus figure 6–16 shows an example of this technique from Dr. Lee's data (Lee et al., 1968). Here we see the response to photic stimulation in a normal subject from a 16-point sampling array shown in the upper right corner of the figure. Responses averaged from these 16 points are then subjected to statistical interpolation so that the equivalent of 400 "statistical" electrodes are developed with appropriate voltages for every 5 milliseconds in time. Four of these time slices of the conventional voltage-time average curves shown above are displayed as the area maps below. Notice that the evoked response is asymmetric in regard to the midline of the head, particularly the positive wave shown in B and D. We have found this type of asymmetry in a number of normal subjects. However, the point of introducing this technique here is to emphasize that it provides a generalized approach to the problem of potential field recording. In the discussions here, there has been reference to the absence of standardization in electrode placement and montage. The present technique allows one to record from any designated point within the array (not necessarily one of the original recording electrodes) to any other designated point

and to ask the computer to plot the resulting voltage-time conventional EEG. Thus it is possible to substitute an electrode placement matching that used by some investigator whose data is under comparison. Furthermore, the field shown in D makes it evident that this particular component would be sampled adequately only by bipolar arrays that were transverse in direction on either side of the midline since these cross the major lines of the field; on the other hand, the D component would be almost eliminated by an anteroposterior directed bipolar montage on one side of the midline since it would be apt to coincide with isopotential lines. This also explains the strategic advantages of transverse recording in some instances as has been emphasized in the "rosette method" of Clynes and collaborators. It is also evident that recognition of voltage-time components and their polarity requires the potential field distribution to be taken into account; otherwise serious errors can result. Apparent differences from one laboratory to another can often be accounted for on the basis of different sampling of the potential field used.

Dr. STORM VAN LEEUWEN: One of my collaborators, Lopes da Silva, has been carrying out investigations in dogs on the threshold of perception. The experimental procedure is as follows. The dog is trained to

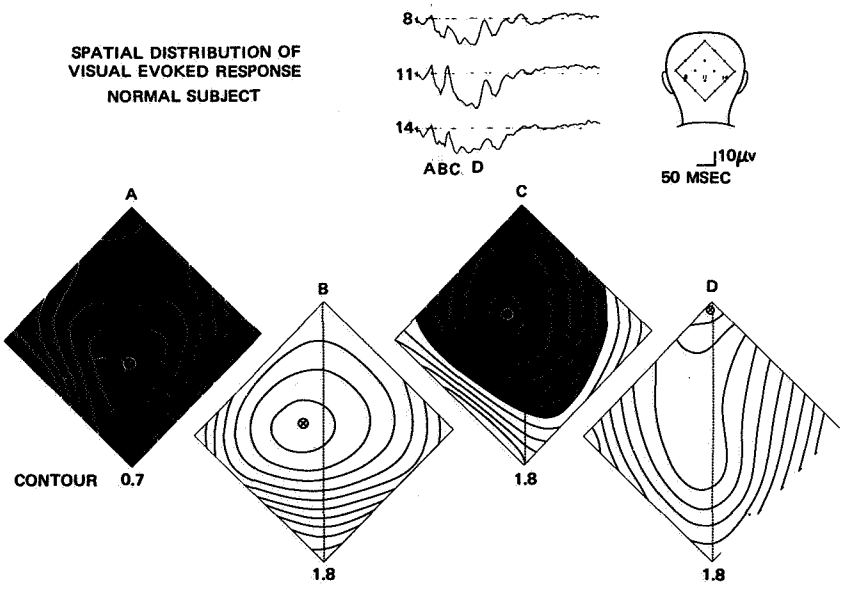

FIGURE 6–16.—Area contour display of photic evoked potential in normal subject. Constructed after interpolation of 16-channel averages of photic responses recorded from electrode shown on head. Three monopolar averages are shown above from electrodes 8, 11, and 14.

FIGURE 6–17.—Dog, pressing pedal, is waiting for food reward which will be thrust through hole in the wall, while sinusoidal modulation of the light is turned on. The animal carries an 8-channel EEG radiotelemetering apparatus on its back.

press a pedal to obtain a food reward whenever sinusoidally modulated light appeared. If the modulation depth was decreased below a certain level, the dog did not press the pedal any more and received no reward.

Dr. Lopes da Silva has constructed diagrams of the parameters at which the dog still received the reward and at which it did not. The dog, in which this investigation was carried out, was a very stable animal having 95 to 100 percent correct answers; therefore reliable data were obtained.

Figure 6–17 shows the experimental animal waiting for the food reward to be thrust out of a hole in the wall. The sinusoidally modulated light was presented for a few seconds. The responses were obtained by means of chronically indwelling electrodes in the lateral geniculate bodies and in various parts of the visual cortex. The electrical signals from the brain were telemetered to the recording apparatus; thus the animal could walk around freely.

Each time the dog received the reward, it walked away for a while and then returned. When the sinusoidal modulation was turned on, the dog looked at it, pressed the pedal and waited for the reward to appear while the modulation continued. In this latter period, constant and repeatable responses are obtained. The first conclusion from this experiment is that in such a situation, the responses have minimal variability. This situation, therefore, was used for the quantification of the results.

Figure 6–18 is an example of responses to sinusoidally modulated light obtained in various brain areas, e.g., in the lateral geniculate bodies and in some areas of the visual cortex. As can be seen, the responses varied considerably from one area to another and from one stimulus parameter to another. From these data, power spectra were obtained, and from these it appeared that the responses could be described to a considerable extent by components at fundamental and second harmonic frequencies.

Figure 6–19 shows diagrams of the stimulus parameters at which the dog pressed and did not press the pedal when the light modulation was presented. These diagrams demonstrate that with increasing frequency, increased modulation depth was needed for the dog to press the pedal. The diagrams are similar to those obtained by De Lange in critical flicker fusion in man, called "De Lange curves". In the fre-

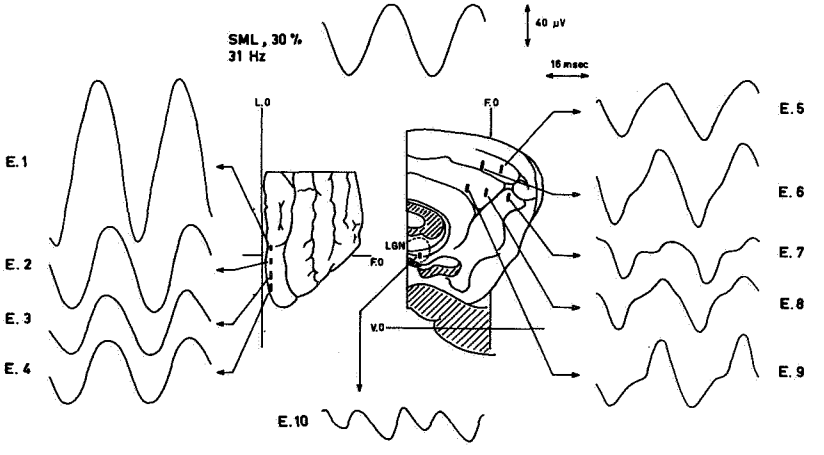

FIGURE 6–18.—Topographic distribution of averaged evoked potentials to SML (31 Hz, 30 percent) over lateral and mesial occipital cortex and LGN. All averages are taken with the same trigger. Note maximum amplitudes in E1 and sinusoidal responses over lateral cortex. More distorted waveform over mesial cortex and clear frequency doubling in LGN.

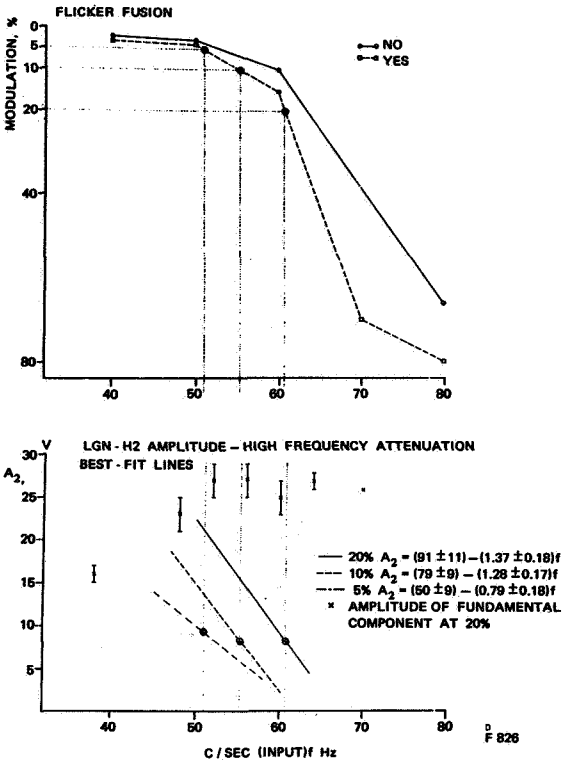

FIGURE 6–19.—Flicker-fusion sensitivity curve for a dog. A "yes" means that at the SML parameters indicated, the dog saw the modulation ($p<0.05$). A "no" means that it did not (<0.05). Log scales: Ordinate—modulation ratio; abscissa—frequency of SML.

quency range between 60 and 90 Hz there was a steep attenuation. This figure also shows the amplitudes of the fundamental and second harmonic components of responses in the lateral geniculate body obtained at these stimulus parameters. From this it appeared that the fundamental components had little or no relation to a dog's "subjective flicker fusion"—assuming that nonpressing indicated nonperceiving. The second harmonic component, on the contrary, did appear to be related to subjective flicker fusion. The various combinations at which flicker fusion occurred (20 percent modulation depth at 62 Hz, 10 percent modulation depth at 56 Hz and 5 percent modulation depth at 52 Hz) produced the same amplitudes of the second harmonic components.

In all cases, as in man, responses could be obtained at stimulus

parameters well below subjective flicker fusion. On the basis of these and other experiments, Lopes da Silva decided that at least two mechanisms are involved. The second harmonic components appear to bear direct relation to the information content of the visual pathway, whereas the fundamental component indicates the condition of the neuronal structure.

DR. LINDSLEY: I would just like to comment that Dr. Arthur Schwartz and I did a similar experiment using a cat and found that the behavioral threshold for flicker-fusion was somewhere in the neighborhood of 45 to 50 flashes per second. But the point that relates to what you have just reported is that the percentage of time that the fundamental frequency was followed by the visual cortex response, while the animal was definitely perceiving flicker, was 80 to 100 percent of the time, whereas when behavioral threshold for flicker-fusion was reached, the percentage of following of the fundamental reduce to 10 percent of the time. Thus, the results are somewhat comparable, and I think these are highly interesting. We have not looked at the second harmonic. We only looked at the fundamental, and the percentage of time that the fundamental frequency was registered in the cortical records as well as in the lateral geniculate nucleus.

DR. SHEVRIN: The usefulness of the AEP for the objective study of psychological factors is underscored forcefully by Sutton's and Callaway's presentations and by Chapman's discussion. Certainly much evidence points to the correlation of attention with AEP components in the 100- to 300-msec range. For those working with scalp electrodes, it is reassuring to learn that generally scalp leads reflect activity isomorphic with activity detected by implanted electrodes, thus providing additional evidence that muscle potentials cannot account for the electrical potentials detected at the scalp.

I would like to make two points in my remarks, addressed mainly to Dr. Sutton's and Dr. Callaway's papers. There is some evidence that (1) the AEP can discriminate between subliminal, unconscious stimuli, and (2) that repression, a central diagnostic concept in dynamic psychiatry and psychoanalysis is correlated with AEP components.

Doctor Sutton refers to Libet's work on subthreshold somatosensory stimuli, and he rightly points out that Libet uses a discontinuous measure for the verbal report, thus increasing the likelihood that some conscious experiences, especially faint and unclear ones, will remain unreported. This important criticism has a considerable history in work on subliminal stimulation going back to the Bricker and Chapanis critique (1953) of the early perceptual defense findings. Those of us working in the area of subliminal stimulation have usually corrected for this source of error by making the verbal report as continuous as possible. Thus, in my own studies, I do not rely on a yes-no

report but on a full qualitative description, usually obtained twice in succession so that omissions in the first report may appear in the second report. When this correction is made so that there is comparable continuity between the neurophysiological and verbal responses, subliminal effects are still detectable. In two recent studies (Shevrin and Fritzler, 1968a, 1968b) we have found that when two stimuli, matched for size, configuration and color, but differing in meaning were flashed for 1 millisecond, that a positive-going component peaking at approximately 160 milliseconds discriminated between the meaningful and abstract stimulus. The meaningful stimulus was a picture of a pen and knee and the abstract one was made up of figures that approximated the pen and knee in size, shape, and color but lacked the distinctive contour features of the real objects. In figure 6–20, the AEP curves for two subjects from the first study are shown. The BC component discriminates between the R and D stimuli for both the two, 1-millisecond conditions, and the 30-millisecond condition, during which the stimuli are perceived.

The electrode array that most clearly picked up these differences was provided by bipolar leads, F–O, with the occipital electrode being active. In view of Goff's careful mapping work, I now would understand this outcome as caused by the fact that for visual phenomena the frontal region is relatively neutral with respect to the occipital region. I am impressed with Goff's arguments for monopolar leads, and in my future work will rely on his wise advice.

I have used two methods for identifying AEP components, both of which can be accomplished with near perfect reliability (interjudge reliability ranging from 96 to 100 percent). One method is the customary sequence determination, in which components are identified, as in Sutton's and Goff's work, on the basis of an alternating sequence of positive and negative peaks. It is assumed by this method that latencies are invariant. If no activity occurs at a given latency, then that component is considered absent rather than shifted to an earlier or later time interval. The second method, an example of which is referred to by Cohen in his paper, is based on a single assumption—the largest amplitude in a given time interval is the most functionally significant. No assumption is made about latencies which may vary within this given time interval. Since in most work significant activity appears to be restricted to roughly the first 300-millisecond poststimulus, and since stimulus and muscle artifacts are likely to occur within the first 40- to 50-millisecond poststimulus, in my recent work I have used the 40- to 260-millisecond time interval in which to identify the peak positive-going amplitude. This peak amplitude can be assessed with near perfect reliability. Both measures reflected the effects of subliminal stimulation. What functional differences exist between the two methods

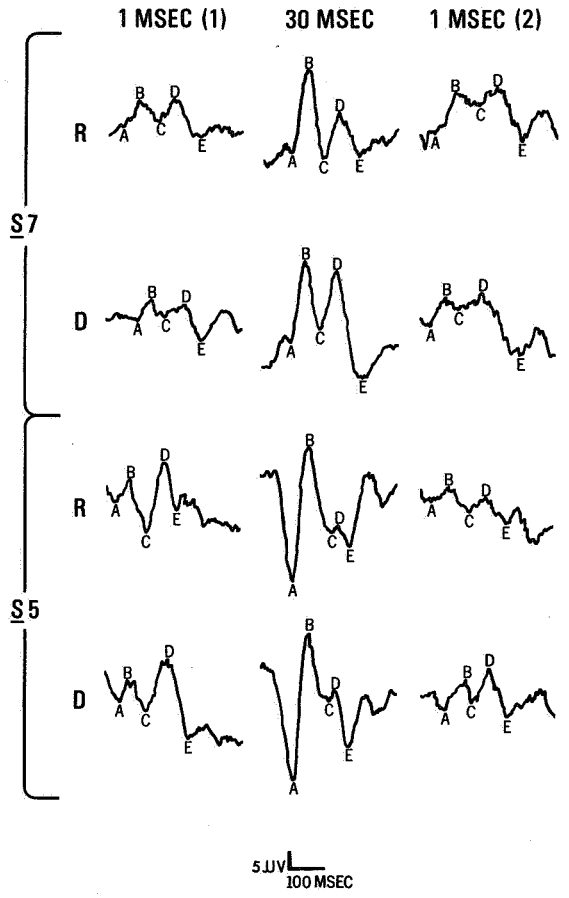

FIGURE 6–20.—Average evoked responses (from subjects 7 and 5) as recorded from frontal-occipital electrodes for each exposure condition and for each stimulus, R and D. Average evoked responses are based on approximately 30 sweeps for each curve (negative up).

remains to be discovered. The peak amplitude measure has the advantage of making the least restrictive assumptions about latency, and this permits determining the role latency may play empirically.

In addition to the electrical findings, certain indirect verbal effects of the meaningful stimulus were found in free associations collected during the course of the experiment. These two findings taken together suggest that the AEP can discriminate between two subliminal stimuli, which then have some determinable effect on subsequent thinking. Furthermore, I would like to suggest that if we examine the overall

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evidence in the field, components in the 100- to 300-millisecond range appear to be associated with attention. Thus we may be dealing with a process of unconscious attention, incongruous as that term may sound.

I would like to describe briefly some work that I have done relating psychological test criteria of repressiveness and AEP components. I am defining repressiveness as a constellation of personality and cognitive factors, which is likely to be present when repression is used as a means of defending against anxiety-arousing stimuli. By repression, I refer to a mechanism by which an individual keeps himself unaware of these anxiety-arousing stimuli. Certain psychological tests, such as the Rorschach, sample the personality and cognitive factors associated with repression. This line of reasoning is based on a probability model: given these particular personality characteristics and cognitive styles, it is highly likely that the given person will rely on individual acts of repression more often than other defensive means and more so than other individuals with different personality characteristics and cognitive styles. The underlying assumption is that the repeated workings of a defense in part result in certain personality and cognitive modifications and in part are based on certain personality and cognitive factors. For example, a person who must see, hear, and say no evil for fear of stirring up anxiety-arousing thoughts in himself is likely to be a naive person who is not inclined to learn much about the ways of the world. Naivete is a prime personality trait of people who rely heavily on repression even though they may be of high intelligence. Clinical ratings of repressiveness, mainly based on the Rorschach, can be made reliably. In our own experience and that of others, interjudge reliability has varied from 0.73 to 0.90. If we can identify relationships between such clinical ratings of repressiveness and AEP components, we have at least taken a step towards the diagnostic use of the AEP.

What we have found in several studies (Shevrin and Fritzler, 1968a; Shevrin et al., in press) can be summarized with the aid of two stimulus dimensions, meaningful-neutral and subliminal-supraliminal. When a stimulus is meaningful and subliminal (e.g., the pen and knee flashed at 1 millisecond) repressive subjects, as compared with nonrepressive subjects, show a significantly reduced positive-going amplitude for the component that has been found to discriminate between the meaningful and abstract stimulus. When the same stimuli are supraliminal, there is a tendency for repressive subjects to have increased amplitudes, mainly to the neutral stimulus. This finding has appeared once with the sequence method, but it has been replicated for the peak amplitude method of identifying AEP components. There is also evidence that repressive subjects show less of the indirect verbal effects in free associations. In figure 6–21, a high-repressive subject (S4) and a low-repressive subject (S5) are compared. For

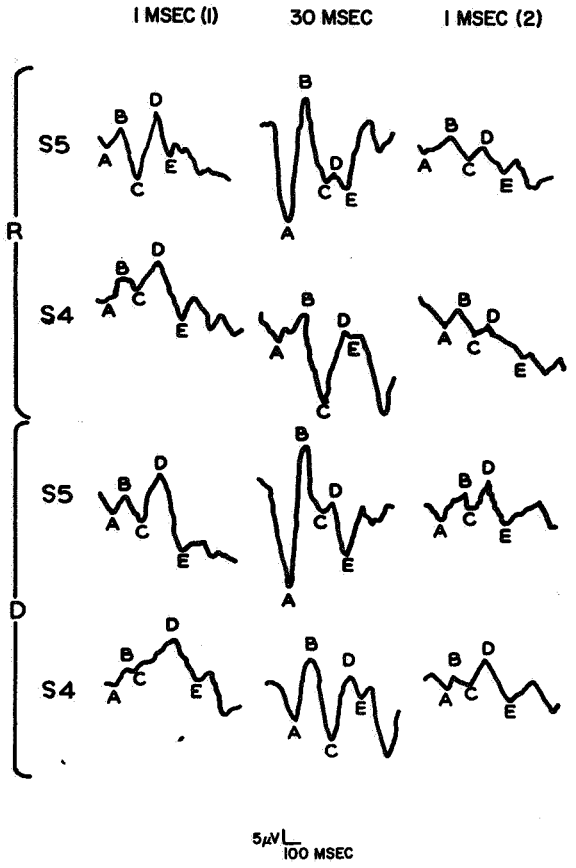

FIGURE 6–21.—Average evoked response (AEP) correlates for most and least repressive subjects. Subject 4 is the most repressive, and subject 5 is the least repressive subject in the sample. The upper pairs of AEP curves for the three exposure conditions are responses to stimulus R, and the lower pair of curves to stimulus D.

the first 1-millisecond condition, the difference between the meaningful rebus stimulus is quite striking. This difference is reversed for the 30-millisecond condition. The difference is greater for the abstract D stimulus than for the meaningful R stimulus. The difference for the 1-millisecond condition is reduced considerably. We have encountered this many times, which has suggested that habituation effects may be affecting amplitudes later in the last series. For these two subjects, the BC components identified by both methods are identical.

If we assume that attention is a correlate of the discriminating positive-going amplitude, then it would seem that the repressive personality depends on the strategic investment or withdrawal of attention to control inputs that are potentially anxiety-arousing. He is readier to attend to a neutral, supraliminal stimulus, than to a meaningful, subliminal stimulus. Certainly considerably more work needs to be done in order to clarify fully the nature of these relationships; yet it does seem, on the basis of these preliminary findings, that the AEP can provide subtle discriminating indices relevant to unconscious mental processes and dynamic personality factors.

DR. GOFF: I would like to ask Dr. Sutton two questions and then explain very briefly why I ask them. First, I would like to know what degree of modality specificity your P_3 component has. Secondly, you mentioned that you had recorded from various electrode locations, and I wondered if you had examined the topography of these locations.

The reason I ask these questions is that in our 1962 distribution study (Goff et al., 1962), to which Dr. Knott referred yesterday, we found that the vertex potential tends to break up into a double positive peak as one progresses occipitally along the midline. We didn't know anything about the psychological significance of this but were simply describing what happened. This second peak appeared with varying amplitudes, and I am quite sure it corresponds to the P_3 component. The separation between the first positivity of the vertex potential and the second positivity, which you are calling P_3, was most common in the occipital area with shock stimuli. I would like your comments.

DR. SUTTON: I can't comment on the last issue. I am simply very interested to hear that, and we will look for it. We have not looked at the scalp distribution of waveforms across modalities. We have looked only at the vertex electrode routinely for light and sound stimuli. Figure 6–22 shows average evoked responses for light and sound stimuli under the same uncertainty conditions. To permit comparison, the waveforms are displaced so as to align the sound and light responses at N_1. Data for five subjects are shown. It can be seen that the P_3 component is very similar for light and sound stimuli.

DR. LANSING: I would like to comment briefly on the use of reaction time as a means of stabilizing attention or estimating vigilance during evoked potential studies. We like to use measures that are comparatively simple and with which we are most familiar; however, I question whether we should become fixed too early on reaction time as an index of the subject's state. An average reaction time, say 200 milliseconds, for each of a group of subjects does not assure a common level of activation among them since this speed of performance is much more difficult for some subjects to achieve than for others. Neither would it be an acceptable index for a given subject over many experi-

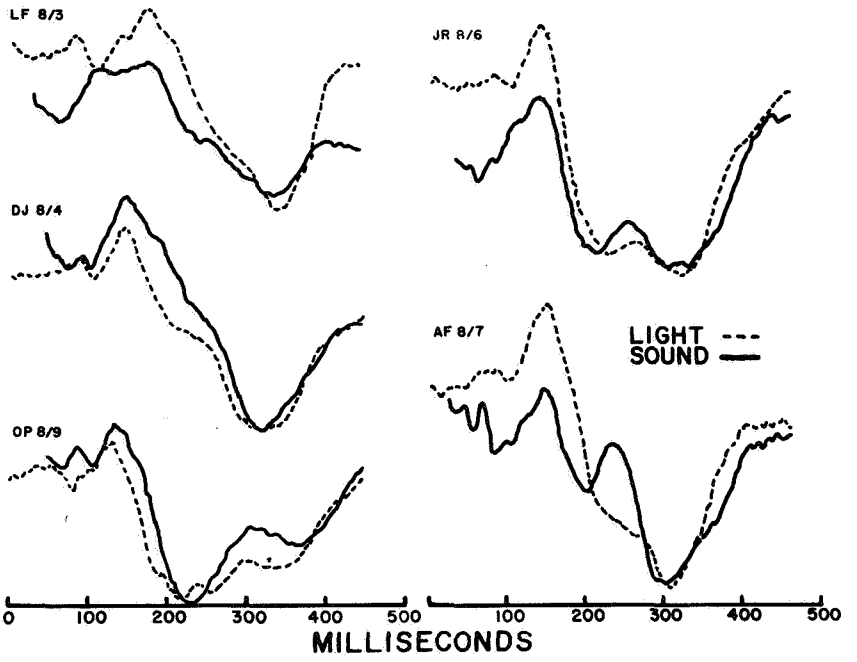

FIGURE 6–22.—Average evoked responses for five subjects to auditory clicks and light flashes under identical uncertainty conditions. Responses to light flashes have been shifted in latency and aligned at N_1 with responses to clicks. The active electrode is one-third of the distance along a line from the vertex to the external auditory meatus. Reference electrodes are attached to both earlobes. Negative is up in these tracings.

mental sessions since the task becomes increasingly easy and automatic. The well-practiced subject begins to think of other things, and his "subject options" increase.

However, it has been shown (Donchin and Lindsley, 1965; Morrell and Morrell, 1966), that reaction time measures can reflect gross changes in a given subject state which are related to changes in evoked potential amplitudes. The question of whether this reflects a waxing and waning of generalized or focused attention is, I believe, not answered.

We have become interested in the possibilities that lie in specifying changes in state by looking at the background activity of the EEG. We have some doubt that simply alpha amplitude, percentage of time, or frequency are necessarily the best criteria; certainly it seems to be for predicting changes of some evoked components such as rhythmic after-discharge. Perhaps Dr. Shagass' report later may help us in this. Certain aspects of the frequency spectra may be more reliable indicants of subject changes that can influence evoked potentials. This source of

variation then could be controlled by averaging responses selected from epochs with similar spectra or with on-line devices, placing stimuli only when certain spectral criteria are met.

DR. LIFSHITZ: I would like first to comment on Dr. Bickford's data (Fig. 6–18). I think that this is the proper direction. This sort of presentation conserves all of the available information, and then as we begin to deal with this sort of presentation, much of the ambiguities of different sorts of systems will be eliminated. But it is very obvious that as the focus shifts around slightly, very different sorts of cross-section representations are obtained.

With respect to Dr. Sutton's and Dr. Lansing's comments about the need for controlling the evoked responses so that the same subjective state holds between subjects, it struck me that there were certain difficulties involved here, and we are perhaps in danger of throwing the baby out with the bath water. This is especially true when we are dealing with pathological states. In studying a very disturbed subject, one may be interested in the nature of the evoked response differences as compared to the normal. It might be misleading to study his evoked responses only at times when he is functioning like a normal person. For example, if you were to measure his reaction time, 90 percent of his reaction times may not be as fast as normal reaction times. It would be improper therefore to use the remaining 10 percent which are in the normal range and to conclude that there are no differences.

DR. SATTERFIELD: I would just like to add a comment to Dr. Donchin's report of an atypical response in some subjects when they are attending to stimuli. A number of years ago when we first began studying attention in the laboratory, we reported on five subjects who consistently and reliably showed reduced potential changes when attending to the stimulus. In a later and more elaborate study utilizing a much larger number of subjects, but utilizing some of these same subjects, it was found in the majority of cases that there was an enhancement of the potential with attention; however, some of these same subjects in fact still showed reliably reduced potentials when they attended to the stimulus. Also, we used different sense modalities in a given subject and found that the same individual might show different kinds of evoked potential changes depending on the sense modality. That is, he may in fact enhance his responses to the auditory stimulus when attending to that stimulus but reduce the response to the shock stimulus when attending to shock, or vice versa (Satterfield, 1965; Satterfield and Cheatum, 1964).

DR. MCADAM: I would like to amplify a comment by Dr. Donchin about what happens to the CNV with certainty and uncertainty by presenting some data on what happens to the CNV when various stimulus intervals are presented either in blocks or intermixed. In the

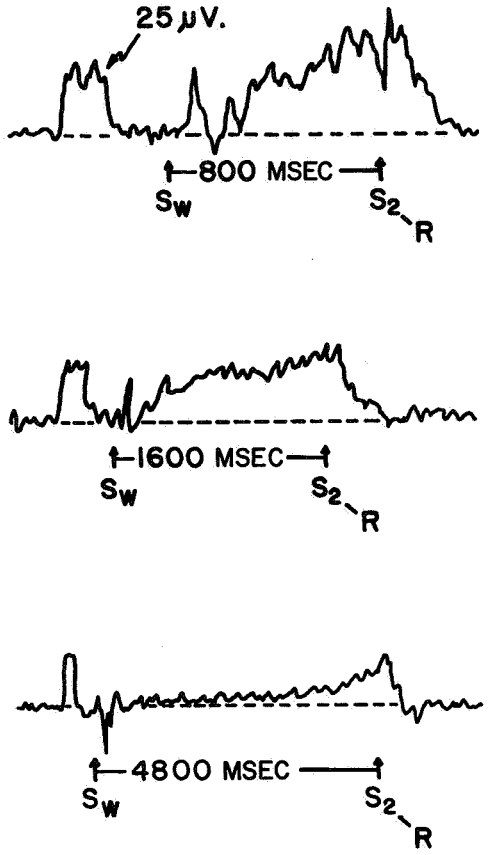

FIGURE 6–23.—CNV from one subject with the three interstimulus intervals; S_w warning click, S_2 second click to which subject was instructed to make button press response R.

first study (McAdam et al., 1969), we presented pairs of stimuli at intervals of 800, 1600, and 2400 milliseconds, instructing the subject to respond to the second stimulus of each pair. The intervals were presented in blocks; i.e., all of the 800-millisecond pairs were given together, followed by all of the 1600-millisecond pairs, etc. In this case, the subject was completely certain as to when the second stimulus was coming. Figure 6–23 shows some sample CNVs obtained under this situation. There are some overall amplitude differences that favor the shorter intervals, but this is not the point I wish to stress here. Figure 6–24 shows the growth of the CNV over quarters of each of the three intervals expressed as a percentage of the terminal maximal CNV value. These are group data from all 24 subjects. The point to note here

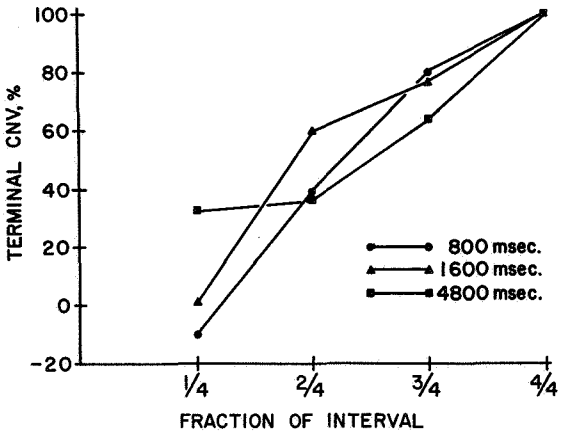

FIGURE 6–24.—Percentage of terminal CNV amplitude plotted as a function of quarters of the interstimulus intervals for all three intervals and all 24 subjects.

is that when the subject is "certain" of the time of occurrence of the second stimulus, there is an orderly ramp-like growth of the CNV to a maximum, coincident with the second stimulus.

Mr. Barry Polsky, a graduate student in my laboratory, is just completing a study of the effects of intermixing interstimulus intervals upon the CNV shape. He is finding essentially the same result that Dr. Donchin reported. When the subject is uncertain about the time of occurrence of the second stimulus, the CNV grows very rapidly at the beginning of the interval, tending to take a square, rather than ramp-like shape. Interestingly, when the CNV from the long intervals are examined, they show a tendency to be hump-backed in shape; the maximum amplitude is reached more toward the middle than at the end of the interval. These data may be interpreted quite simply as being consequences of the amount of uncertainty that the subject has about the occurrence of the second stimulus. Early in a given trial, the timing of S_2 is completely unknown. In the case of the long interval trials, the time of S_2 becomes apparent (or certain) as the trial progresses.

We have yet another set of observations which bear on this point. In a second portion of the first study cited, eight subjects were given pairs of clicks separated by either 1200 or 2400 milliseconds in an intermixed fashion and were asked to make a pretrial prediction of the interval they would next receive. The data show that the form of the

CNV will vary as a complex function of the prediction and of the level of uncertainty about the prediction. At 1200 milliseconds, CNV amplitude was higher, and reaction time shorter when subjects correctly predicted the short interval than when they predicted the long interval. On the other hand, when the long interval was received, any uncertainty about the prediction was dissipated when 1200 milliseconds had passed, and this dissipation of uncertainty was accompanied by a drop in CNV amplitude measured at 2400 milliseconds and compared with the value at 1200 milliseconds. As with the short interval, both faster reaction times and higher CNV amplitudes accompanied correct, as opposed to incorrect, prediction.

In summation, the rules seem to be as follows. When the subject is certain about the time of occurrence of the stimulus to which he is to respond, the CNV takes a ramp-like form with the maximum deflection being reached at S_2. When there is a near-total early uncertainty about the time of occurrence of S_2, the CNV assumes a square form, the maximum value being reached shortly after the occurrence of S_1. With the dissipation of uncertainty, such as occurs when the interval is long and the time for other S_2 presentations is passed, there is a coincident drop in CNV amplitude. Thus the form of the CNV is dependent upon the complex of motivational and cognitive factors involved in moment-to-moment certainty and uncertainty about when to prepare to respond.

DR. LEHMANN: I would like to comment briefly on Dr. Bickford's interesting field distribution studies. I think there is a certain danger in interpolating between electrodes over too large a distance, particularly when few electrodes are used. Considering our results of field studies in a pathological subject (Lehmann, Kavanagh, and Fender, 1969), I expect a normal subject to have at least two sources in the electrical field evoked by visual stimuli, i.e., one source over each hemisphere. If the two sources are located symmetrically in reference to the midline within an array of 4-by-4 or 5-by-5 electrodes, interpolation of the results probably will indicate the existence of only one source very near or at the midline.

DR. GARDINER: I would like to make one point, indicating how some of the material that Dr. Walter presented yesterday relates to today's discussion. This material is from a recent study (Gardiner, 1969; Gardiner and Walter, 1968). A brief description appears in the supplement at the end of this volume. This study investigated properties of the evoked potential with the aid of measurements of behavior. Subjects received short tone bursts (50 milliseconds) and made "absolute judgment reports" (Rosenblith, 1959) on pitch, ignoring loudness, or on loudness, ignoring pitch. The judgment tasks were balanced

for difficulty and for average rates of selective information transmission; yet we have found that the same tones could still elicit reliably different evoked potentials in the two different tasks.

Both tasks required the subjects to analyze the stimuli and make some response contingent on the results of their analysis. Such tasks may be termed "information processing tasks". MacKay has shown (MacKay, 1956) that the average amount of selective information transmitted by a stimulus is not the only parameter that must be considered in a complete specification of the informational "meaning" of that stimulus. The fact that changes, such as we have employed, differentiating two information processing tasks can influence as gross a sign of brain function as the average evoked potential could perhaps provide new clues to assist in modeling the information processing faculties of the human brain.

DR. GARCIA-AUSTT: Dr. Sutton, were there any changes in the evoked responses after training?

DR. SUTTON: I need to give several answers to that question. First, our experiments were designed to reduce the influence of learning variables on our evoked potential data. Subjects were informed of the probabilities to be used at the beginning of each block. In addition, the "certain" condition for a given probability was always run immediately before the "uncertain" condition at each probability. Therefore our evoked potential data do not reflect the early stages of the learning of a probability. Secondly, the probability conditions were counterbalanced within the day and across 4 experimental days. In this way, we reduced differential effects of learning and habituation on the relationship between probability and evoked potential amplitude.

There was, nevertheless, a tendency for evoked potential amplitude to decrease within each day and across 4 experimental days. This "habituation" was significantly less marked for P_3 than for earlier components. For the curves shown in this presentation (fig. 6–2 through 6–6), the data were averaged over 4 experimental days. When we plotted the data separately for each experimental day, the curves were quite similar, except that they were noisier. However, one could detect a displacement of the curve downward on the y-axis from the first to the fourth day. In other words, the slope of the relationship between P_3 and probability was unaltered, but there was a decrease in P_3 amplitude on the order of 20 percent across the 4 days.

DR. MORRELL: I would like to ask Dr. Sutton if he has looked systematically at earlier components than the several to which he refers because in experiments that we have done, these remain very stable in latency and are correctly identifiable over a variety of task altera-

tions, whereas the later components do tend to change their morphology.

DR. SUTTON: At vertex, with our amplifiers set for an upper cutoff of 100 Hz, and under our specific experimental conditions, we have not been able to identify components earlier than P_1 (Hallowell Davis' terminology) with any consistency. We routinely identify P_1 (75 msec), N_1 (110 msec), P_2 (200 msec), N_2 (250 msec), and P_3 (350 msec). Of course, all of these latencies are approximate and are subject to alteration under different experimental conditions. Except for N_2, all of these components show the same trend of relationship with our experimental variables as reported for P_3. The N_2 component has an inverse relationship to our experimental variables. However, for all of these components, the trend of relationship to our experimental variables is much weaker and noisier than reported for P_3.

CHAPTER 7

Diagnostic Uses of the Averaged Evoked Potential[1]

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INTRODUCTION

Of all the AEP techniques that hold promise for clinical application, only one at present has the status of a routine procedure—AEP audiometry in neonates. In neonates, vocal and other motor functions have not developed to a very useful point so that electrical activity from the head has much to recommend it as an output device for the computer inside the infant's skull. In most cases, however, language is the output device of choice for humans.

To be applied in the clinic, a technique must be useful in addition to being feasible. Here, I will discuss technical feasibility, but I want to emphasize that these technical possibilities are not useful in practice unless, for some reason, there is something wrong with simply asking the subject what we want to know.

There are roughly three classes of situations when just asking doesn't work, so that evoked response procedures hold real promise. These are (1) when neurological factors such as lesions or lack of maturity block verbal exchange, (2) when psychological factors such as cultural difference or mendacity interfere, and (3) when the state we're testing for is not accessible to introspective report, and its behavioral consequences are most inexpensively tapped by our evoked potential measures.

SENSORY TESTING

Hearing

The appropriate starting point for this review is the auditory evoked

[1] Work carried out under support from Office of Naval Research Contract NONR 2931(00), with the assistance of Mrs. K. LeVasseur.

potential test for hearing loss (Davis, 1965b; Rapin et al., 1966; Davis, et al., 1967). The procedure is straightforward. A tone, a tone-pip, or click, is presented and repeated a number of times. Using vertex-to-ear leads, the averaged evoked potential is computed. If an AEP is distinguishable from the background activity, the subject is inferred to have heard the sound. This is close enough to the truth to be quite useful. By this method, estimates of auditory threshold approximate those obtained by conventional techniques in cooperative subjects.

The purist may complain that averaged evoked potentials can be obtained with subthreshold stimuli (Libet et al., 1967), that deaf subjects may have AEP because of a myogenic reflex (Cody et al., 1964) to the vestibular effects of loud sound, and that the absence of a sound may even evoke a response (Barlow et al., 1965). All of the foregoing is true; however, good audiometry can be done using AEP. Some of the foregoing points, of course, have practical consequences. For example, an AEP evoked by a very loud sound does not rule out total hearing loss if vestibular function remains intact although the myographic responses usually are earlier than the actual auditory evoked potentials. More important are those cases where gross brain damage prevents the appearance of the AEP although hearing may be relatively intact.

Also, the auditory AEP is very responsive to repetition. The evoked response may be reduced if the stimulus is delivered only as frequently as once every 10 to 20 seconds. At such slow rates, an average of 100 would be impractically time-consuming in a clinical situation. Davis feels that an interstimulus interval of between 2 and 3 seconds represents a good compromise between the demands of time and the effects of habituation or adaptation. Irregular intervals and intermixed tones of different pitches also will tend to yield higher-amplitude AEPs. At the other extreme, Goldstein and Rodman (1967) have introduced a 10-stimulus per-second presentation technique that may have advantages enough to outweigh the disadvantages of habituation.

Marked moment-to-moment variability in AEP amplitude occurs without apparent cause. In addition, background EEG and state of arousal are confounded and both probably also affect the AEP. Although these must be considered in evaluating a record, good AEP can be obtained during sleep. Although slow wave sleep raises the auditory threshold about 10 db in adults, it has no measurable effect on the thresholds of infants. This is fortunate because it is difficult to find a time when a small infant is quiet except when he is asleep. For inducing sleep in infants before AEP audiometry, Rapin and Graziani (1967) find chlorpromazine more useful than phenobarbital.

Vision

The visual evoked response is potentially useful for testing the

presence or absence of vision. In addition, both color and form resolution can also be assessed. Finally, since the averaged electroretinogram (ERG) and the averaged occipital EEG (AEP) both can be computed, lesions along the optic pathways can be localized.

Different colors apparently induce different AEP in individuals with color vision, but this differential responsiveness is absent in the color-blind. Several methods of obtaining color AEP have been suggested (Seigfried et al., 1965; Shipley et al., 1966; Regan, 1966); however, the one described by Clynes and Kohn (1967) is probably the most feasible for clinical use. Use is made of a patch that alternates between two test colors at about 24 Hz. If the colors are matched for brightness, these alternations will evoke a response in normals, but will not do so in subjects blind to the particular color change. This procedure has certain obvious advantages for, at 24 Hz, epochs of 2 in length can be averaged a number of times in a very short period. By having two or more cycles in an average, an estimate of the reliability of the AEP can be obtained by simply looking at the record. However, it should be noted that Shipley et al. (1968) found the most dramatic effects of color in 4 to 8 Hz Fourier components; therefore slower stimulus repetition rates may have some advantages that still need evaluation.

Clynes et al. also recorded from four bipolar pairs derived from a rosette of electrodes at the occiput. This arrangement demonstrates color evoked potentials in some leads and not in others. It would appear from his data that the use of multiple leads increases the precision with which a response can be detected and hence increases the confidence in identifying cases where the response is absent. The more recent work of Regan (1968) also indicates some peculiar interactions between color and stimulus frequency for maximum response amplitude.

Pattern also influences the AEP, and it seems clear that lateral bipolar leads, e.g., O_Z–O_1 may be more sensitive than an AP arrangement at right angles as, O_z–C_z (Clynes et al., 1967; Rietveld et al., 1967). In general, the amplitude of the AEP and particularly the 200-millisecond component increases with the number of contrasting borders resolved at the fovea. If the number of contrasting borders is increased stepwise and the AEP is recorded at each step, the AEP is found to drop abruptly at the point when resolution is lost.

The fovea is almost entirely responsible for the visual AEP (DeVoe et al., 1968). Thus in infants with severe retinal disease with macular sparing, the retinogram may be absent, and the visual AEP may be almost normal (Walsh et al., 1966).

There are, naturally, pitfalls. For example, the effect of pattern can be obliterated by using very bright flashes. The results depend on the subject fixing and focusing on the target; thus the procedure is not

applicable to very uncooperative or sleepy subjects. However, Carol White, in a personal communication, has suggested that the use of brief flashes can allow clinical refraction without cycloplegia because the flash can be brief enough to supply the stimulus before pupillary constriction can compensate for refractive errors.

Lesions in the optic pathway distal to the optic nerve will reduce both the ERG and the AEP. More central lesions, however, will leave the ERG intact and abolish or diminish the AEP. Asymmetry of the left and right occipital AEP with stimulation of one eye occurs as would be predicted from the anatomy of the optic nerve (Kooi et al., 1965; Bergamini and Bergamasco, 1967; Gévin et al., 1966).

Somatosensory

In somatosensory evoked responses to electrical stimulation of the nerve, the peripheral nerve action potential can substitute for the ERG in the visual analogue (Rosner and Goff, 1967). There are, however, some additional interesting complexities. The somatosensory AEP to electrical stimulation of the nerve seems to reflect primarily the activity of the dorsal white columns since total lesions of the anteriolateral columns can leave the AEP quite normal. When lesions involve a peripheral nerve, latencies of almost all AEP peaks are lengthened. Wave durations increase, and the whole AEP may be prolonged because an afferent peripheral lesion reduces excitability and results in a temporal dispersion of the afferent volley.

Bergamini and Bergamasco (1967), in their discussion of the foregoing points, give an interesting clinical application of the somatosensory evoked potential—although one that is not likely to present itself every day in clinical practice. They encountered a pair of 6-year-old Siamese twins who were joined through a partial dorsal fusion of the lumbar sacral spinal column. Before surgical separation, it was important to determine whether any nerves or roots were fused. Clinical evaluation was unsatisfactory, but somatosensory evoked potentials saved the day. Evoked potentials could only be recorded from the scalp of the twin receiving the electrical stimulus. With this evidence that the twins had no spinal nerves in common, surgical separation was undertaken and successfully completed.

Other Sensory Pathways

There is no reason that other sensory modalities could not be assessed using AEP. Allison and Goff (1967), for example, have described an olfactory AEP that might be applied to testing smell. Greiner, et al. (1967) have shown that vestibular evoked responses can be obtained by rocking the individual (other than by 1000-db clicks!). This is an interesting AEP for it is of long duration and

almost completely unilateral (temporo-occipital), being on the right side in right-handers and on the left in left-handers.

Evoked potentials can be produced by using touch or a puff of air as a stimulus. Although there is still some doubt on the matter, the consensus is that hysteria does not abolish the evoked potential. Therefore, the differentiation between organic and hysterical sensory loss could be made by using the AEP. However, touch evoked potentials, unlike shock evoked potentials, can be almost totally abolished by distraction (Ervin and Mark, 1964). This is not surprising in view of the rapid accommodation of touch and the contrasting stability of vibration and position sense over long periods of stimulation.

NEUROLOGICAL DISEASE

As the search for pathology leads us rostral along the neuraxis, we come to consider neurological diseases of the cerebrum. For our purposes, these may be divided into disorders of maturation, destructive lesions, and irritative lesions.

Disorders of Maturation

Evoked potentials show dramatic changes with maturation. The auditory evoked potential is obtained easily in infants as noted earlier, but it does not show the marked changes with maturation that are found in the visual evoked potential (Engel and Benson, 1968). Recording from inion and presenting flashes to a sleeping infant, a primary visual evoked response can be recorded. The latency of the onset of this component is linearly related to conceptual age and ranges from about 200 milliseconds at 35 weeks gestation to 400 milliseconds at 45 weeks. Engel used the onset rather than the more conventional wave peak as the point for measuring latency since he found that blink artifacts tend to obscure the peak. This recommends itself as a pediatric technique for distinguishing full-term "runts" from premature infants.

Maturational changes continue in a fairly dramatic fashion up to and perhaps past puberty, to be followed by evidences of aging, such as increased amplitude and length of latency commencing at about age 40 (Dustman and Beck, 1966; Straumanis et al., 1965).

The interval between infancy and puberty holds great promise but is still being explored. Eventually, the AEP should provide a handy measure of central nervous system developmental age that could be used for comparison with chronological age, skeletal age, and so on. This should be of particular interest to those doing cross-cultural studies. Arakawa et al. (1968) found that children about age 9 with ariboflavinosis showed prolonged AEP latencies to light. This needs to be confirmed and compared with developmental changes. Does a child with ariboflavinosis simply have a less mature AEP, or does he

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have a distinctly different AEP? Actually, the reported effects of ariboflavinosis on the AEP are much less obvious than effects on power spectra of background EEG. However, these preliminary reports are enough to merit further study.

Destructive Lesions

Destructive intracranial lesions make themselves known by marked asymmetry in the AEP. Later, we will indicate how AEP asymmetry may be a correlate of intelligence. This, however, relates to the 150-millisecond parietal AEP to flashes. The asymmetry produced by cortical lesion is nonspecific, gross, and total. For example (Goff, 1967), in a patient with a rather small, superficial parietal lesion on the dominant hemisphere, nerve shock contralateral to the lesion produced little or no response on the affected side and an abnormal response on the unaffected side. Nerve shock ipsilateral to the lesion evoked a normal response on the unaffected side and a slightly reduced, but otherwise normal, late response on the diseased side. This is of some theoretical interest since it indicates that the late somatosensory AEP apparently requires a functioning lemniscal pathway for its normal development. The AEP also may be grossly asymmetrical when the raw EEG is symmetrical; thus, the AEP gives some gain over conventional electroencephalography (Bergamini and Bergamasco, 1967).

A prognostic test for brain damage caused by cerebral circulatory insufficiency has been proposed by Crighel et al. (1966). They observed that normals show an increase in visual AEP amplitude and recovery after breathing O_2. Hyperoxia also increases AEP responsiveness in patients with circulatory insufficiency when the prognosis for return of function is good but may actually have a reverse effect and may further diminish AEP in cases that subsequently show no recovery.

Irritative Lesions

In epilepsy, the AEP may not even offer as much as does the conventional EEG. Amplitudes may be increased during spike and wave discharge, and the late "ringing" of the visual AEP may be more marked during interseizure periods (Bergamini and Bergamasco, 1967; Mirsky and Tecce, in press). In general, however, the raw EEG serves as well as, or better than, the AEP. Morrell (1965), however, has reported the interesting case of a patient who had an epileptogenic lesion in the auditory cortex. Recording over the area of the lesion ordinarily revealed little or no response to flash. However, by a prior repetitive pairing of flash and click, the patient could be "conditioned" so that his auditory cortex would give an abnormally large

visual evoked response. The generality of such a phenomenon, however, remains to be explored.

INTELLIGENCE

The first study relating intelligence to averaged evoked potentials was reported by Chalke and Ertl (1965). They used a population with widely dispersed IQ and found shorter latencies in the brightest subjects. This has been confirmed in essence by Plum (in preparation) although the correlations between latency and IQ in the study of a more homogeneous group of subjects were not impressive.

Whitaker et al. (1967) have made another approach to the problem. They filtered the EEG into alpha, beta, and theta bands before averaging. Thus, to a single series of light flashes, they derived three averages. For each of these averages, they computed the mean periodicity of the recorded waves. They then used an empirically derived formula that has given truly remarkable predictions of intelligence over the normal range on three subsequent replications. The empirical formula is complex and somewhat obscure, but in general it seems to give high scores to subjects whose alpha, beta, and theta AEP periods are in perfect harmonic relationships. For example, an alpha period of 100 milliseconds, a beta period of 50 milliseconds, and a theta period of 200 milliseconds would predict a veritable genius.

The most recent work on intelligence is that of Rhodes et al., in press. They recorded flash evoked responses from parietal leads and found that the negative-going wave at about 150 milliseconds is larger on the right than on the left in the bright subjects, but almost identical on the two sides of the dull subjects. The larger right-sided potentials in the bright children were also more stable than those of the dull children.

Unpublished studies from a number of laboratories (American Psychological Association meeting, 1968 Symposium: Brain Function, Cognitive Performance, and the Developing Child, San Francisco) suggest that various AEP measures may be related to both age and adequacy of performance in children under the age of 9 years. These same measures also seem related to performance in the children when age is held constant.

In summary, good (older) performance goes with high amplitude, asymmetry, stability (i.e., low single-sample variability), and long latency. This last is notable since it seems opposite to the finding in adults noted earlier.

PSYCHIATRIC DIAGNOSIS

The sensitivity of the AEP to subtle psychological and physiological influences makes this potential application very intriguing. Certainly for the psychiatrist, electroencephalography has been more impressive

in promise than in pay-off. Although work such as that by Stevens et al. (1968) and L. Goldstein et al. (1965) would suggest that all the potentials of the standard EEG have not been exhausted, the AEP has a great appeal.

Recovery Cycles

One of the first applications of averaged evoked potentials in clinical psychiatry was made by Shagass and his group (Shagass, 1968). They examined the recovery cycle of the early components of the somatosensory AEP, using carefully placed bipolar leads over the appropriate sensory field. They then gave pairs of shocks to the ulnar nerve. The first, or conditioning shock, was presumed to produce a phasic inhibition and recovery. This recovery cycle was then probed by the second, or test, shock. By varying the time interval between the conditioning and test shock, the time course of the recovery cycle could be plotted.

Psychiatric patients were found to have slower and less adequate recovery than normals. As studies progressed, however, it appeared that the situation was more complex. Some of the patients studied had abnormally large initial responses so that a delayed recovery might be relative (i.e., a small percentage of a large conditioning response) rather than absolute. Older patients were found to have larger responses, and females were found to have both larger responses and responses with shorter latencies. This problem was solved by means of statistical procedures that removed the effect of the conditioning response amplitude. In spite of this, the reduced recovery cycle was still observed.

This appears to be a rather general phenomenon. For example, they counted 10 peaks in the first 80 milliseconds of the somatosensory averaged evoked potential and found the recovery cycle effect to a greater or lesser degree in all of these peaks. Furthermore, the phenomenon was found in almost all psychiatric conditions. In fact, the only psychiatric patients who did not differ from normals were a group composed of psychoneurotics with anxiety and depression and a group suffering from psychophysiological reactions.

These studies were done with fairly intense stimuli. More recent studies using milder stimuli have shown that some subjects who show a delayed recovery with high intensity stimuli may show a supernormal recovery with low intensity stimuli.

The recovery cycle phenomenon seems to be a real one, for other laboratories have confirmed it, using visual evoked potentials (Speck et al., 1966; Heninger and Speck, 1966; Floris et al., 1966). However, since depressed recovery to intense stimuli can be observed in such a variety of conditions, it would seem premature to attempt any clinical

use. However, as the complexities of the recovery cycle are unraveled and the underlying neurophysiology is clarified, this technique may offer promise for clinical use.

Intermodal recovery cycle effects have been described by Goff (1967). These effects are highly subject-dependent and can be noted with interstimulus intervals as great as 1 second. This intriguing effect has yet to be investigated for possible clinical significance.

Contingent Negative Variation

If the active electrode is placed somewhere over the front of the head, a slow negative-going wave can be observed during the period that the subject anticipates a stimulus. This slow wave has been called the contingent negative variation (CNV). Because of its slow time course, it must be recorded with direct coupled amplifiers and relatively nonpolarizable electrodes. In the usual experimental situation, a warning stimulus is presented, and then, after a predetermined interval of, say, 2 seconds, a second stimulus is presented to which the subject must make some response. The CNV goes to a maximum just before the final or "imperative" stimulus, then resets to normal. (See Ch. 4.)

This phenomenon was discovered by Grey Walter's group (Walter et al., 1964a; Cohen and Walter, 1966). They observed that in reaction-time experiments, the amplitude of the CNV is related to the speed of response. The greater the negative contingent variation, the faster the response. It seemed to them as though this reflected a kind of expectancy—the greater the expectancy, the higher the negative wave, and the faster the reaction time.

The CNV can be observed when the second stimulus does not require any gross motor response as for example in viewing the presentation of a picture. However, the amplitude of the CNV has been shown to be related to the amount of energy required by the motor response if a motor response is, indeed, required (Rebert et al., 1967). If the second stimulus is occasionally omitted, then, presumably, the subject's expectancy is reduced, and the negative contingent wave is also reduced.

Grey Walter has suggested that some level of intelligence is necessary for the development of the contingent negative wave; therefore, it can be used to estimate intelligence. It is reduced in anxiety and in schizophrenia, is increased in obsessive neuroses, and is absent entirely in psychopaths. Thus, it would appear that the contingent negative wave might be the basis for an entire psychodiagnostic inventory (Walter, 1968).

There are, however, some problems with this. DC recordings in an uncooperative subject can be difficult because lead sway may cause blocking of the amplifier. Eye movements also are difficult to exclude as a factor in slow wave changes, particularly with frontally placed

electrodes. Näätänen (1967) has presented evidence that phasic arousal of any sort causes a negative dc shift and that this is the cause of enhanced AEP amplitudes with attention. I suspect other papers in this symposium will indicate why this is not the entire answer to AEP amplitude enhancement; however, Näätänen's work does indicate one factor that could be playing a role in the CNV.

Finally, and perhaps most important, is a series of objections raised by Vaughan et al. (1968). He finds that the contingent negative wave actually occurs over motor cortex and parallels an inhibition of motor activity that sets the stage for a sudden release of a motor response. Vaughan suggested that most of Grey Walter's findings could have been predicted by examining the distributions of the reaction times. For example, the relationship between reaction time and the CNV reflects the fact that when reaction times are slower, their distribution is more spread out. In such a case, if peak CNV coincided with response, peak CNV would not be well time-locked to the stimulus when reaction times were slow, and the average CNV would be smaller than in a more closely time-locked average associated with fast reaction times. To demonstrate this, he averaged backwards from the motor response in situations of fast and slow reaction times and showed that the CNV was not different in the two conditions when one thus time-locked the averaging to the response rather than to the stimulus.

The CNV is also accused of being a motor inhibitory potential because the amplitude of the H-reflex (the monosynaptic reflex observed by stimulating the nerve in the popliteal fossa and recording from the gastrocnemius) is reduced in proportion to the amplitude of the CNV. Obviously, the CNV supports considerable controversy. Nevertheless, the potential of the CNV for psychodiagnostic procedures should not be discounted at this time.

Stimulus Intensity Control

Buchsbaum and Silverman (1968) introduced the averaged evoked potential amplitude in the investigation of a phenomenon that they call stimulus intensity control. Based on the work of Petrie (1967) and of Silverman (1967) they assume that some people are able to reduce their responsiveness to strong stimulation. Petrie had used a kinesthetic figural-after-effects measure to assess this tendency. She found that after interposed tactile stimulation, some subjects would judge the width of a bar to be narrower than previously. Such people who did this were called "reducers"; she found such people to be less sensitive to pain. Silverman also had noticed that nonparanoid schizophrenics tended to be reducers. Buchsbaum and Silverman then reasoned that the characteristic of these people was an ability to reduce their re-

sponsiveness to strong stimulation, and if this was the case, they should show a reduced AEP to intense light stimulation.

They used a mastoid-to-vertex derivation and varied the flash of a light provided by a Grass photostimulator. They found that the subjects classified as reducers on the kinesthetic figural-after-effects measure showed less increase in the amplitude of evoked potentials as the intensity of the stimulus was raised (and some showed a paradoxical decrease!).

This correlation between "reducing" as determined by visual AEP and as determined by kinesthetic judgment has been confirmed using 10-Hz sine wave light as a stimulus (Spilker and Callaway, 1968). Thus, the phenomenon seems to be a genuine cross-modality perceptual style. The relevance of this for clinical work (e.g., pain sensitivity, schizophrenia, etc.) remains to be determined. However, preliminary data from our laboratory indicate that chronic LSD users tend to be "reducers", and feeble-minded children tend to be "augmenters."

The Two-Tone Averaged Evoked Potential

The thought disorder of schizophrenia is characterized by variability of behavioral responses. It appears that an increase in auditory AEP variability parallels this behavioral variability.

Some years ago we designed an AEP procedure to study schizophrenic thought disorder. In this procedure, tones of 600 and 1000 Hz are repeated in a haphazard order, and the subject is told to ignore the tones. The subject, in a quiet, semidark room, watches his brainwave (C_z–A_1) on an oscilloscope monitor. After being shown the effects of tensing muscles, rolling eyes, and so on, he is asked to maintain a steady EEG. Under such conditions the tones seem trivial, and in nonschizophrenics, the high (1000-Hz) tone averaged evoked potential and the low (600-Hz) tone averaged evoked potential will be almost identical. In other words, the two physically different tones evoke almost identical responses when no particular psychological distinction is being made between them. However, when a normal individual has reason to distinguish between the tones, there is then a difference between the two AEP.

A variety of models of schizophrenia ranging from Shakow's (1963) notion of segmental set to McGhie's (1966) notion of overinclusiveness predicted that schizophrenics would behave as though they had some reason to make a distinction between these tones. In assigning psychological significance to difference between tones, the schizophrenic should also show a differentiation in his AEP. That is to say, the averaged evoked potentials to the two different tones should be more dissimilar in the schizophrenic.

In the situation just described, schizophrenics tend to have more dissimilar AEP than do nonschizophrenic psychiatric patients. Also, among schizophrenics, disturbed nonparanoid patients have the most dissimilar AEP (Callaway et al., 1965; Jones et al., 1965; Jones et al., 1966).

There are, of course, a number of possible explanations for such an observation. One possibility is the effect of drugs. In our hospital, we have no good facility for keeping schizophrenics drug-free for the several months that are probably required. However, we are able to follow patients as their clinical course fluctuates and have been able to show that two-tone averaged evoked response test results vary in parallel with the thought disorder even while drug dose remains relatively constant. Furthermore, normal values are obtained from neurotic patients and patients with affective psychoses even though such patients may also be on fairly large doses of phenothiazines.

Our findings also could result from the use of correlation coefficients as a measure of similarity between the two AEP. Such a measure cannot be interpreted as ordinary correlation coefficients since the points along an AEP are not serially independent. Nevertheless, a high correlation between two averaged evoked potentials indicates that the two curves are very similar. Two dissimilar curves (yielding low correlations) could result from consistent distinction being made between individual evoked potentials. On the other hand, low correlations also could be produced by a low signal-to-noise ratio (e.g., a large amount of background activity, considerable irregularity in evoked potentials, or low voltage evoked potentials). This is a serious problem for schizophrenics tend to have low voltage evoked potentials. Furthermore, we have found both a correlation between amplitude and clinical state and also a correlation between the two-tone evoked potential measure and evoked potential amplitude.

In our most recent study, we used the old two-tone procedure and, in addition, a mock two-tone procedure where both "tones" were 1000 Hz. The correlation measure distinguished schizophrenics from normals in both the old and mock procedures. When only a single tone was sounding, the correlation measure could only be reflecting sample variability.

This matter of AEP variability is made more explicit by computing the standard deviation at each AEP time point. If, for each AEP, the maximum peak-to-trough amplitude is plotted against the largest one of the standard deviations, then it can be seen that the two are highly correlated. A regression line, however, will separate schizophrenics (low-amplitude, high-standard variations) from normals.

The elegant discriminant function measures described by Donchin in this conference were the only one of several methods tried that dis-

tinguished the real two-tone from the mock procedure. Yet schizophrenics did not differ from normals significantly on this measure. Although some problems of background EEG remain to be solved, it seems that auditory AEP variability accounts for the two-tone correlation's sensitivity to schizophrenic thought disorder.

This two-tone AEP test is rarely of value clinically. Occasionally, it has helped confirm the diagnosis of hysterical pseudopsychosis. Although patients with depression and with character disorders usually have normal two-tone AEP scores, an abnormal score is not specific to schizophrenia. For example, Korsakoff patients have low scores (low correlations), and two-tone AEP scores correlate with clinical rating of confabulation and confusion in such patients (Malerstein and Callaway, in preparation).

CONCLUSION

The AEP has been feasible as a routine procedure for almost 10 years. Except for the diagnosis of deafness in infants, it still remains a research technique. The promise of clinical utility seems brighter each year, however, and the challenge for the researcher to close the gap between laboratory and clinic is becoming harder to ignore.

DISCUSSION

DR. SHAGASS:[2] Callaway has given us a systematic and comprehensive review of the possible diagnostic uses of averaged evoked potentials. Proceeding from the relatively simple to the relatively complex, he began with the application of the AEP to the testing of sensory functioning in various modalities and then discussed possible diagnostic uses in neurological disease, the measurement of intelligence, and psychiatric evaluation. He concluded that the only true clinical application was in the diagnosis of deafness in infants and that, apart from this, AEP recording presently remains a research procedure.

I find myself virtually in complete agreement with Callaway's conclusion, and I can add little to his thorough coverage of the literature. In this discussion, I should like, therefore, to consider some of the issues involved in using AEP recordings for diagnostic purposes and to try to indicate some possibilities for the future.

AEP recording is not a test, but a method. The method may be used for many tests by varying stimulating and recording conditions and data analysis procedures. The reliability and validity of each specific procedure as a test for a given criterion needs to be established. Nu-

[2] Research supported (in part) by grant MH 12507 from the National Institutes of Mental Health.

merous methodological factors must be evaluated in the process of developing any such test. I shall not dwell here on methodological problems since many of these have received detailed consideration elsewhere in this symposium. It is clear, however, that the user of a test must know how results can be influenced by biological and instrumental artifacts and by such factors as age, sex, diet, time of day, state of awareness, expectancy, intelligence, socio-economic status, etc. There is no AEP test procedure for which such information is completely available. It is possible that such factors may be of low relevance for some purposes such as testing of sensory deficits and neurological lesions.

Establishment of reliability and validity, although necessary, is not sufficient for an AEP test to be adopted as a diagnostic procedure. As Callaway has indicated, it must be relevant to a clinical problem and provide information that cannot be obtained more easily and economically in other ways. The electrocardiogram would hardly have reached its present status if its sole use were to count heart rate although it is a highly reliable and valid method for this purpose.

The issue of cost is intimately related to clinical relevance or usefulness. Usefulness is a relative matter. If an AEP test were shown to provide unique information of a nature decisive for clinical management, such as provided by radiological procedures, it would be used without much regard to cost. Thus far, most AEP tests cannot claim to be worth their high cost although Callaway's survey indicates that many may be as contributory to particular clinical diagnostic problems as some of the blood and chemical determinations carried out with high frequency in hospitals. For example, Callaway's two-tone procedure may contribute as much to a psychiatric evaluation as a random blood sugar to a medical evaluation. However, AEP procedures are much more costly in every respect than most biochemical procedures, and their cost usually far outweighs the potential information to be gained. At least in the psychiatric field, this may be caused as much by deficiencies in the clinical question as by the inadequacies of the AEP procedure.

Future diagnostic applications of AEP methods almost certainly will be influenced by the orientation and traditions of those using them; AEP investigators come from many backgrounds, relatively few of which involve routine laboratory diagnosis. Two contrasting major groups are the electroencephalographers and psychophysiologists. The EEG has the status of a routine diagnostic method, whereas psychophysiological methods remain research procedures. The diagnostic status of the EEG was acquired quickly largely because of the information it provided in convulsive disorders. The relevant information is essentially qualitative in nature—characteristic waveforms,

recognizable by inspection. Furthermore, the patient need not be having a clinical seizure during the recording, and information bearing on anatomical localization of lesions is often obtainable. The traditions of clinical electroencephalography are thus strongly oriented toward qualitative diagnostic signs, and, apart from counting frequencies, quantitative methods have not been prominent in clinical EEG work. Since Callaway's review indicates that there is a paucity of qualitative AEP diagnostic signs, we can hardly expect electroencephalographers to be in the forefront of enthusiasm for AEP diagnosis if this is to depend almost entirely on measurements of events not readily apparent to naked-eye inspection. This is not to say that they are not in the forefront of AEP research. On the other hand, although we can expect the psychophysiologists to be more enthusiastic about measurements than electroencephalographers, they are even less likely to apply them since this would represent a new venture for them.

There seems to me little doubt that future diagnostic developments involving both AEP and EEG methods will be highly dependent upon techniques for rapid data reduction by computer. This is hardly a novel prediction. We have been seeing a great deal of research effort devoted to quantification procedures, particularly of EEG. However, to achieve adequate diagnostic utility, computer methods must reduce data automatically to a reasonably small array of meaningful numbers, preferably on-line and certainly within 72 hours after testing. Rapid reporting is a sine qua non of diagnostic utility. Until automatic methods of this sort are achieved, we can be reasonably certain that only the simplest and most obvious quantitative AEP deviations will find clinical application. I can support this view from experiences with barbiturate sedation threshold measurements; EEG responsiveness to the drug was assessed by means of a careful and tedious measurement (Shagass, 1956). I recall the eminent electroencephalographer who visited my laboratory, saw the measurement procedure, and proclaimed "That kind of thing is not for me!" Our computer programs, of course, will depend upon what we learn about the clinical correlates of evoked response characteristics. However, in agreement with Callaway, I believe that this information will be obtained.

I have some other reasons to believe that our diagnostic future—if there be one—lies in rapid computerized reduction and manipulation of our data. Particularly in the area of psychiatric disorders, the evoked response studies that have yielded the most encouraging results have focused upon the interrelationships between responses evoked at different temporal intervals (Shagass, 1968) or with slightly varying stimulus conditions (Callaway et al., 1965). Potential diagnostic utility has not emerged from the examination of a single AEP but from the relationships between at least two. Figure 7–1 gives an

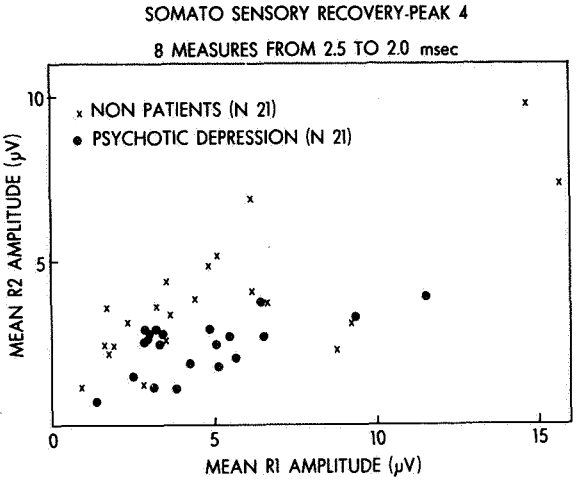

FIGURE 7–1.—Comparison of nonpatients and psychotic depression patients with respect to relationship between mean R1 and R2 values obtained in somatosensory recovery function measurement. There were eight interstimulus intervals increasing in 2.5-msec steps from 2.5 to 20 msec. Initial positive peak latency (about 25 to 30 msec) measured as μV deviation from estimated isoelectric line. "Conditioning" and "test" stimulus intensities equal at 10 ma above sensory threshold; stimulus duration 0.1 msec. Note that R1 values were similar for the two groups but that for any given value of R1, the R2 amplitude was generally higher in nonpatients.

example from some of our work on somatosensory recovery functions. Instead of plotting the recovery curve, I have here calculated for each subject the mean amplitude of the initial positive component evoked by each of a pair of stimuli for eight different interstimulus intervals from 2.5 to 20 milliseconds. In this scatterplot, the abscissa and ordinate respectively represent the mean amplitudes of the responses to the first and second stimuli at these eight intervals. The graph compares 21 patients with various kinds of psychotic depressions with an equal number of nonpatients matched to them for age and sex. It shows that there is a rather good correlation between the amplitudes of R1 and R2 and that the average R1 values do not differ much between patients and controls. However, note that for any given value of R1, the R2 value for the nonpatients is generally greater than that for the patients; this reflects the reduced recovery that we have repeatedly found in psychotic depressives (Shagass and

Schwartz, 1966). The two groups are clearly quite different populations with respect to the slope for the regression of R2 on R1. The recovery function difference between patients and controls lies in the relationship between R2 and R1. Unfortunately, these differences are not specific for depressions; they are found also in other kinds of patients (Shagass, 1968).

Recently, we have been examining more complex evoked response interrelationships by applying trains of nine conditioning stimuli in studying somatosensory recovery functions. We have also been examining the effects of varying the intensity of conditioning and test stimuli. Exploratory results suggest that the application of conditioning trains may accentuate the differences between patients and nonpatients that we have found with single conditioning stimuli or even bring out differences not otherwise apparent. As an example of the latter, figure 7–2 shows some very preliminary data comparing a small heterogeneous group of eight patients with seven nonpatients with respect to interrelationships between mean responses to (1) the

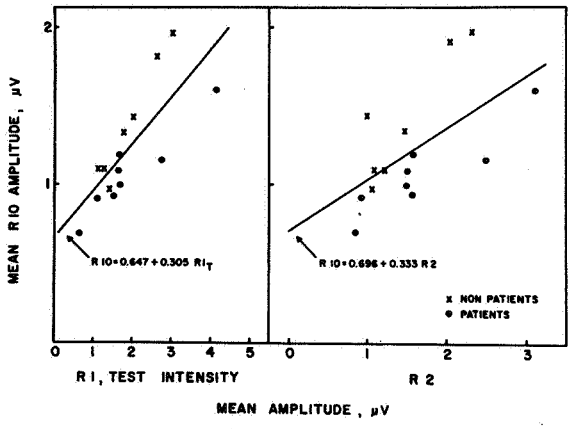

FIGURE 7–2.—Relationships between mean amplitude of somatosensory response to tenth and last stimulus in a 100-per-sec train (R10) and response to an "unconditioned" test stimulus of equal intensity ($R1_T$) and a test response "conditioned" by a single stimulus (R2). Individual test stimulus parameters as in Figure 7–1; five "conditioning" stimulus intensities were used. Eight psychiatric patients compared with seven nonpatients. Amplitudes, automatically calculated by digital computer, represent the average deviation about the mean for the epoch 15 to 31 msec after stimulus.

tenth (test) stimulus of a train (R10), (2) the second (test) stimulus of a pair (R2), and (3) the unconditioned test stimulus ($R1_T$). The interval between all multiple stimulus pulses was 10 milliseconds. For these particular groups, R1 and R2 amplitudes did not differ as can be seen by comparing the groups with respect to the abscissae. However, the addition of eight conditioning stimuli in the train produced considerable differential response to the test stimulus. Note that most of the nonpatients are above the regression lines for the group as a whole, and most of the patients are below it. The regressions of R10 on $R1_T$ and R2 are steeper for the nonpatients. Only one or two subjects would be misclassified if one used the regression lines as a basis for dividing patients and nonpatients.

If these preliminary results should prove valid, we may have a procedure of diagnostic import. However, I am sure that it will seldom, if ever, be used for diagnostic purposes unless the results can be obtained quickly and at reasonable cost.

The current research program of my laboratory is based on the belief that to apply AEP recording effectively to pathophysiological problems, it should be integrated with study of the EEG. We have known for some time that AEPs are not completely independent of the EEG from which they have been extracted (Rodin et al., 1965). More recently, we have obtained evidence that the interrelationships between EEG and evoked response characteristics are, in themselves, variables of probable importance. In a group of healthy college students (Shagass et al., in press) we found that visual and somatosensory evoked response amplitudes both correlated positively with EEG amplitude; AEP amplitudes were measured peak-to-peak over uniform time intervals, and EEG amplitude was measured with a Drohocki-type integrator (Goldstein and Beck, 1965). The correlations were significant, but not large (r about 0.4). However, when we subdivided our subject group according to whether performance on simple perceptual tests was above or below average, it turned out that the EEG-evoked response relationship differed considerably in the subgroups defined by perceptual performance. Figure 7–3 gives an example of the results. The two perceptual tests measured thresholds for lifted weight discrimination and accuracy of recognition of tachistoscopically presented letters. We see that the correlation between EEG and visual evoked response amplitude was quite good in the subjects with above median perceptual performance (r about 0.6), whereas the correlation in the below-average perceivers was poor (r about 0.2). These findings have been confirmed independently by Callaway with auditory evoked responses obtained in an entirely different recording situation and using a different perceptual test (Shagass et al., in press). Therefore, it appears that the interrelationships between different kinds of electro-

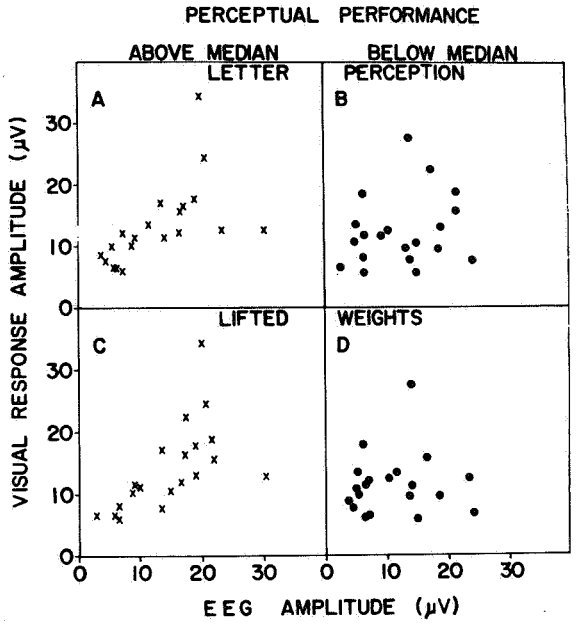

FIGURE 7-3.—Scattergrams showing correlation between EEG and visual response amplitudes in 40 healthy subjects classified according to performance on tests of letter perception and lifted weight discrimination. VER amplitude is maximum peak-to-peak within 200 msec after flash. EEG taken at "rest" after VER recording. Perceptual tests administered at different time. Note that the EEG and VER amplitudes are well correlated in above median and poorly correlated in below median perceptual performance group.

physiological variables can yield psychologically meaningful data not obtainable with individual variables.

In conclusion, it may be appropriate to state that provision of diagnostic tests is by no means the only goal of clinical neurophysiological research and that it would be unwise to make premature clinical use of available procedures. It seems quite likely that, as we proceed toward our main goal of understanding physiological mechanisms, diagnostic applications of our procedures will occur. Even now, if we could reduce our data quickly and inexpensively to numbers, we would probably find our knowledge, poor as it is, in diagnostic demand. Perhaps we will be able to produce these numbers in the future and, hopefully, at that time they will have more validity then we are able to ascribe to them today.

DR. LIFSHITZ: I think that some of Callaway's results and also some of the things we have been doing can be thought of not in terms of diagnostic questions, but rather in terms of etiology, and in this case, in terms of a possible underlying pathology in some schizophrenics. We have been considering the possibility that a basic physiological malfunction in some schizophrenics is the excessive variability of the spatio-temporal electrical patterns of specific sensory representations in the brain (Lifshitz, 1968). Along somewhat similar lines of thought, Drs. Ornitz and Ritvo (1968) have postulated that perceptual inconstancy is basic to the difficulties encountered in many autistic and schizophrenic children.

If an individual were never quite certain of sensory input information, it would seem that this could account for many of the symptoms seen in schizophrenia. It would be impossible to be certain about one's sensory perceptions if the brain's electrical representations of these perceptions were excessively and randomly variable. For example, an individual might look at himself in the mirror and feel that his appearance had changed, or look at his hand and feel that it looked like someone else's hand. The basis of this type of misperception could be an altered central representation of the sensory input.

In order to test this hypothesis, we need a sample of the brain's representation of sensory input. The easiest way to obtain this is by recording the averaged evoked potential. Of course, we are not sure what we are looking for. However, an increased variability in the evoked potentials of schizophrenics would be indicative of this sort of phenomenon although it is not known whether the disease causes the variability in evoked potential, or the variability in evoked potential causes the disease.

In any event, in looking at a group of schizophrenic patients and a group of normals, we find that there are statistical differences between the two groups in the degree of reliability of the reproduction of the evoked response. We have used various measures of variability including point-by-point variance determination, and the correlation between two waveforms. The correlation coefficient between two waveforms is similar to other measures such as the distance between vector representations of waveforms in an N dimensional time-point space. Although statistical statements cannot be based directly on the correlation coefficient, it can be considered as a monotonic function of waveform similarity; therefore, ordinal statistics can be applied to sets of correlation coefficients.

Table I presents some of our results obtained from 16 chronic schizophrenic subjects and 16 normal controls. Averaged evoked potentials were obtained from 50 presentations of a visual stimulus consisting of a blue light projected on a screen for about 1 second. The data are

TABLE I.—*Correlation Coefficients (r) Between AEPs to a Repeated Blue Visual Stimulus, Lead Cz–Pz*

Parameter	Mean r	Standard Deviation r
Controls, N=16	0. 785	0. 167
Patients, N=16	0. 428	0. 362
Tests of difference	U=67 P=0. 01	F=4. 68 P<0. 005

shown for AEP recorded from a lead 2 cm lateral to C_z–P_z. Correlation coefficients were computed between the first half-second of evoked potential to the initial presentation of the stimulus, and to a repeated presentation about 1 hour later. As can be seen from the table, the mean correlation between the first and second AEP was 0.785 for the controls and 0.428 for the patients. This is significantly different from chance, at the 0.01 level, using a single-tailed Mann-Whitney U Test. It may also be noted that the variance among the schizophrenics was significantly greater than among the controls. Using the somewhat inappropriate F test, this was significant at the 0.005 level. These results were also similar for a lead 2 cm lateral to P_z–O_z.

DR. BICKFORD: I would like to answer the question that Dr. Lehmann raised concerning the accuracy of the interpolation methods used in this technique. This is, of course, an important point, and Dr. Harris examined it thoroughly in his thesis on interpolation methods. It turns out that for evoked potential fields, a distance between electrodes of 3 cm is adequate for the interpolation methods employed, and you get a good match between estimated and actual results because evoked potential fields are fairly smoothly distributed in space. This might not be the case in all other fields such as we might find in epilepsy, for instance.

In viewing figure 7–4, a technique similar to that of figure 6–16 is used except that here the patient has a complete right homonymous hemianopia. Samples of the conventional field taken from points 8, 11, and 14 are shown above, and it is remarkable that there is no absence of potential gradient in the area corresponding to the hemianopic defect. When compared with the normal shown in figure 6–16, it is clear that there is considerable asymmetry, a negative peak appearing in the "blind" cortex quite early in the response at a time when a positive peak asymmetric with the former is appearing on the normal side. This positive peak shown more clearly in B and C appears to shift

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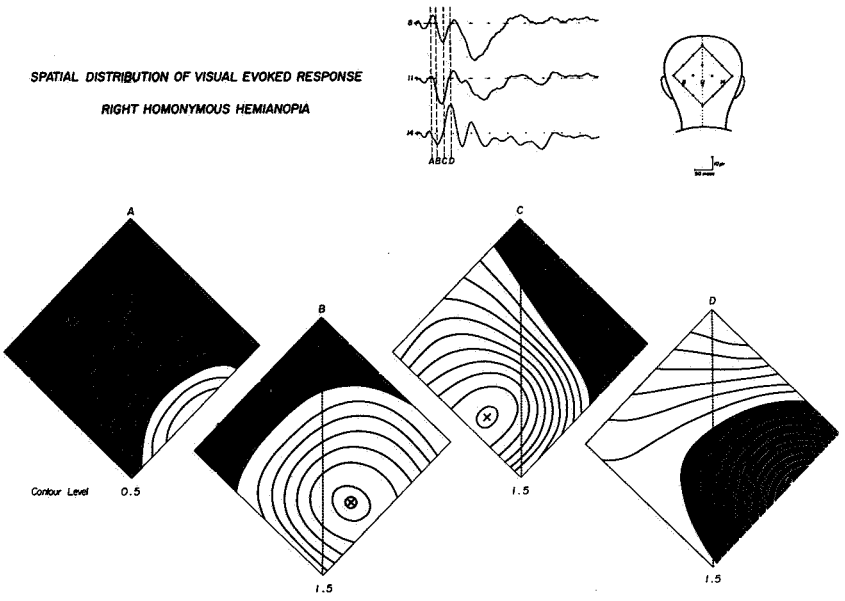

FIGURE 7–4.—Effect of a complete right homonymous hemianopia on the spatial distribution of the photic evoked potential. See Figure 6–15 for comparable findings in the normal subject.

across the visual field from the visually intact to the blind side. Since these are pilot studies, it is not possible to say to what extent similar findings will be discovered in other cases of hemianopia. At this time, it is evident that complex changes are occurring that could hardly be interpreted on the basis of the conventional voltage-time trace alone. My object in bringing Dr. Harris's technique to your attention is to urge others engaged in evoked potential work to adopt some form of area display since this provides the generalities of approach necessary in this complex area.

DR. SATTERFIELD: I would like to present some unpublished data from our laboratory. This is a study of the recovery cycle for the late component of the click-evoked vertex response in a group of depressed patients and in a normal control group matched for sex and age (fig. 7–5). It can be seen that for normal subjects, we get a distribution that is much like the bell-shaped curve, and for the depressed patients we get a curve that is skewed on both ends. Eight depressed patients fell within ± 1 standard deviation of the mean for the normal group, five were out of this range on the low end, and nine on the high end. These data suggest that some depressed patients differ from normals in that their late response recovers faster or slower than that of normals.

It is interesting to conjecture that there are at least two types of disorder in depression—one in which the excitatory systems of the nervous system are overactive and the other in which the inhibitory systems are overactive. If this is true, the first type of patient should respond best to tranquilizers, and the second type would respond best to psychic energizers. This idea is consistent with reports that some depressed patients do respond best to tranquilizers, whereas others respond best to energizers (Rickles et al., 1967; Hollister and Overall, 1965; Rickles et al., 1964).

DR. DAVIS: I would like to discuss briefly the question of audiometry in children that was mentioned in the course of Dr. Callaway's presentation, partly in its own right and partly because it illustrates some of the principles and points that have been discussed previously today. In the first place, I believe that we have, in this particular application,

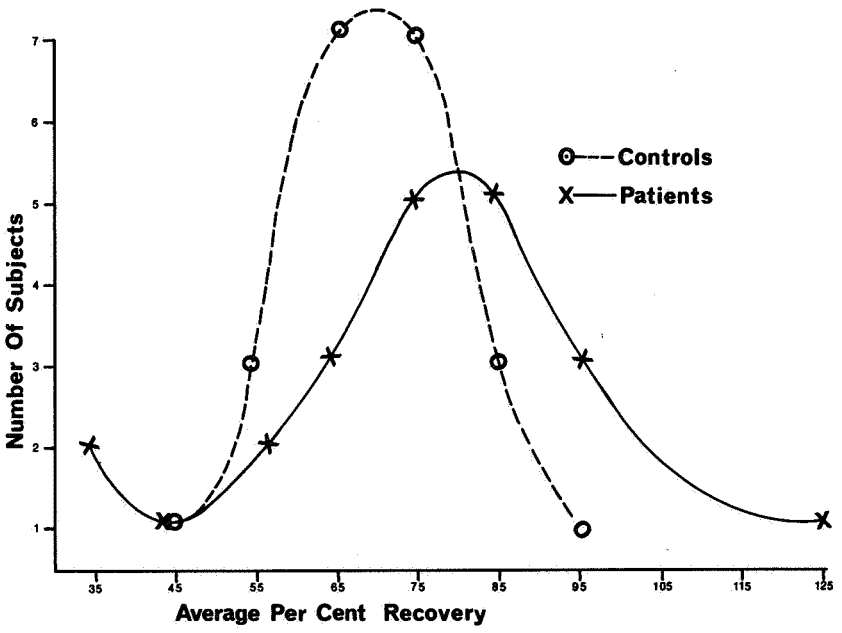

FIGURE 7–5.—Frequency distributions of depressed patients and normal subjects for percent recovery of the evoked cortical response. Percent recovery is defined as the response amplitude at each of the faster rates divided by the amplitude of the slowest rate (one stimulus every 8 seconds). The faster rates were 1 per second, 1 per 2 seconds, and 1 per 4 seconds. The average percent recovery equals the percent recovery at the three faster rates divided by three. The amplitude measurement used was the peak-to-peak amplitude of the larger negative to positive vertex potential occurring at about 100 msec latency.

a really valuable, although somewhat expensive, clinical method. We have been using it for some time in our clinic now, and I am willing to argue that although the number of children for whom this particular method really makes a difference is not very large, nevertheless, the method allows us to make an important early decision as to the handling of the young child. This justifies the expense of the method. We have tried to bring the expense down by simplifying the method as far as possible.

It is not simply the neonate for whom evoked response audiometry is appropriate. It is useful for any child who is uncooperative or whose responses are not to be trusted. We find that we have a very formidable competitor in our regular behavioral clinical audiology, and I have come to respect more and more the conclusions that can be drawn by a skillful audiologist in observing the startle reactions, the orienting responses, and the conditioned responses in a child, even a very young child. On the other hand, we have become very good friends because each of us gains great confidence and comfort in having a totally different method support his own conclusions, and we agree extremely well.

We have been able to do most of our work without sedation because most of the children who come to us are more than 1½ years old and can be persuaded to cooperate. But I need not only my EEG equipment; I need a skillful handler—a skillful nurse to get the electrodes and earphones on the child and to get the child in the proper psychological state. The psychological state is important. The child is amused by pictures, puppets, and toys; and we find that the child can take an active part with a moderate degree of manipulation of toys. If we use electrodes on the vertex and high in the post auricular region, we can reduce the movement artifacts sufficiently. But I emphasize the importance of the psychological state. It is a happy child—an amused child with his attention on something else—that we want.

We must pay great attention to efficient use of patient time, because the proper state will not last indefinitely. We find that about 40 minutes working time is the maximum, ultimately divided into two or possibly three shorter periods. After that the evoked responses "run down." This is very close to what we call the "chair effect" in our experimental work with adults, and it is a severe limitation when we want really precise, reproducible, properly controlled data. We do not speak of it as habituation. We simply call it the "chair effect." The adult period of proper state is about twice as long as in the child, just less than 2 hours, with a 10-minute coffee break in the middle.

We plan to make the best possible use of patient time. We find experimentally that one stimulus per second and a block of about 50 or 60 stimuli is about right for identifying the N_1P_2 complex of vertex

potentials. The trick of having an instrument that writes out a graphic record immediately on-line, without the need for an X–Y plotter to get the information out of the memory, is a great help.

We make estimates of threshold. We make them on-line, because making them on-line determines the subsequent strategy to make best use of our precious patient time. We are able to estimate thresholds with considerable accuracy, on the average. We take advantage of extrapolation. We do not try to work down to the minimal responses. We collect two or three blocks of responses at a given frequency at different intensities and watch the change in size of the average response as a function of the intensity of the stimulus, and also the prolongation of latency. These two indicators allow us to estimate "thresholds" that agree very well with the behavioral response. We have used for validation hard-of-hearing children who are old enough to make a good "finger response" and have had training in doing so.

There is a problem of criterion here. The feedback of experience gained from such children is very important. We test such older children from time to time just to keep our criteria fresh and make sure that we are still effective.

We were afraid at one time of maturational changes in infants; however, we did not find them as serious as we had feared. What we do find troublesome are individual differences. Differences are greater at the younger ages, but I have really equated maturational changes and individual differences.

We have a really difficult task when we are not sure there is any auditory response and do not know whether to look for a typical well-formed response or one with some other individual characteristic. The best help we have here is to use another sense modality—usually touch, a vibratory stimulus to the fingers—and observe the tactile evoked response. There is sufficient kinship between these two sensory modalities for us to use the tactile evoked response as a guide for selecting the auditory evoked responses successfully. We superimpose the record of a doubtful auditory response on the record of a tactile response, using transillumination from beneath. We have found this to be an extremely helpful maneuver, and I would point out that the tactile responses are a good guide. Visual responses are not so good. There is much greater kinship between audio and tactile than between audio and visual evoked responses.

Some children are difficult to work with. If you get the combination of a poorly formed, abnormal pattern and a large EEG background, then you are just unfortunate. We make the same mistake again when we retest such a child.

DR. ORNITZ: When a child was too intractable and would not sit in the chair at all, or when he did not respond well to medication, we

found it helpful simply to darken the room and wait until he fell asleep while clicks were coming regularly (Ornitz et al., 1967b). We used a 2-second interval and obtained almost complete habituation—that is, no response to the clicks; however, as soon as drowsiness set in and the first sleep spindles appeared, we obtained "dishabituation." If responses get through to the cortex, we get a rather large wave N_2.

DR. RODIN: I just wanted to make a comment on the schizophrenic patients which Dr. Callaway mentioned. I think it may be fallacious to talk about schizophrenia in the singular. This leads us to believe that there might be one disease—schizophrenia—when actually it is a group of disorders in which there are some clinical features in common, but the etiology is probably of considerable diversity. Therefore, to look to the evoked potential for one common denominator in these patients may not be realistic. I am saying this because if you take a group of chronic schizophrenic patients and average their VEP and compare them with normals, you find no differences. But if you consider individuals, you find that there are differences, and they seem to be in the two extremes. One group of patients has an unusually low evoked potential, and another group of patients has a high evoked potential, higher than the normal population. If you combine these two groups, the intragroup differences are lost, and, as group schizophrenics, they do not differ from normals.

There is also some biochemical evidence of differences in schizophrenic patients in terms of carbohydrate metabolism, and these patients do behave differently electrically. So combining them gains nothing.

There is one other question that I would like to ask Dr. Callaway. We have observed (Rodin et al., 1968) that visual stimulus intensity seems to be very important to schizophrenic patients. If we raise stimulus intensity, we wash out differences that may exist between schizophrenic patients and normals, but if we work with lower intensities the differences may be more apparent.

As some of you may know, we have recently studied evoked responses induced through movement of a joint by finger lifting (Rodin et al., in press). We have also done this in the schizophrenic population because it is thought that they may have proprioceptive disturbances. Again, if you take the whole group and average the results and compare them with results from normals, no important differences are revealed. Although we may still discover some statistically significant differences, it is not likely that these results will be useful clinically on an individual basis.

DR. RUHM: I would like to underline Dr. Davis' statement regarding the need for experience in the interpretation of evoked response audiometry in very young children. We have observed that neonates

produce a number of response configurations, rather than a single "template," and that these patterns seem to be coordinate with the gross activity of the child. An elucidation of these relationships and a close acquaintance with their existence is requisite to performing electroencephalographic audiometry with young children.

DR. STORM VAN LEEUWEN: I agree that we should study as many stimulus parameters and as many response parameters as we possibly can. One form of stimulation that we have been using in human subjects these last years is sinusoidally modulated light. With this form of stimulation, the light intensity is modulated, in sine wave form, around a constant average light intensity. By increasing the amplitude of the modulating sine wave, the "modulation depth" is increased without change of the average light intensity.

Among other investigations, my collaborator, Kamphuisen has studied the effect of change of modulation depth on the overall amplitude of the response at the scalp (fig. 7–6). Kamphuisen has found, in agreement with van der Tweel, that generally the response amplitudes at small modulation depths are smaller than those at large modulation

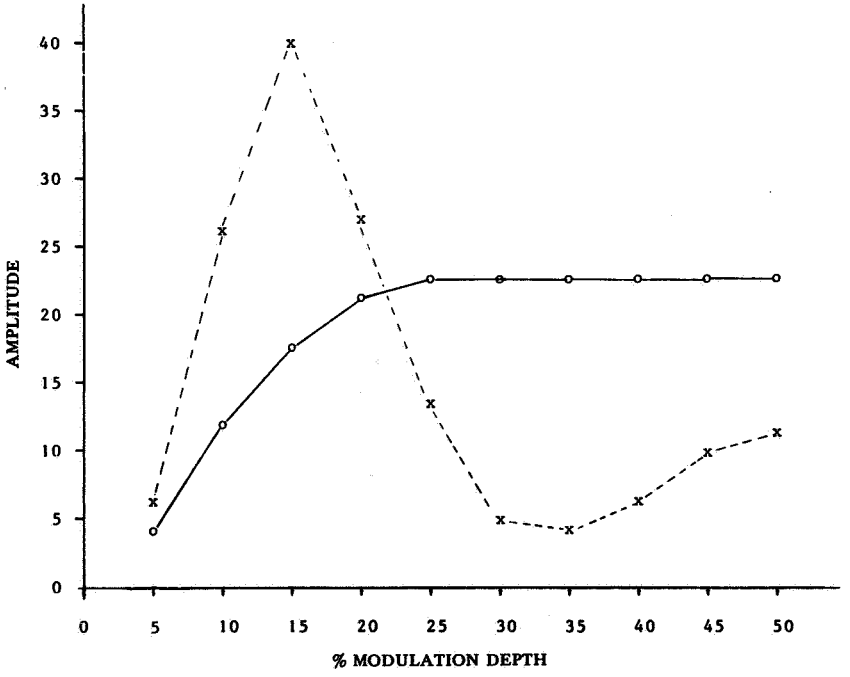

FIGURE 7–6.—Constructed drawing of amplitude (in arbitrary units) against modulation depth. The drawn curve shows saturation at approximately 20 percent. The stippled curve shows paradoxical diminution, maximal at 30 to 35 percent.

depths. Often, increase of modulation depth from 1 to 2 percent to a level of approximately 15 to 20 percent produces a gradual, near-linear, increase of the overall response amplitude. However, above this level, the response amplitude gradually ceases to increase. This phenomenon has been called "saturation" by van der Tweel. In some cases the response amplitudes not only cease to increase at approximately 20 percent but actually decrease at larger modulation depths. We call this phenomenon, also described by van der Tweel, "paradoxical diminution".

Studying these phenomena in homologous areas on the right and left side of the head, Kamphuisen has observed that "saturation" and the "paradoxical diminution" may be asymmetrical. The modulation depth at which saturation and/or paradoxical diminution sets in may differ on the right and left sides. Thus at small modulation depths, the response amplitudes may be equal on both sides, whereas at large amplitudes, they may differ. This may be seen occasionally in normal subjects. It appears to occur more pronouncedly in patients having unilateral irritative EEG disturbances, and, therefore, tentatively the phenomenon of paradoxical diminution is associated with irritative disturbances. In the case of hypofunction of the posterior cortex, as caused for instance by space occupying processes, no paradoxical diminution is observed on the affected side, and the overall response amplitudes at all stimulus parameters are smaller on this side than on the unaffected side.

Dr. Clynes: It is quite evident from this conference that the study of evoked potentials may make a significant contribution to answering, in part, the question "what is man?" and more specifically to answer the diagnostic question "what kind of man is this man?" In answering that question, we encounter the problem of the one-to-one-to-one correspondence, the correspondence between the stimulus, the evoked response, and the perception. If we are to make continued progress in the clinical area, we must try and determine the nature of this one-to-one-to-one correspondence.

One clue is the phenomenon of common natural language—a natural process of development that has not been raised here. For example, in color, we have such words as red, blue, and green; we also have such a word as orange. Orange is an externally related word—a word related to an object—whereas the others are related to internal entities.

The same thing is true about sensory modalities such as sweet, sour, and so on if we consider these as denoting separate data processing entities. In the auditory field, the problem is that we are analyzing a waveform by Fourier analysis; however, the sensitivity of the ear to amplitude and frequency are very different. If you change frequency,

let us say, by 0.5 percent, this is readily audible; but you must change amplitude by about 20 times that much to reach the perceptual threshold. (This is true for sine waves and pulses, even of two rectangular pulses separated by a variable time interval that determines the pitch sensation.) Therefore, a harmonic analysis that mathematically gives equal weight to changes of frequency and amplitude is wrong from our data processing point of view. We found, for example, with auditory potentials that you get a threshold evoked potential from the vertex for small changes in frequency, or a 15 or 20 times larger change in percentage of amplitude. Also, vertex auditory evoked potentials are produced by having the same tone appear alternately from two different sources in space. But surprisingly, alternating ramp frequency changes such as a siren rising and falling, produced by triangular modulation, will give no response although highly audible. So here, basically, the one-to-one-to-one correspondence really breaks down, and we have to seek a data processing clue as to why the brain can perceive a siren very loudly and clearly, but there is no vertex evoked potential. I am mentioning these examples as the types of questions we should try to ask.[3]

In regard to the 24-Hz question that was brought up earlier, my papers, Dr. Sutton tells me, are very difficult to read, and I am sure I agree with this. They are harder for me to write. What the 24 Hz referred to was not only a question of color discrimination, but a new concept of control, using the evoked potential as a probe. The reason we used 24 Hz was to speed up the operation of this probe.

We introduced into the center field a small steady light, and the steady light produced a change in the average evoked potential at 24 Hz. Within about 4 seconds, one could easily detect a variation of the response to the presence or absence of this steady light in the central field. I believe that this may have clinical application—this type of probe use of the evoked potential, where we could not have the response to the stimulus itself (it may occur only once). To observe quickly the change in probe response shape caused by a steady presence of the stimulus—for this the 24 Hz is preferable to the 4 or 5 Hz, but otherwise from the color point of view—it is an entirely different consideration, and there are many slow components sensitive to color that we have demonstrated.

DR. BROUGHTON: It seems to me that there are two very important aspects that must be considered in relation to the diagnostic utility of evoked potentials. The first concerns the sensitivity of this technique as compared to other established investigative procedures. The second aspect concerns the possibility of analyzing evoked potential changes

[3] This question is discussed in Supplement F.

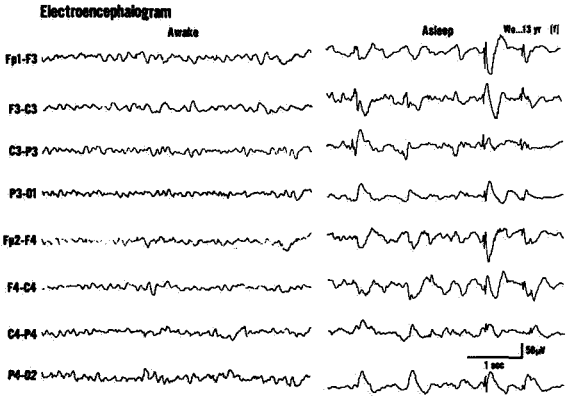

FIGURE 7–7.—EEG during wakefulness and sleep in an epileptic subject. Note diffuse slowing of background activity with rather minimal localizing features in the left-frontocentral region (minimal slowing and depression of beta activity during wakefulness and slightly high voltage spike and wave complexes during sleep).

in terms of altered function of individual cerebral systems. Figure 7–7 shows the EEG during wakefulness and slow-wave sleep of a patient with frequent generalized tonic-clonic seizures of occasional right-sided predominance and with several rare right local motor seizures. The waking EEG shows obvious diffuse slowing of background activity, but little of localizing significance. A slight asymmetry is present in the frontocentral regions, with less beta activity on the left where the background activity is also a bit slower. The right columns of records, taken during sleep, shows bilaterally synchronous spike and wave discharges, including one of the few that was apparently more marked on the left.

Figure 7–8 shows the somatosensory evoked potentials on the two sides of the patient's scalp following percutaneous stimulation of the contralateral median nerve at the wrist. The right scalp response in solid lines shows a fairly normal SEP with components 0–8 easily identifiable. The left-sided response in dotted lines contains marked depression of early components that are present on the right at C–4: that is, of components 1 (neg. at 19 msec, surface negative is up), 2 (pos. at 26 msec), 3 (neg. at 35 msec), 4 (pos. at 43 msec), and 5 (neg. at 55 msec). The later components (see right column of the figure), however, although diminished, are not suppressed to the same extent. The latencies of the evoked potential components on the right are in fact quite similar to those of normal subjects (table I) except for some-

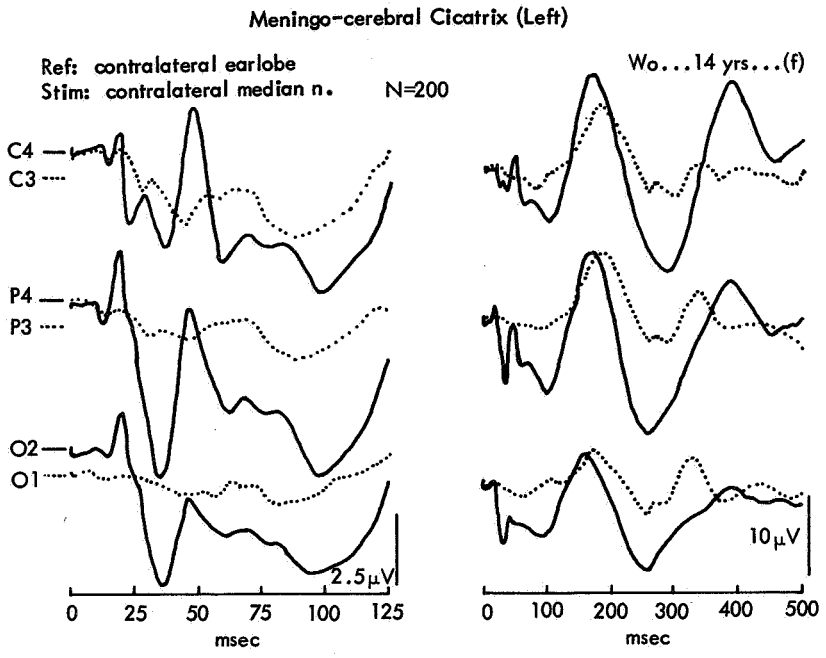

FIGURE 7–8.—Somatosensory evoked potential in same subject (positive down). Percutaneous electrical depolarization of the median nerve was performed at the contralateral wrist to each hemisphere. Two different analysis times are shown. A very marked depression of early components of the SEP is present on the left, despite less striking changes in background EEG activity there (see fig. 7–7).

what longer latency of later components, probably related to antiepileptic medication.

Figure 7–9 shows the pathology found at operation. This consisted of a very diffuse and superficial cicatrix on the left hemisphere. It was most obvious along the Fissure of Sylvius near the bottom of the figure and spreading upwards over the parietal and central regions, leaving the frontal and upper central cortices relatively spared.

The presence of lateralizing and even localizing evoked potentials in the absence of striking changes in background EEG activity, has been documented in a number of other patients who also came to operation and in whom the pathology was known (Broughton, 1967). In at least some cases, therefore, evoked potentials are a more useful diagnostic tool than the routine EEG.

The other point concerns physiological analysis of the evoked potentials and is stimulated by Dr. Callaway's comment about the sup-

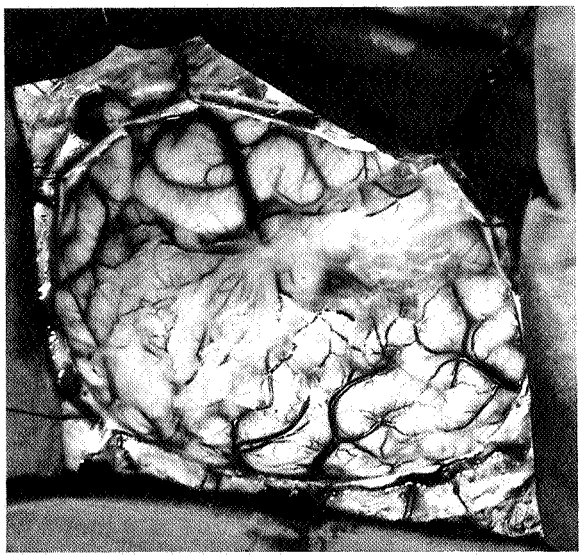

FIGURE 7–9.—Exposed left hemisphere at operation (same subject as figs. 7–7 and 7–8). A large cicatrix is revealed.

pression in the SEP of early contralateral components and later both ipsilateral and contralateral components in patients with a stroke. This suggests that the primary somatosensory cortex is necessary for all SEP components (Williamson et al., 1968).

Such important findings should not lead to a pessimistic rejection of the possibility of interpreting selective changes of evoked potential components in terms of the localization of cerebral lesions. Rather they should cause us to reexamine the way in which we believe such systems are organized in the production of the complex response.

There is, in fact, a considerable amount of evidence indicating that selective alteration of evoked potentials can result from localized lesions. The results of Kooi and Sharbrough (1966) in a patient with post-traumatic cortical blindness, who showed loss of occipital visual evoked potentials in the presence of a prominent vertex potential, is an example. Patients such as the one just illustrated perhaps also exemplify this. Also, of course, Dr. Lindsley yesterday showed us results of selective changes of individual components of the visual evoked potential following various ablations in the visual system.

DR. LEHMANN: I would like to support Dr. Clynes' suggestion to use the stimulus as a probe, i.e., to keep constant the parameters of the response-evoking stimulus; one may then observe changes of the evoked potentials as a function of manipulation of experimental conditions

that per se do not cause evoked potentials. In a series of experiments in collaboration with Dr. D. H. Fender, we have used this approach to study the effect of various stimuli that were continuously shown to one eye of the subject, while the other eye observed light flashes with constant parameters. This dichoptic viewing condition assures that the effect observed in the evoked response is of central origin. We investigated the effect of visual pattern seen in normal vision versus stabilized vision, the affect of light versus darkness (Lehmann et al., 1967), and the affect of different amounts of visual pattern (Lehmann and Fender, 1967, 1968).

DR. MORRELL: Recordings from homotopic regions of both hemispheres may offer information that is not available if one relies only on midline recording. Figure 7–10 shows a subject's averaged evoked responses to clicks presented binaurally under varying conditions.

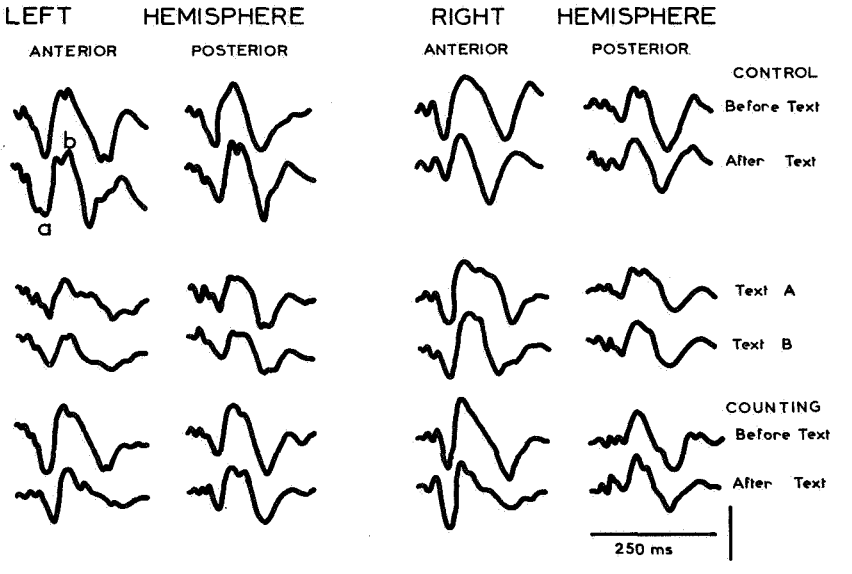

FIGURE 7–10.—Averaged evoked responses (each based upon 100 stimuli) to binaural clicks under varying experimental conditions. Anterior derivations: T3–C3 (left) and T4–C4 (right). Posterior derivations: electrode midway between T5 and P3 referred to C3 (left), and electrode between T6 and P4 referred to C4 (right). Top two rows: subject instructed only to listen to clicks; 3rd and 4th rows: same series of clicks presented while subject listened (binaurally) to two different texts for which they were to be tested for recall; bottom two rows: subject counted the series of clicks silently and was asked to report the total after 100 had been presented. Note greater attenuation of response while attending to text at left derivations (contrasted with control) than at right derivations.

Bipolar recordings were made from the left and right hemisphere for the anterior temporal region (overlying primary auditory cortex) and the more posterior temporal-parietal region (overlying Wernicke's area on the presumed dominant left side). One observes a greater attenuation of the evoked response to clicks presented while the subject is listening to text in recordings from left hemisphere derivation, when compared to the right side. In some subjects, while attenuation of response amplitude as compared to control is also observed in right hemisphere records, the effect is generally of greater magnitude and more consistent among subjects for left hemisphere data. Such topographical analysis might be explored further for the study of language processing, using the evoked potential as a probe.

DR. CALLAWAY: Since it is so late, all I will say is that I will send Dr. Rodin some of our papers that show how one can study the thought disorder of schizophrenia as an entity in itself without assuming that schizophrenia is a unitary disease. I hope that we make that abundantly clear. Not all people who have been diagnosed as having schizophrenia have thought disorders all of the time, and as the thought disorder comes and goes, so the evoked response measure changes. I think we are looking at something related to shifting plans or sets rather than something that is a particular biochemical or physiological process.

Supplements

THE PAPERS in this supplement were submitted by several of the conference participants subsequent to the conference. As the discussion progressed, it became clear that some of the participants did not have the opportunity to expand their comments to the full extent they felt necessary. For this reason, we have decided to enable any participant to submit a short manuscript expanding on matters he discussed at the conference.

THE EDITORS

SUPPLEMENT A

Differences Between Human Evoked Potentials Elicited by the Same Acoustical Stimuli During Loudness Discrimination Tasks and Pitch Discrimination Tasks[1, 2]

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Space Biology Laboratory
University of California, Los Angeles

COMMENTS by Walter and by Gardiner earlier in this conference referred to material from an unpublished Ph.D. dissertation (Gardiner, 1969). We would like to describe briefly the experiments and discuss a few of the results.

Human evoked potentials have been reported to change with shifts of the focus of attention between sense modalities (Spong et al., 1965; Spong, 1966; Debecker and Desmedt, 1966; Satterfield, 1965) or between stimuli within the same sense modality (Donchin and Cohen, 1967). We now present a comparison of human auditory evoked potentials (AEPs) recorded during two tasks, each of which focuses subject's attention on a different physical property of physically similar stimuli.

METHOD

Subjects sat in a small (approximately 3 feet x 4 feet x 6 feet) anechoic chamber. They received short (50-msec) tone bursts generated by a modified coherent tone burst generator (General Radio 139–A) and presented by monaural earphone (Permoflux PDR 600)

[1] Supported in part by U.S. Public Health Service Mental Health Training Grant 5–T1–MH–6415, the Advance Research Projects Agency of the Department of Defense under contract DADA 17–67–C–7124, the Office of Naval Research under contract Nonr 233(91), and the U.S. Public Health Service Grant NB 02501.

[2] The basic experimental design and some findings have been reported previously (Gardiner et al., 1967; Gardiner and Walter, 1968).

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to the right ear at a comfortable listening level, with the unstimulated earphone covering the left ear. Background noise, when used, was introduced directly into the chamber by loudspeaker. Subjects sat at a writing desk and wrote down their discrimination judgments. A record was made of the time during which the writing pen was on the writing surface, to permit study of possible motor-associated influence on evoked responses. During discrimination tasks, the EEG was recorded continuously between vertex and left mastoid process. The subject was grounded at the ear. An Offner Type R polygraph was used with 0.3-sec time constant. The EEG, an eye movement record, and time-of-stimulus and time-of-response data were recorded on FM magnetic tape (Sanborn 3900) for later analysis.

For each session, each tone could be one of two intensity levels, and one of two frequency levels. An equal number of the four possible stimuli were presented in a random order during each "data collection run." During "loudness" tasks, the subject was required to identify the intensity of each stimulus presented, having been told that only two possible intensity levels would be used. He was told to make the classification disregarding any other stimulus change that might occur. During "pitch" tasks, the subject was asked to report which of the two possible frequencies was presented on any trial. The stimuli were chosen in pilot studies so as to equate the tasks in average difficulty (as shown by report scores). The tasks were difficult. High levels of alertness were required throughout a session to obtain a consistently good score. Music students or persons with strong musical interests attained the best scores in this experiment.

Each session began with an "acclimatizing period" during which the subject read while stimuli were presented under the same conditions that were to be used during the remainder of the session.

Periods of data collection during a session were broken into short 5-minute "data collection runs." Forty-eight stimuli, twelve of each type, were presented in predetermined, randomized order in each data run at the rate of one stimulus every 5 seconds. Two-minute rest periods and illustrative stimulus presentations separated the data runs, and each run began with six "warmup" stimuli to which the subjects did not respond. The tasks were reversed after each pair of data runs, and stimulus presentation schedules counterbalanced the presentations.

DATA ANALYSIS

Pilot experiments showed that differences between evoked potentials in the two different stimulus-discrimination situations would be difficult to analyze objectively solely by inspection of averaged records. A statistical procedure using discriminant analysis (Anderson, 1958;

Rao, 1965) was therefore incorporated into this study to assist in the comparison between evoked potentials. We used a step-wise discriminant analysis program (Dixon, 1968). Donchin discussed some applications of step-wise discriminant analysis earlier in this conference, and Walter described some details of our application of this procedure in his comments that follow Donchin's paper.

The statistical procedures required the presentation of more stimuli than could be obtained in a single data collection session. At least 125 records of EEG following each of the four stimuli in each of the two discrimination tasks were required—i.e., at least 1000 single-trial records per "data analysis set." The results to be reported here are based on data analysis sets that pooled data from at least three, and usually four, sessions. Although such pooling may suppress some characteristics of the individual sessions, it highlights similarities between the sessions.

To date, data have been analyzed only from sessions that met the following criteria:

(1) Sessions were rejected if the EEG contained noticeable artifact caused by poor electrode contact, eye blink, etc., or if subjects did not obtain roughly the same report scores on the two tasks.

(2) Only those sessions were included in which subjects performed at, or near, the highest report scores for the given experimental condition.

RESULTS

The statistical techniques to date have been applied to an analysis of data collected during discrimination tasks under three different experimental conditions. In type A sessions, the stimulus intensity levels differed by 4 db, and the frequency levels by 10 Hz. The signal-to-noise ratio was approximately 45 db, and the mean stimulus frequency was 315 Hz. Type B sessions used stimuli identical to those used in type A sessions; however, background noise level was increased to reduce the signal-to-noise ratio approximately 25 db. In type C sessions, the stimuli were presented with the "soft-low" stimulus level as in B, but spacing between levels was increased to 6 db on the intensity axis, and to 20 Hz on the frequency axis. We have observed changes in the AEP with changed discrimination task requirements in data collected in all three types of experiments. However, the most marked and consistent changes have been found in data collection during type B sessions. A few results from analysis of data from type B sessions will be described in this paper.

Most of the subjects tested in type B sessions reported that they found both discrimination tasks difficult. Some subjects, however, attained high correct-report rates on both tasks. Two data analysis

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sets were prepared from data collected from subjects who performed most successfully on both type B tasks. Set B_1 combined data from the three type B sessions in which subject AD was tested. This subject achieved higher scores than any other subject tested in condition B, averaging 93 percent correct on both tasks.

Set B_2 combined data from four other subjects, taking for each subject his first session under condition B. These subjects scored, on the average, 88 percent correct on loudness discrimination tasks, and 87 percent on pitch tasks. All five subjects had engaged in five or more previous sessions, under other stimulus conditions, and were familiar with the basic procedures of the tasks.

To test for the influence of discrimination on the AEP waveshape, we first subdivided the data in each data set into two groups according to task. Each group combined single-trial records from all four stimuli, equally represented. The average evoked potential obtained by averaging all single trial records obtained during loudness discrimination tasks (V) is shown in Figure A–1 with the equivalent average evoked potentials from single-trial records during pitch discrimination tasks (P) for both data sets.

Both V and P AEP conform to the general configuration of auditory evoked potentials at vertex previously described by several investigators (Davis et al., 1966; Rapin et al., 1966). This is a sequence of positive and negative deflections of which the most prominent, in the first 350 msec, are a negative deflection (N_1) peaking at approximately 140 msec in condition B data, a positive deflection (P_2) peaking at approximately 220 msec, a second negative deflection (N_2) peaking at approximately 330 msec, and another positive deflection (P_3) peaking later than 330 msec after stimulus. However, the V and P AEP differ from one another, and in roughly the same manner, in both data sets. The most prominent features of the V AEP are the N_1, P_2, and N_2 deflections and a positive-going deflection peaking between 350 and 550 msec after the stimulus. The P AEP, on the other hand, have N_1 deflections of roughly the same strength as those in the V AEP, but have weaker P_2 and N_2 deflections. The P waveforms also differ from the V waveforms in the range 320 to 700 msec after stimulus. The most prominent features of the P AEP in this range are a positive deflection peaking earlier than the late positive deflection in the V AEP, a strong negative deflection peaking between 450 and 550 msec after stimulus (which is not present with any prominence in the V AEP), and a positive-going deflection that carries the P AEP positive relative to the V AEP at delays greater than 600 msec after stimulus.

The results from discriminant analysis suggest that the enhancement in V relative to P in the vicinity of the P_2 deflection and the

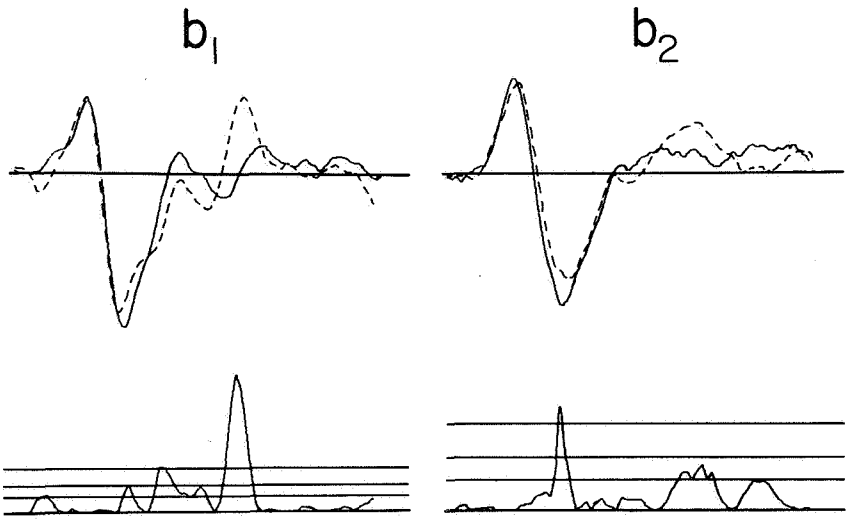

FIGURE A–1.—Different average evoked potentials from the same short tone burst stimuli when recorded from vertex during a loudness discrimination task or during a pitch discrimination task. Each average is based on at least 500 stimulus presentations; B_1, B_2; two data analysis sets composed from type B experiments, in which subjects had to discriminate 10-Hz differences in frequency or 4-db differences in stimulus intensity in the presence of background noise. Sets are composed of data from subjects who reported correctly on approximately 90 percent of the stimuli in both task conditions. Selective information transmitted between stimulus and reported response was therefore essentially the same under both task conditions. Composition of the sets is described in the test. Above: Solid: within-set average EP from data obtained during loudness discrimination tasks (V), with responses to all stimuli equally represented. Dotted: Within-set average EP from the same stimuli during pitch discrimination runs (P), with response to all four stimuli equally represented. Each trace shows evoked potentials for 710 msec commencing with stimulus onset. Negativity is indicated by an upward deflection. Below: Reliability of difference function (F) obtained as the first step of discriminant analysis, as described in the test. Horizontal lines intersecting the F_0 function show the 5-, 1-, and 0.1-percent confidence levels for F_0 statistic for normal distribution. The two sets show a similar change in waveshape with change in discrimination task and the most reliable change in waveshape appearing at long delays (between 200 and 700 msec) after stimulus presentation.

differences between V and P in the vicinity of the strong, late negative peak in the P AEP, are significant in both data sets (Gardiner, 1969). The differences in the vicinity of the N_2 deflection appear to be significant for set B_1, as do the differences appearing in the range 550 to 650 msec after stimulus for set B_2. This may be seen, in part, from the initial F tests calculated by the program at 10–msec intervals commencing with stimulus presentation, the outcomes from which are

plotted as a smoothed curve (labeled f) on figure A–1 below the evoked potentials. The similarity of the difference between V and P in the two data sets provides additional support for the reliability of this difference in each set.

The influence of discrimination task on single-trial records was examined with the aid of the discriminant analysis procedure. The discriminant analysis program, given the task to discriminate between single-trial records of which V and P were the averages, chose to use the measurements at the following delays after stimulus, selected in the order shown:

set B_1—440, 290, 370, 70, 270, 220, 210, 250, 570, 560;
set B_2—220, 500, 600, 250, 260, 210, 170, 340, 320, 450.

Note that these first selections fall principally at peaks of the F_0 function shown in figure A–1. We tested the discrimination rates achieved by the discriminant functions, formed on the basis of the first five selections, against the null hypothesis of random classification. In both data sets, the discriminant functions were successful in distinguishing single-trial records according to discrimination task at rates that were clearly "above chance" (random classification could be rejected at or above the 1-percent level).

We have grouped by subject the discrimination rates achieved by the discriminant functions in data set B_2. The distribution of correct classification among subjects indicates the degree to which each subject's trial records contain at least some of the features that are chosen by the analysis algorithm to discriminate between single-trial records, separated according to task, in the data set taken as a whole. The distribution was quite uniform among three of the four subjects, and even for the fourth subject, more than 50 percent of his single-trial records were distinguished correctly.

A more detailed analysis of these two data sets, taking into account the effects of stimulus parameters on average changes between evoked potentials in the two task conditions, is described elsewhere (Gardiner, 1969).

The results of analyses performed on data recorded in type A are described elsewhere (Gardiner, 1969; Gardiner and Walter, 1969). Evoked potentials recorded in type A sessions, which used the same stimuli as in type B sessions but with a higher signal-to-noise ratio, showed changes in average shape with changes in task requirements that were in many respects similar to those found in data from type B sessions. However, they were weaker and less consistent among subjects. On the other hand, evoked potentials that have been analyzed so far from type C sessions (which employed stimuli spaced farther apart, and thus were easier tasks) showed somewhat different changes

in average shape with task change from those found in data from type A and type B sessions.

Control studies, as reported by Walter earlier in this symposium, and elsewhere (Gardiner, 1969) have suggested that differences in evoked potential waveshape that we have observed during the two different discrimination task situations cannot be attributed to potentials time-locked to the subject's response movements, and are unlikely to be caused by eye blinks or eye movements.

DISCUSSION

We have reported differences in evoked potentials from the same acoustical stimuli when presented in two different discrimination task situations. In one task, subjects were required to discriminate stimulus intensity; in the other, stimulus pitch. The stimuli were presented from the same randomized presentation schedules during both tasks, and with equal presentation probabilities for all four stimuli in each schedule. Since data were analyzed, only where the stimuli were identified at nearly identical rates under the two task conditions, the tasks were essentially equal with respect to the average amount of selective information transmitted between stimulus and reported response (Shannon and Weaver, 1949; Garner, 1962). It therefore appears unlikely that differences between average evoked potentials during the two tasks should be attributed to differences in subject uncertainty regarding the stimuli to be presented (Walter, 1965a; Black and Walter, 1965; Sutton et al., 1965a), or in the average informational importance of the stimuli in the two tasks (Sutton et al., 1967). Our results cannot be attributed to consistent differences in degree of subject attention required toward the stimuli in the two task conditions (Davis, 1964; Satterfield, 1965; Spong, 1966; Spong et al., 1965; Chapman and Bragdon, 1964; Donchin and Cohen, 1967). Sutton and his colleagues (1967) have recently shown that the time at which task-relevant information appears during a stimulus presentation can influence the waveshape of the AEP associated with that stimulus. It is not yet clear whether this finding can assist in accounting for the results that we have reported because of the very brief stimulus presentations that we have used.

The most consistent differences in evoked potentials from the two tasks were found in experiments where both tasks were difficult. The differences appeared most reliably at delays of 200 to 500 msec after stimulus presentation, in the latency range preceding the motor acts used for reporting the required decisions. They could not, however, be accounted for by potentials time-locked to the response acts themselves. Furthermore, the differences appeared in data that were

averaged among subjects and across sessions. We suggest that the differences that have appeared in our experiments between evoked potentials recorded during loudness discrimination tasks and evoked potentials recorded from the same stimuli during pitch discrimination tasks might perhaps hold clues to task-related differences in late steps of underlying physiological mechanisms by which the stimuli are evaluated and the required decisions made.

SUPPLEMENT B

Changes of Occipital Evoked Response During Luminance Discrimination in Man[1]

ELIO GARCIA-AUSTT, WASHINGTON BUNO, JR., AND PABLO HANDLER [2]

THE WAVESHAPE of an evoked response is determined by two principal properties of the stimulus—its physical parameters that can be controlled by the experimenter and its significance or meaning as determined by subjective experience. While the physical characteristic of the stimulus is important, we believe that the scalp evoked potentials are affected more by the central processes of perception and attention, as has been contended by one of us since 1959 (Garcia-Austt et al., 1961).

However, there is much confusion in this field. When the human retina is stimulated by short-duration stimuli, the different potentials are recorded on the scalp in the occipital region and in the more anterior regions. We reported previously (Garcia-Austt, 1967) that with the technique we used that the occipital visual evoked response (VER) is associated with the processing of specific visual information and, consequently, that it is pertinent to call it a visual response. There is general agreement that all the other responses, recorded preponderantly over the vertex, are unrelated specifically with visual information and are related to more general processing of information.

A number of results will be presented here regarding changes of occipital VER waveshape when a subject was required to discriminate changes in the luminance of a spot.

MATERIAL AND METHODS

Nine adult human subjects were used. The subject sat in an almost entirely dark room, with his head in a holder 40 cm from the source

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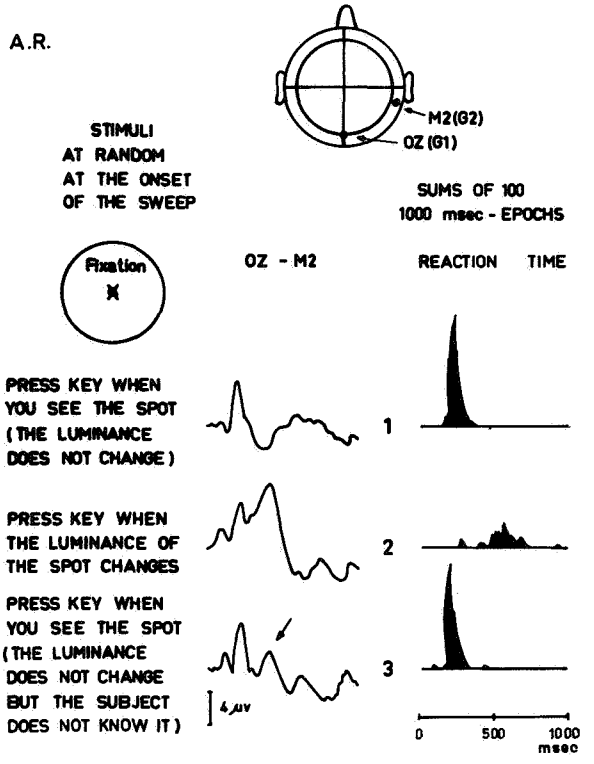

FIGURE B–1

of the stimulus. Motor performance consisted of pressing a key or calling out a few words. Each key-press was recorded. The bioelectrical responses were summed with a computer of average transients (CAT 400 B). The histogram of the finger movements (reaction time) also was computed in the same apparatus concomitantly with the sums of the responses.

Visual stimuli were delivered by a cathode ray oscilloscope (Tektronix 502) with a short-persistence screen (P_{11}). In general, the stimulus consisted of a 1-mm-diameter, low-luminance spot (of about 10 microlamberts) that appeared for 8 to 10 msec in the center of the screen at a random frequency; the gaze was fixed on the same point. The luminance of the spot was varied according to different programs that will be described later.

RESULTS

Figure B–1 shows the changes in occipital VER when the subject was comparing the luminance of one spot with the luminance of a

previous one. Electrodes were placed according to the 10/20 system, and their respective connection with the amplifier grids are shown. The characteristics of the stimulation, the duration of the epochs, and the number of summed responses are indicated in each figure. The left column shows the VER, and the right column shows the histograms of the motor performance. Response 1 was obtained when the individual was instructed to press a key every time he saw the spot. Response 2 was recorded when the subject was requested to press the key only when the luminance of the spot changed. Hence he had to compare the luminance of spot N with that of spot N_{-1}. Twenty percent of the spots delivered at random had a lower luminance, but all the responses were summed. Occipital VER changed considerably in these circumstances, the amplitude of the first components diminished, and a high-amplitude negative waveshape appeared with the peak at 400 msec.

The motor performance was more dispersed and was delayed by about 300 msec as is seen in the histograms. Response 3 was obtained when the first program was repeated; again, the subject had to press the key every time he saw the spot. Motor performance was similar to that in the first run, but the VER was different; a clear negative peak indicated by the arrow was still present though of a lower amplitude than in response 2.

Figure B–2 shows the changes in occipital VER in two individuals when they are discriminating luminance. VER A was obtained when the subject was instructed to press the key every time he saw the spot. Epoch durations were 500 msec for case E.W. (left column), and 1000 msec for case A.R. (right column). The VER are very different; the VER from E.W. consists primarily of a wide positive wave. Conversely, the VER from A.R. had a well developed negative wave. Responses labeled B were recorded when the subjects were requested to press the key only when the luminance of the spot changed. Twenty percent of the spots had a lower luminance and were delivered intermingled at random with the higher luminance spots. Responses of both lower and higher luminance spots were summed. Occipital VER changes considerably with this program. In case E.W., two negative waves appeared (the second one marked by an arrow). In the other case, the amplitude of the first negative wave diminished; a second, also negative wave of a higher amplitude shown by an arrow, appeared. Both responses have in this instance a similar pattern despite their different shape in the first program.

It seems logical to assume that to the first wave A was summated another wave, which appears as a consequence of the process of comparison between the luminance of spots N and N_{-1}, its result being response B. Obviously, this wave equals B–A. This was the opera-

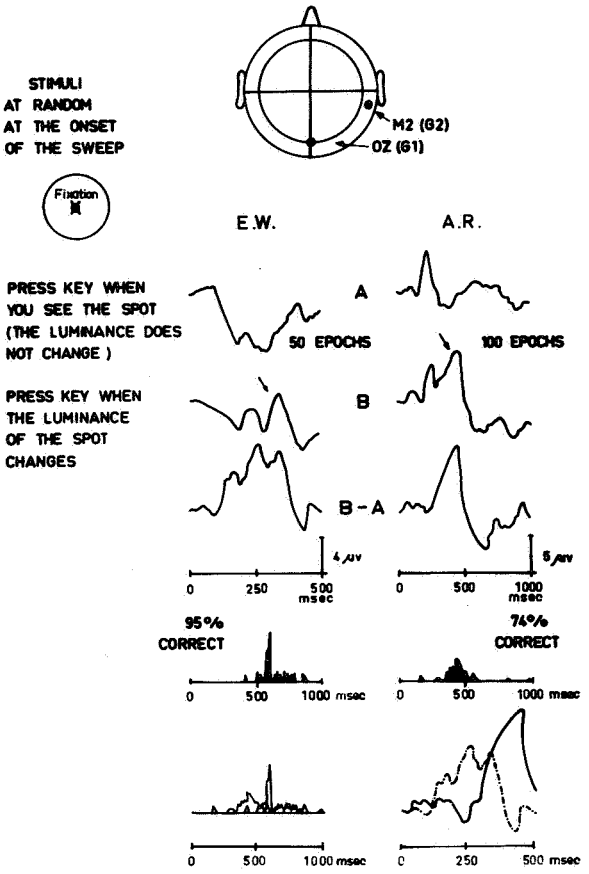

FIGURE B–2

tion carried out with the computer, which yielded the last responses B–A. In both cases, these responses consisted of a high-amplitude negative wave preceded and followed by a lower positive wave. In case E.W., the negative wave was doubly notched; in the other case, it was simpler. In case E.W., the negative variation developed wholly before the 500 msec of the epoch; in the other case, it ended after the 500 msec. For this reason, a double duration of analysis time was used in the last case.

Below these responses, the histograms of motor performance are shown, both obtained with the same time base. The performance was correct in 95 percent and 74 percent in cases E.W. and A.R., respectively. Superposition at the bottom of the figure on the left side shows that the motor performance of E.W. is delayed with respect to that

of A.R. by about 150 msec. Superposition of both waves B–A at the bottom on the right, in this instance both having the same analysis time of 500 msec, exhibited an inverse delay of about 165 msec in the response of A.R. with respect to the response of E.W.

Similar occipital VER changes during luminance discrimination were observed in all subjects.

DISCUSSION

There are important changes in the response when the subject is discriminating luminance, characterized by an amplitude reduction of the first negative wave and the appearance of a second high-amplitude negative wave. These modifications appear from the very beginning of the response, a finding that supports the idea that occipital VER recorded in these experimental conditions is fully related to, or at least concomitant with, the processing of visual information—that is, with perception, and not with the inflow of retinal messages that did not change or were only reduced when the luminance was decreased.

The response changes persist when returning to the first nondiscrimination program. This is an indication that the individual is carrying a subjective program other than that requested. Even though he presses the lever every time he sees the spot, he keeps on comparing, although with less interest. Hence it is important to consider, when observing these changes, the true nature of the subjective program that he is performing. Obviously these changes in the response are not correlated directly with the motor performance since the second negative wave has about the same latency despite the fact that the peak of the histogram can be displaced by about 330 msec as observed in Figure B–1 (responses and histograms 2 and 3).

In two subjects, the "luminance discrimination wave" obtained by subtraction showed a similar waveform and a different latency. Maybe the latency of electrical changes concomitant with the operation of comparing luminances would be better correlated with efficiency in performing the program than the speed of the motor performance because subject E.W. has a better performance than A.R. (fig. B–2). However, a definite statement in this regard, with far-reaching implications, would call for the study of additional cases.

The findings described, together with the fact that we are concerned with a long-latency response, suggest that the occipital VER is not related directly with the crude cortical visual flow. It has been postulated that this response is unspecific and may be obtained with similar features through auditory stimulation (Ciganek, 1967h). Under specific conditions, an auditory evoked response may be recorded over the occipital region using low-intensity clicks (Garcia-Austt, 1967). Despite their characteristics and conditions of appearance, they

are very different from the visual evoked response. The occipital VER recorded with the foregoing characteristics is therefore regarded as related to, or concomitant with, the specific processing of the visual information and differing considerably from the responses recorded at the vertex, which are unspecific and related to a more advanced stage of information processing.

SUMMARY

The scalp averaged occipital visual evoked response in man was obtained on a computer of average transients. Visual stimuli of low intensity were used. During luminance discrimination, a reduction of the first positive wave and the appearance of a secondary negative peak were observed.

SUPPLEMENT C

The CNV and the Vertex Evoked Potential During Signal Detection: A Preliminary Report

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THE contingent negative variation (CNV) reportedly occurs during anticipation or expectancy of sensory stimulation (Walter, 1965b; Cohen and Walter, 1966; Cant et al., 1966; Irwin et al., 1966a), but rarely has its role in perception or processing of sensory information been investigated (Walter, 1965a). When the energy of an expected stimulus is reduced, making it difficult to detect, the anticipatory CNV grows in amplitude (Low et al., 1967; Rebert et al., 1967), but it has not been ascertained if the observer's (O) ability to distinguish the stimulus from background noise (sensitivity) is correspondingly enhanced. The present study used signal detection procedures (Green and Swets, 1966) to show that the trial-to-trial fluctuations in CNV amplitude are correlated with the correctness of O responses and hence with his sensitivity (d').

The experimental paradigm used repeated presentations of a warning flash, which was followed on 50 percent of the trials by a faint 1000-Hz. tone "pip" (signal), lasting 0.3 second. Thus, on a given trial, the probability was 0.5 that a signal would occur at the appointed time, which was 2.3 seconds after the warning flash. The O task was simply to report "yes" if he heard the signal, and "no" if not; this report was given 2 seconds after the signal point in order to dissociate the CNV accompanying the perceptual task from the CNV that preceded any motor activity. About 50 trials were obtained from each O after extensive pretesting had established a signal intensity that was distinguished from the background white noise on about 50 percent of the trials.

TABLE I.—*Yes–No Responses and Electrophysiological Responses for Each Outcome on Signal Detection Task**

Outcome, response/stimulus	Occurrence of each type of trial (%)	CNV Amplitude before tone (μV)	Positive evoked potential after tone (μV)
Yes/signal	27	10. 6	21. 2
No/signal	25	4. 7	6. 0
Yes/noise	5	----------	----------
No/noise	43	10. 7	2. 4

*Mean values from three subjects.

There were four possible types of trials or outcomes since the signal could be present or absent, and the response in either case could be "yes" or "no". These outcomes are colloquially known as "hits" (yes/signals), "misses" (no/signal), "false alarms" (yes/noise), and "correct rejections" (no/noise). The sensitivity of O is high if the number of hits and correct rejections is large in relation to the number of misses and false alarms.

The CNV and nonspecific evoked potentials produced on each trial were recorded from a vertex-mastoid montage and stored on FM magnetic tape for subsequent summation with a CAT computer. CNVs were quantified by measuring their mean amplitude throughout the 0.5-sec interval before the signal point, relative to the preflash baseline voltage. Contamination of the CNV by ocular potentials was eliminated either by visual fixation or by subtraction of the artifact (see Hillyard, this symposium).

The simplest way to relate the CNV to perceptual sensitivity would have been to segregate trials into those with high and low CNV, and to compare the proportion of correct responses on the two kinds of trials. This proved impossible because the CNV was too small to be distinguished from background EEG on a single trial; it was, therefore, necessary to proceed backwards and divide trials into the four categories, and to computer-average separately the CNV attending each type of outcome, in blocks of 10 or 12.

The percentage of each type of trial is given in Table 1; unfortunately, all O responded conservatively and made too few false alarms for the CNV to be ascertained in that condition.

As shown in figure C–1, the averaged CNV amplitude was larger on the trials when signals were detected correctly (yes/signal) than when the signals were missed (no/signal). Reasoning conversely, this means that if the CNV happened to be large during the warning interval,

and a signal was then delivered, it would have been detected with greater likelihood than when the CNV was small. A substantial CNV was also present on trials of the (no/noise) variety, proving that larger CNV do not simply precede "yes" responses. In sum, CNVs were larger when they preceded correct yes and no responses and smaller when they preceded misses. To date, only three Os have been analyzed in this manner (table I), but their CNVs were reliably larger on correct trials than on incorrect trials ($t=2.01$, $df=7$, $p<.05$).

The waveshape of the CNV following the signal also depended upon the stimulus-response outcome. In J. L., the CNV fell sharply to the baseline after a hit, but tapered off slowly when the response was "no", as if the searching process continued beyond the expected arrival time of the signal. In L. E., the CNV was sustained beyond the signal point only in the (no/noise) condition. In M. E., the CNV was sustained in all three conditions until the yes-no response was given, prob-

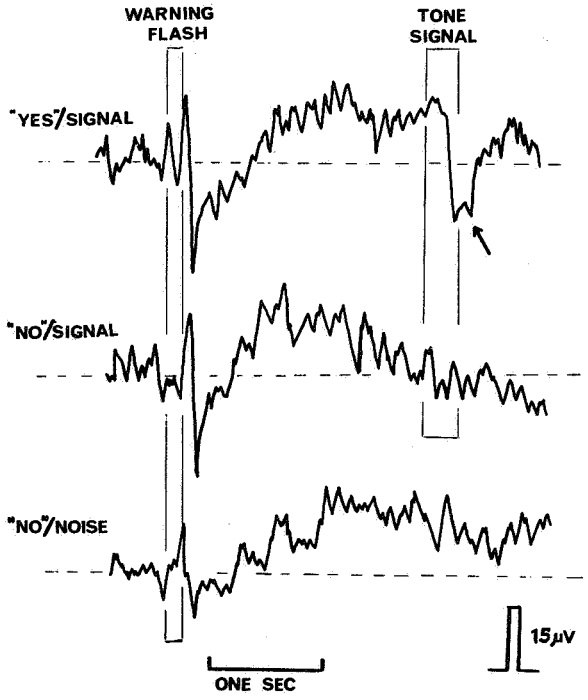

FIGURE C–1.—Computer-averaged CNVs and evoked potentials from 10 trials of each type in one O (L.E.). In the top tracing, the CNV is large preceding a "hit," and the "P300" component (arrow) is large. At the center, the CNV is smaller preceding a "miss." Below, the CNV is large and sustained during correct "no" trials.

ably because an additional numerical "degree of certainty" judgment was also required from this O.

An electrophysiological correlate of signal detection more striking than the CNV was a long-latency positive wave in the potential evoked at the vertex by the signal (fig. C–1, arrow). This wave has been labelled "P300" because of its latency (300 to 500 msec after the signal onset), and it was greatly augmented when the signal was detected. Mean amplitudes of P300, relative to the preceding negative peak, are given in Table I for each type of outcome. The mean difference in P300 amplitudes following detected versus undetected signals was significant ($t=3.44$, $df=4$, $p<0.02$). Since P300 was very large despite the miniscule energy of the detected stimulus, it presumably indexes a higher-order decision or discrimination process rather than a simple sensory elaboration.

These findings support the contention that CNVs can appear during purely sensory tasks, as well as in preparation for motor activity (Low, this symposium). Furthermore, the CNV amplitude fluctuated from trial to trial, such that larger CNVs more often accompanied the correct detections and rejections. This seems to question the assumption made frequently in signal detection research that observer sensitivity is a constant over a long series of trials, since an objective physiological index apparently can serve to divide trials into sets having greater or lesser sensitivity. It may be postulated that the CNV correlates with selective attention towards the expected signal, and that his attentional function waxes and wanes from trial to trial.

The P300 component evoked by the signal on the "hit" trials has been observed during different kinds of detection and discrimination tasks. In the simplest case, Walter (1965b) found a large, prolonged positive wave following complex, "interesting" pictorial stimulation. In a signal detection task, Desmedt et al. (1965) observed simultaneous increases in P300 and in O sensitivity, when signals were preceded by a warning click. Furthermore, a P300 was evoked only by a stimulus in the attended-to modality, when clicks and flashes were alternated (Desmedt, 1965), and by the attended-to configuration within a single modality (Donchin and Cohen, 1967). Sutton et al. (1965a) recorded large P300 following stimuli that resolved uncertainty as to the expected modality, and, finally, Sutton et al. (1967) found that P300 was evoked only by the clicks in a sequence that delivered the information required to solve an intensity, numerical, or temporal discrimination.

Considering these facts, the P300 wave seems to reflect the detection of a stimulus belonging to a particular category, which O is prepared to receive because of its relevance in solving his immediate problems. If O has his attentional "filters" selectively tuned for a particular

stimulus configuration, has evaluated its implications, and is set to respond to it accordingly, then that stimulus should evoke a P300 when detected. The CNV would then indicate that the environment is being scanned for a specific, expected stimulus configuration, while the P300 indexes the decision that it has indeed arrived.

If the P300 represents the resolution of uncertainty and a decision, it may be asked why a similar degree of resolution did not occur on the (no/noise) trials. One possibility is that the "no" decisions were not precisely time-locked to the stimuli, so that its P300 referent was not computer-averaged; another is that a negative inference (absence of signal) may be psychologically less decisive than the receipt of positive evidence.

It is regrettable that too few false alarm trials were obtained for analysis because the behavior of the CNV and P300 on those trials should add to our understanding of their meaning. If, for example, P300 is as large on (yes/noise) trials as it is on (yes/signal) trials, this could be interpreted as support for the signal detection model, in which noise distributions are said to generate stimulus levels that are equivalent to the signal on some trials. A brain response to a "hallucinated" stimulus should, in any case, be of some interest. Perhaps it is best to await the facts, forthcoming in this laboratory, before pursuing such conjectures.

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SUPPLEMENT D

A Note on the AEP of Autistic Children Recorded During Sleep

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DR. LIFSHITZ referred to our clinical observations of autistic, that is, of young schizophrenic children (Ornitz and Ritvo, 1968). We observed that these patients get either too little or too much sensory input. They are thus in a state of perceptual inconstancy. These young schizophrenic patients show clinical phenomena (alternating and sometimes almost simultaneous overreactivity and underreactivity to auditory, visual, tactile, and vestibular stimuli) which are consistent with the increased variability of evoked responses found in the data presented by both Dr. Lifshitz and by Dr. Callaway at this conference. We postulated that this perceptual inconstancy is caused by an inadequate or defective modulation of sensory input, that there is faulty filtering of sensory input. We would therefore expect to find both excessive and deficient inhibition of averaged evoked response amplitudes. We have, in fact, found that the normal phasic inhibition of averaged auditory evoked responses (AER) in children during the eye movement bursts of REM sleep (Ornitz et al., 1967b) does not occur in young autistic children (Ornitz et al., 1968). We measured averaged AERs at the vertex in age-matched groups of normal and autistic children during Stage 2 and REM sleep and during the ocular quiescent and eye movement burst phases of REM sleep.

Amplitudes of wave N_2 of the AER were compared during these different sleep stages. We found that in a group of 16 autistic children under 5 years 1 month old, the relative amplitude of wave N_2 during REM sleep (relative to Stage 2 sleep) was significantly greater than in a group of 16 normal children. In these young

autistic children, the relative amplitude at wave N_2 during the eye movement bursts (relative to ocular quiescence) was greater than that measured in the normal children. In the normal children under 61 months old, there was no appreciable difference between amplitudes of wave N_2 obtained during the ocular quiescent phase of REM sleep and Stage 2 sleep. In contrast, amplitudes of wave N_2 obtained during the eye movement burst phase of REM sleep were significantly smaller than during Stage 2. On the other hand, the autistic children showed significantly larger relative amplitudes of wave N_2 during both the ocular quiescent and the eye movement burst phases of REM sleep (relative to Stage 2 sleep) than did the group of normal children. The relative reduction of response amplitude during the eye movement bursts in normals was markedly overridden in these autistic subjects.

The significance of the decrease of the normal inhibition of the AER associated with eye movement bursts in the autistic children is in the fact that phasic inhibition of sensory responses during REM sleep has been shown to be under vestibular control (Pompeiano and Morrison, 1966; Carli et al., 1967). Clinical observations, e.g., agitation in elevators and during self-induced whirling (Ornitz and Ritvo, 1968), and nystagmography (Colbert et al., 1959; Ritvo et al., in press) suggest the possibility of central vestibular dysfunction in autistic children. A number of the autistic children in this study showed reduced postrotational nystagmus. Therefore, it is possible that the postulated disturbance of phasic inhibition observed in these autistic children may reflect a basic disturbance of vestibular function. This postulated central vestibular dysfunction may be related to a central nervous system dysfunction in adequate regulation of the secondary elaboration of information received over afferent pathways. Such a hypothesis is compatible with the clinical observations that prompted this work. While pathways of direct sensation are probably not disturbed in autistic children, they seem to fluctuate between changing states, wherein sensory input or its significance to the child is either excessively depressed or enhanced (Ornitz and Ritvo, 1968). We are currently seeking other indications that the perceptual inconstancy or variability found in schizophrenia may be related to defective inhibitory mechanisms, possibly involving central vestibular function.

SUPPLEMENT E

An Examination of Evoked Potentials as Indicators of Information Processing in Normal and Schizophrenic Subjects[1]

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THE AVERAGE evoked potential (AEP) appears to bear a relationship to the processing of information by the brain. If it were possible to identify in the evoked potentials to stimuli containing multiple informational elements those characteristics that represented the individual informational elements, it might be possible to obtain insight into the nature of brain information processing and, additionally, to identify processing abnormalities. In schizophrenia, there is commonly an increase of difficulty that occurs with an increase in the density of information input. This may be related to such mechanisms as the gating or filtering out of information, the distortion of individual informational elements, or a disproportionate emphasis on particular informational elements. Our initial efforts along the lines indicated by the foregoing involved expressing the AEP to a "compound" stimulus as a sum of the responses to the contained "simple" stimuli. This approach, which is essentially linear, has been taken for the sake of simplicity although it is recognized that there is evidence,

[1] The author would like to express his indebtedness to Dr. Drossman for his aid and cooperation in mathematical formulations and data collection. We would also like to thank H. Vander Meulen and J. Arnold for their able assistance in the collection of data. Computer calculations were performed by the Computer Sciences Laboratory at the Rockland State Hospital Research Center under the direction of Dr. Laska. This work was presented, in part, at the 1968 annual meeting of the American Psychiatric Association and has been supported, in part, by Grants MH-07292, FR-05561, FR-00268, and MH-14934.

particularly for stimuli within a single sensory modality, that certain nonlinearities exist (i.e., Clynes et al., 1964; Schwartz and Shagass, 1964).

The AEP to a compound stimulus C_i is expressed $F_i(t,C_i)$, where t is time after stimulus presentation; the AEP to simple stimulus S_j is expressed as $f_j(t,S_j)$. The hypothesized relationship between the compound stimulus AEP and a simple stimuli AEP is $F_i(t,C_i = a_o + \Sigma a_j f_j(t,S_j)$; a_j are loading constants, chosen by multiple regression analysis program having the constraint that $a_j > 0$.[2] This constraint is introduced to avoid having the negative of an AEP enter into the summation, an event that would appear to be physiological nonsense. The regression program chooses the a_j coefficients for the minimum mean square difference between the left and right sides of the equation. As a familiar indicator of the success in replicating the compound stimulus AEP by the summation procedure, a correlation coefficient is determined between the synthesized AEP and the actual AEP.

METHODS

For recording, the AEP subjects were seated in an 8 x 10 ft shielded room. Extraneous sounds were masked by the noise of a ventilating fan. The electroencephalogram was registered with silver-silver chloride electrodes spaced 2 cm parasagittally to C_z–P_z over the dominant hemisphere. The recording bandpass was 3 db down at 0.1 Hz and 250 Hz. Stimulus presentation was initiated only when EEG muscle artifact was absent and the subject was attentive. Averaging was performed with a TMC CAT 400, which produced a punched tape digital output for further processing with an IBM 360/30 system. Visual stimuli were produced with a 35-mm slide projector, whose image size was 70 cm x 47 cm. The auditory stimulus consisted of a moderately loud tone with a fundamental frequency of 555 Hz. Stimuli were presented for slightly longer than the 1-second averaging epoch, with a semi-random on and off time. The simple stimuli consisted of a blank red field (S_1), a blank blue field (S_2), a dark grey and white checkerboard pattern (S_3), and a tone burst (S_4). The compound stimuli were a red and blue checkboard pattern (C_1), and the simultaneous presentation of a blank red field and a tone burst (C_2). It is considered that the information contained in the simple stimuli is a subset of the information contained in the compound stimuli. Fifty stimulus presentations were averaged subsequent to the discarding of an initial 10 stimulus presentations. The subjects consisted of 16 male controls with a mean age of 28 years and 16 male, chronic schizophrenic patients (evaluated for correctness of diagnosis) with a mean age of 39 years. The mean

[2] The program for this procedure is structured about a "nonlinear parameter estimation program" by Yonathan Bard, IBM NYC Scientific Center.

length of patient hospitalization was 11.3 years. In 20 subjects, a stimulus was presented sequentially 50 times and in 12 in interleaved groups of ten.

RESULTS AND DISCUSSION

Figure E–1 illustrates the type of data recorded for one of the control subjects. To indicate the order of AEP variability for the repetition of a stimulus, the AEP to a second blue field stimulus (about 1-hour separation) is included. The curves labeled 2SD are two standard deviations from the mean curve as calculated from the means of five groups of 10 presentations each. This is somewhat smaller than one standard deviation calculated from individual sweeps. The curve labeled SYN. RED + TONE is the computer-derived synthesis of the RED + TONE AEP, which in this instance was calculated as follows:

(Synthesized Red + Tone AEP) =
1.14 (Red AEP) + 0.01 (Blue AEP) + 0.21
(Black and White Check AEP) + 0.88 (Tone AEP).

The correlation coefficient between this synthesized AEP and the actually recorded red + tone AEP, over the first 0.5 second, is 0.931.

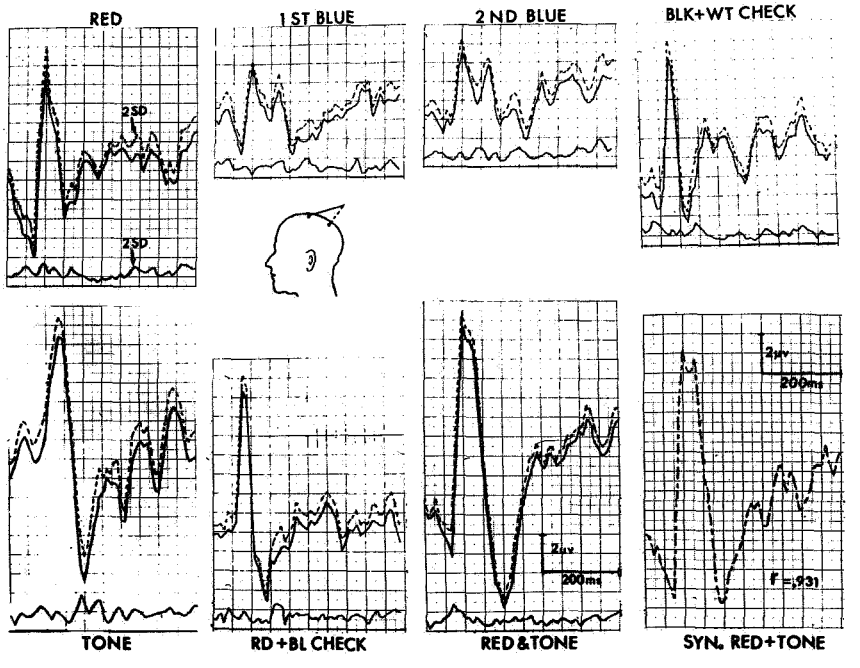

FIGURE E–1

In this instance, four simple stimuli were used in synthesizing the compound stimulus. If we assume the compound stimulus is an unknown combination of any two simple stimuli, we can utilize the a_j loading constants in an identification paradigm. In the illustrated instance, since red and tone contained the two highest loads, we would have succeeded in a correct identification; this would happen by chance only one time in six.

Using the foregoing procedure in the 16 control subjects, we were able to identify correctly the red and tone AEP (C_2) seven times; this is significant at the 0.01 level. In the patient group, correct identification was made for only four subjects—not significantly different than chance. The loading constants used in the synthesis of the red and blue checkerboard AEP (C_1) were not significantly successful in identifying the AEP in either the control or patient groups. This may have been the result of nonlinearities of stimuli interaction in a single sensory modality. The summation approach was also used in an identification paradigm in which the AEP to a second blue stimulus was synthesized from the AEP to the other four simple stimuli. This can be considered to be related to the identification problem faced by the brain when presented with a new stimulus in determining which of a group of previously produced patterns is most similar to the new pattern. It differs from a multiple correlation approach in that amplitude is a significant factor. In this instance, where we would expect a correct identification by chance one time in four, we were able to identify correctly the stimulus in 15 of 16 control subjects; this is a highly significant result, $p<10^{-8}$. Identification was successful for only four patients—not significantly different than chance. These latter results are a dramatic demonstration of what the lower order of correlation presented above (see table I, ch. 7) does to the reliability of identification processes.

The AEPs to the compound stimuli (C_1 and C_2) were also synthesized by a linear addition of the AEPs of only the contained simple stimuli. This gives a more appropriate indication of the applicability to brain function of our (approximately) linear summation model. Tables I and II present the results of the synthesis of the first half-second of the AEP to the red and blue checkerboard pattern (C_1) and the red and tone stimuli (C_2). It may be noted that the correlations of all the waveforms produced by this approach, in the patients and controls, with the actual AEP is at a level of the same order of magnitude as the correlation between two replications of an AEP to the same stimulus. However, it is apparent that our approach is much more applicable to the synthesis of the red and tone AEP since the correlations in this instance are appreciably higher, despite the fact that the synthesis is produced from fewer initial waveforms (the

TABLE I.—*Synthesized AEP to Red-Blue Checkerboard from* S_1, S_2 *and* S_3*; Lead 2 cm; Lateral* C_z–P_z

Parameter	Correlation with C_1		a_j loading constants of S_1, S_2 and S_3						Multivariate t (for a_j)
	Mean r	S.D.* r	Mean a_1	S.D. a_1	Mean a_2	S.D. a_2	Mean a_3	S.D. a_3	
Control N=16	0.787	0.138	0.163	0.233	0.184	0.131	0.487	0.190	N.S.
Patient N=16	0.650	0.294	0.159	0.163	0.118	0.172	0.438	0.288	
Tests of difference	U	F=4.56	t	F	t	F	t	F	N/A
	N.S.	P<0.005	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	

* S.D.=standard deviation.

TABLE II.—*Synthesized AEP to Red-Tone from* S_1 *and* S_4*; Lead 2 cm Lateral* C_z–P_z

Parameter	Correlation with C_2		a_j loading constants of S_1 and S_4				Multivariate t
	Mean r	S.D.* r	Mean a_1	S.D. a_1	Mean a_4	S.D. a_4	
Control N=16	0.834	0.098	0.740	0.416	0.727	0.315	t (2,29)=3.32
Patients N=16	0.713	0.179	0.483	0.382	0.622	0.385	P≐0.05
Tests of difference	U=86	F=3.35	t=2.18	F	t	F	N/A
	P≐0.05	P<0.02	P<0.05	N.S.	N.S.	N.S.	

*S.D.=standard deviation.

greater the number of initial waveforms, the greater the likelihood of a randomly good synthesis). In each instance, the syntheses are more successful for the control than the patient subjects, and in the case of C_2, this is significant at the 0.05 level when the magnitudes of differences between the correlation coefficients are tested by the nonparametric Mann-Whitney U Test. It is interesting to note, in the case of the red and blue checkerboard pattern, that pattern information enters to an appreciably greater extent in the synthesis than does color information. In the synthesis of the AEP to red and tone in the control subjects, approximately equal amounts of red and tone AEP were utilized. However, the schizophrenics appeared to use significantly less of the visual than the auditory components in this synthesis. On a two-tailed t test, the amount of red utilized by the schizophrenics was significantly less than the controls at the 0.05 level, and on a multivariate t test, the combination of red and of tone in the schizophrenics was significantly different from the controls at the 0.05 level.

Possible contaminants of our results include a larger mean patient age. However, if the control and schizophrenic subjects are divided into young and old groups, there do not appear to be any consistent trends. A possible factor involved in the schizophrenic group is the presence of medication. However, five of the schizophrenics had received no medication for 6 months, and the results in this group were not separable from the other schizophrenics. This is consistent with the findings of Callaway and Jones (in press) relating to medication effects on tone-evoked AEPs. There are other indications that phenothiazines can affect the flash-evoked AEP (Heninger and Speck, 1966), but it is not clear whether this is a purely amplitude effect, which would not alter our correlation coefficients. The differences that we find in the schizophrenics would, in part, be explainable by a greater variability in the schizophrenic's AEP, a finding that would be consistent with some of the results of Callaway and Jones (in press). The greater success of the summation procedure when stimulation of two different sensory modalities are utilized is in agreement with earlier findings of Walter (1964b).

SUPPLEMENT F

Dynamics of Vertex Evoked Potentials: The R–M Brain Function

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THIS REPORT is concerned with the dynamics of the vertex evoked potentials. Vertex potentials are reported to be recordable over wide areas, Gastaut et al. (1967), Walter (1964b), Vaughan, and Goff et al. (this volume) and others have reported that vertex evoked potentials are elicited by stimuli from several sensory modalities. Our data suggest that these potentials, especially a peak with a latency of about 200 ms, reflect the activity of a sophisticated dynamic control function with remarkably precise features.

Our prime concern is the ability of the central nervous system to differentiate between states of "sensory rest" and "motion".

THE R–M BRAIN FUNCTION—A GENERALIZED REIN CONTROL FUNCTION

The state of rest of a biologic variable is not simply a point on a continuum between opposite polarities. The recognition of a state of rest itself constitutes a relationship of non-zero character. The principles of unidirectional rate sensitivity and rein-control imply this,[1] and it is in accord with experience (Clynes, 1961, 1967a, 1968, 1969; Clynes and Kohn, 1967; Clynes et al., 1964, 1967). Here we provide evidence that the "nonspecific" vertex evoked potentials function in a manner based on rein control which allows the organism to distinguish between a state of motion and a state of rest of various sensory variables. This response occurs predominantly when a sensory variable

[1] Unidirectional rate sensitivity tends to make zero an end point—not a point intermediate between two polarities. There is no monotonic transition in such a single channel between two polarities.

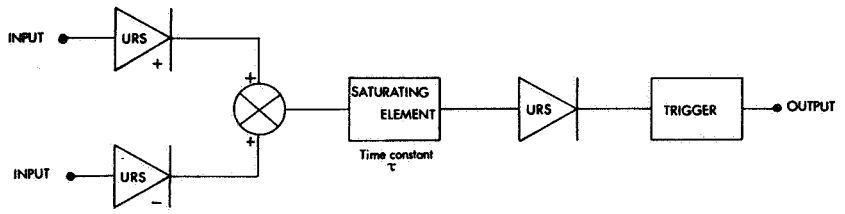

FIGURE F–1—Block diagram for the R–M function. Two URS channels are combined as inputs to a saturating element with time constant. (The saturating element may be in the nature of a self-inhibiting synapse such that the output inhibits the input, preventing any further input increase from being effective.) The output of this synapse or saturating element is a URS channel which triggers the output transient. The two input URS channels might be increase in pitch and decrease in pitch respectively, or other combinations of two variables belonging to the same sense.

leaves the state of rest and enters the state of motion, we will refer to this as the rest-motion (R–M) function. Once in the state of motion, further changes within this state do not generally elicit another R–M reaction.

The R–M function is non-linear and may be represented dynamically by two unidirectional rate sensitive (URS) channels added in a full wave rectification manner (rein control) followed by a low level saturating element (A) [2] which triggers the response through another differentiation and rectification. (Only increasing change in the output of element (A) triggers a response—another unidirectionally rate sensitive dynamic element.) The analog of this is shown in figure F–1. As long as there is a state of motion, the element (A) remains saturated even if the direction of motion changes, and another response is not triggered. A slow initiation of motion also will not trigger the response.

The momentary passing through zero when the direction of motion reverses does not bring element (A) out of saturation; its integrating time constant relates to the refractory period.

The overall system response displays acceleration sensitivity with three essential non-linearities (rectifiers). The system is sensitive to acceleration in both directions, but not if there is an initial velocity, and it displays a refractory period once triggered of 0.3 to 0.5 second (at half amplitude).

EXPERIMENTAL METHOD

Evoked potentials were recorded simultaneously between a vertex electrode and electrodes at left parietal, left occipital, right occipital

[2] A physiologic description of this low level saturating element may be a synapse whose output inhibits the input.

and right parietal locations. The subject sat in a chair in ambient light. The modulating signals were ramps generated by an integrator, using operational amplifiers, or triangular and square wave signals from standard Hewlett-Packard function generators. Sound frequency modulation was carried out using a Hewlett-Packard frequency modulator. For amplitude modulation the signal is introduced as the x input of an electronic multiplier, the modulating signal, as y.

Oscilloscope traces were used for visual stimulation. The unmodulated trace consisted of a circle produced by phase splitting a sinusoidal signal of nominal frequency, say 1000 Hz, so that a steady circle is obtained visually. This circle is then intensity modulated by modulating the intensity of the beam or, it is caused to move concentrically inward or outward by amplitude modulating the 1000-Hz sinusoidal signal through an electronic multiplier. The visual experiments were carried out both in ambient light and in darkness. Experiments with touch are being conducted using a servo mechanism on which a feather or point contact moves according to the electric modulating signal. Responses (usually 100) are averaged on the CAT computer. Experiments were also conducted in supine position and during various phases of sleep.

THE R–M FUNCTION FOR SOUND PITCH

The R–M response may be readily observed using changes of pitch, at a constant loudness. An intensity level of 40 db above threshold is a convenient level. It can be easily shown that the potential arises from the vertex region by taking simultaneous measurements between the vertex and other points, on either side of the head, parietal or occipital, and observing the similarity of the response.

In the following, the basic phenomena are reviewed in the sequence that they were actually discovered.

In the course of experimenting with changes of pitch we noticed that small step changes in the pitch of a continuous tone produced vertex evoked potentials. When the frequency was modulated by a triangular wave form, no vertex potentials were evoked, even though the triangular modulated sound was of siren-like character.

In response to auditory stimuli whose frequency is modulated in a trapezoidal manner the vertex potential appears only at the two corners of the trapezoid, those departing from a straight line—and never at the two corners arriving at the straight lines. The responses were present whenever a slope was initiated, but not where a slope was terminated (fig. F–2). The responses were independent of the polarity of the change. As the horizontal parts of the trapezoid were shortened, making the modulating stimulus gradually triangular, the responses disappeared altogether. (If the horizontal segment of the

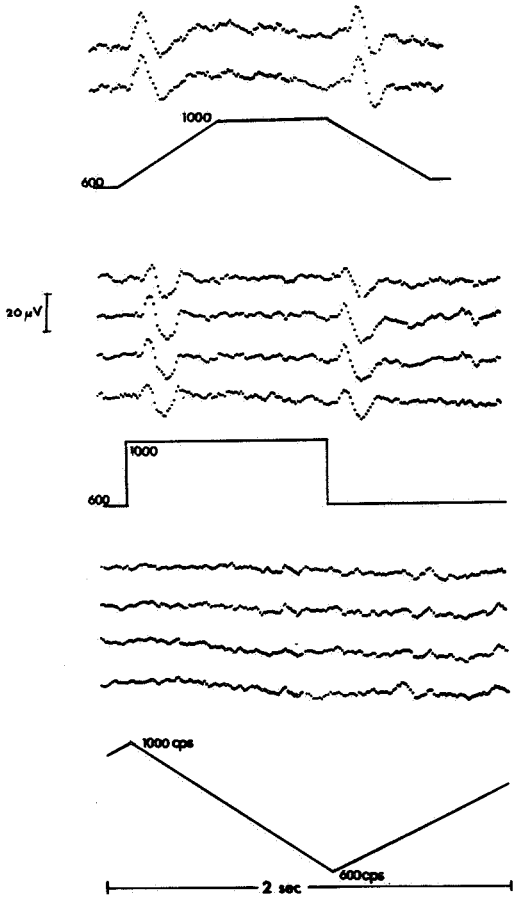

FIGURE F-2.—Changes in pitch of sound of constant amplitude. Note the absence of responses for triangular frequency modulation.

trapezoid is shorter than one second, the response amplitude diminishes. It disappears completely if the horizontal segment is less than 0.3 second; this turns out to be the refractory period for the R–M function.) Thus:

(1) A departure form horizontal produced a response.
(2) A reversal of slope did not produce a response.
(3) A response would not occur for a continuous slope.

In carrying out experiments to confirm these findings, a very surprising result was found. Not only did the response appear and disappear in the expected way, but even a slight departure of horizontal slope of the first leg of the stimulus served to inhibit the response to

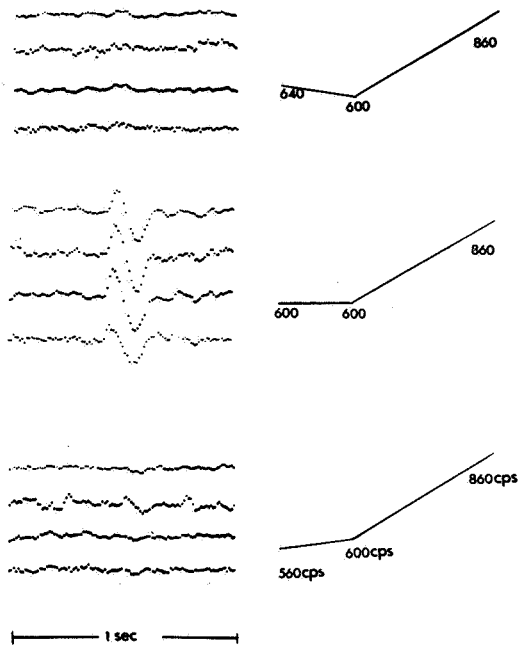

FIGURE F–3.—Inhibition of the R–M response (center) to change in pitch by a previous change in pitch in either direction. The stimulus pattern shown on the right corresponds to the particular group of traces to which it is opposite and is on the same time scale.

the second leg (fig. F–3). This was so for either direction of the slope. It thus appeared that even a slight slide of pitch inhibited the response to a large subsequent pitch change. Further investigation showed that the degree of pitch slide that was effective in producing this inhibition was roughly parallel to the auditory psychological threshold at which the tone was heard as sliding, rather than steady. This corresponds to a pitch change to the order of 2 percent per second. This was sufficient to inhibit the vertex response to pitch changes tens or hundreds of times greater in either direction (fig. F–4).

The effect may be summarized as follows:

(1) A vertex potential is evoked when the pitch of a sound changes from a previous steady state or from rest.

(2) Once a pitch is in a state of motion, this state inhibits further response, i.e., change in the state of motion will not generally evoke another vertex potential (figs. F–5 and F–6).

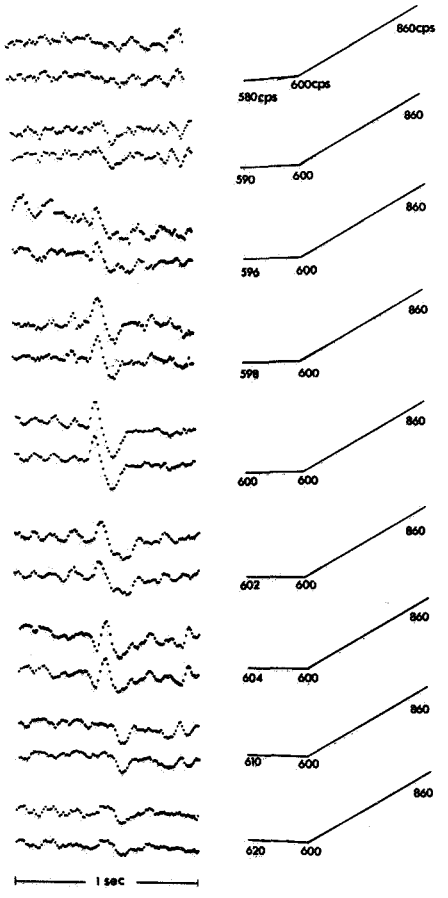

FIGURE F–4.—Gradually increasing inhibition of the R–M response to pitch modulation by previous changes of pitch in either direction. Note the very sharp inhibition produced by small previous changes in pitch.

We have thus called this potential the R–M reaction (rest-motion) to indicate that it is obtained only when the state of the variable is changed from rest to motion. A change from motion to rest does not evoke such a potential. The R–M potential has a refractory period of about 0.3 second. This means that a state of rest has to be maintained for this length of time in order before another R–M potential can be evoked. The R–M potential is comprised of a tri-phasic wave form of a total duration of about 300 msec. It thus takes about 500 msec. before the completion of the R–M reaction.

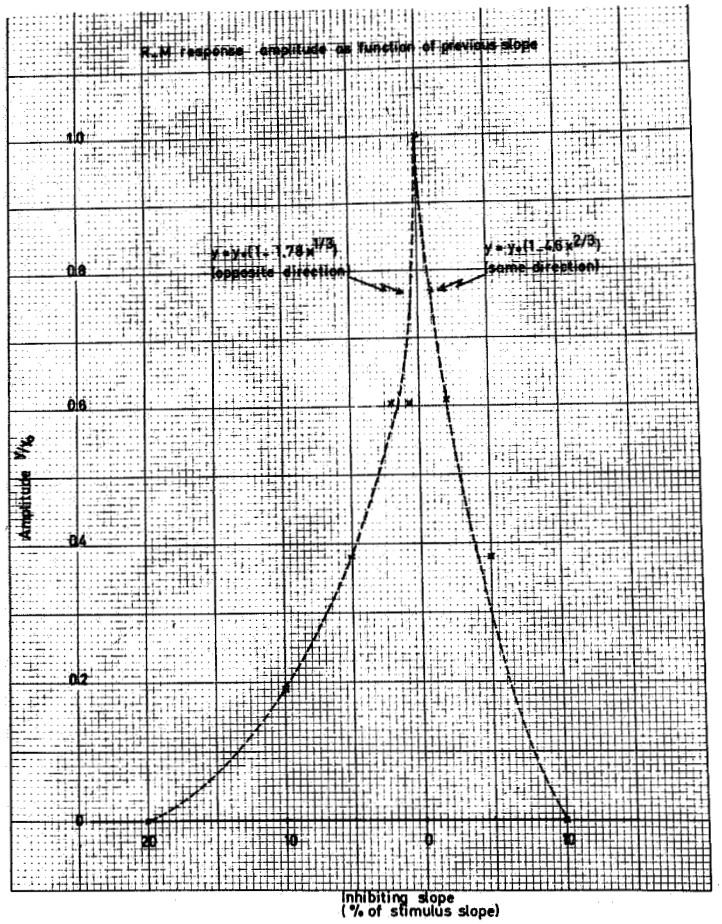

FIGURE F–5.—Mathematical relationships of the inhibition of the R–M response by a previous change in pitch. The effectiveness of positive and negative ramps of various slopes is plotted. The equation relating effective amplitude (Y) to inhibiting slope (X) is a power function as shown. The power function arises probably from the fact that there are two essentially logarithmic processes involved: the effectiveness of increasingly steep inhibiting slope and the amplitude sensitivity of the response.

SOUND AMPLITUDE MODULATION

A dynamic action generally similar to that described above can be observed when another auditory variable—loudness—is modulated. An R–M response is produced by a change of sound amplitude. The reaction is observable from the same brain locations at the vertex. There are, however, some notable and interesting differences related to the different nature of this sensory variable.

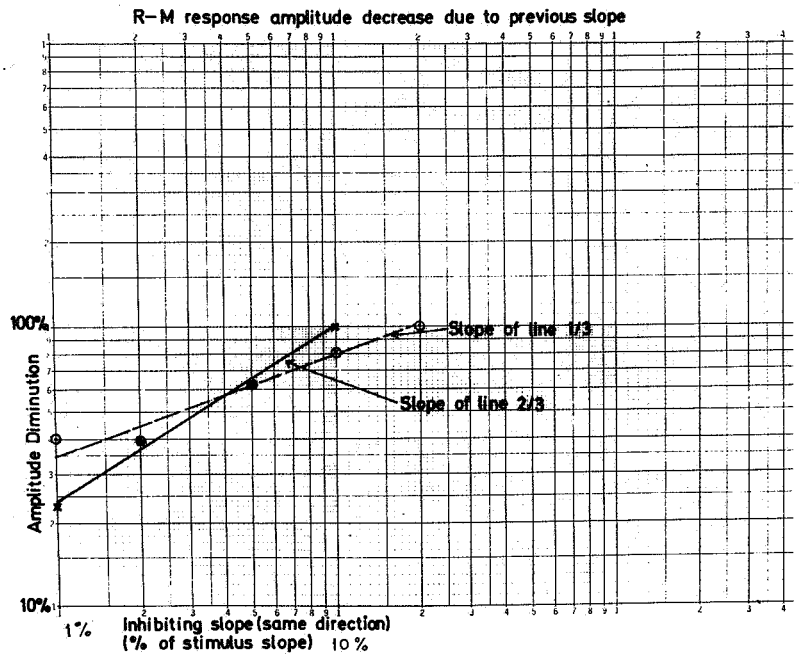

FIGURE F–6.—Quantitative inhibition of R–M response by a previous stimulus slope of the opposite and same direction, respectively, for auditory pitch.

For frequency, incremental changes in either direction are equally effective in producing an R–M reaction. However, for amplitude, there is a considerably greater sensitivity to increases in amplitude than there is to decreases. The response to a trapezoidal amplitude modulation generally shows one R–M reaction, at the beginning of the amplitude increasing slope as compared with two for frequency modulation. (A sharply decreasing slope does initiate a response but the threshold is considerably lower than for an amplitude increasing slope.) (fig. F–7).

It is, of course, surprising that an antecedent decrease in sound amplitude will diminish the response to the increase. One would expect the opposite.[3]

It can even more easily be demonstrated that an increasing ampli-

[3] To exclude the possibility that this effect may in part be due to adaptation to the previous sound level, the comparisons between flat and negative initial slopes were made from such starting points in that the rising slope always exceeded the initial starting point in the same way for the various conditions. In all cases the decreasing slope was of one second duration to avoid the possibility of the influence of the refractory period.

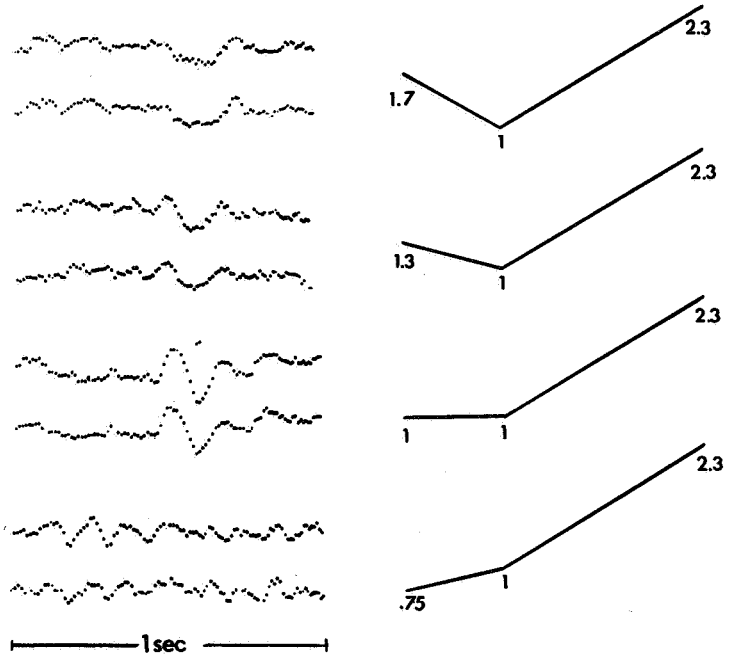

FIGURE F–7.—Inhibition of R–M responses to change in sound amplitude by a previous change in sound amplitude in either direction. Note especially that a decreasing amplitude will inhibit the R–M response to an increasing amplitude (top) in spite of the considerably greater change in slope.

tude in turn inhibits the R–M response to a decreasing sound (when the decrease is rapid enough to provide one).

Again the maximum R–M response is obtained from a condition of previous steady amplitude or "rest". (A special case of this steady state is silence. The R–M reaction evoked from previous silence is not generally different from that evoked from a previous steady tone.)

THE R–M FUNCTION IN THE VISUAL MODALITY

One can translate the dynamic stimuli described above in terms of moving light in a visual field. There are, however, many variables in the visual modality that one has to control. For example, one needs to eliminate eye movement. Eye movements interfere in three ways.

(1) The evoked potentials may be due to eye movements.
(2) The nature of the stimulus changes when the eye follows a movement.
(3) Tracking also has an effect on the electric responses.

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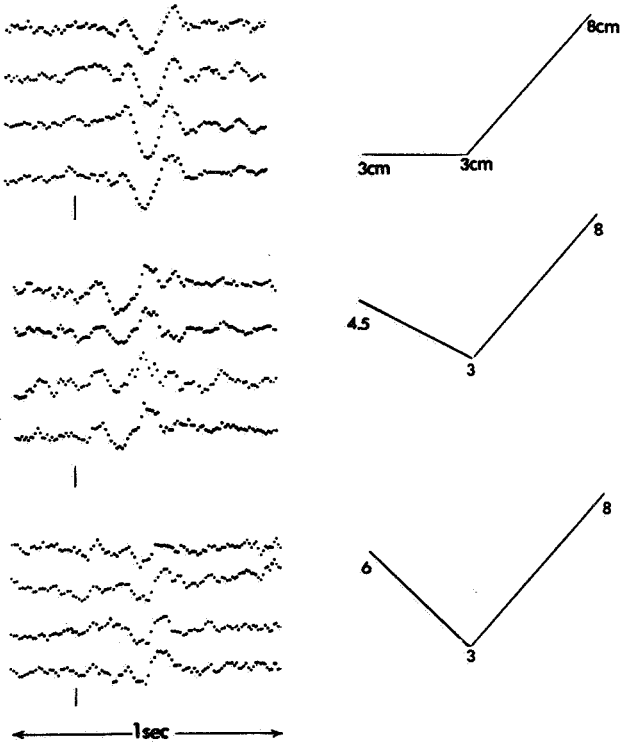

FIGURE F–8.—Inhibition of R–M response to visual movement. Stimulus consists of contracting and expanding circles on an oscilloscope. Bottom group illustrates how the response to an expanding movement from 3 to 8 cm in diameter is inhibited by a previous contracting of the circle. Stimulus slopes drawn on the right correspond to the respective groups to which they are opposite and are on the same time scale.

To eliminate eye movement, the light source is a luminous circle on an oscilloscope whose diameter is changing with the modulation. The eye fixates the center of the circle. The data parallel findings in the auditory sense (fig. F–8).

Similar results may be obtained for light intensity modulation and also for the sense of touch.

It appears probable that the dynamics would be similar for any independent sensory variable.

R–M FUNCTION AS A HIERARCHICAL URS CONSTRUCT

The integral construct of several unidirectional rate sensitive channels as shown in figure F–1 produces a simple, "higher" form of URS

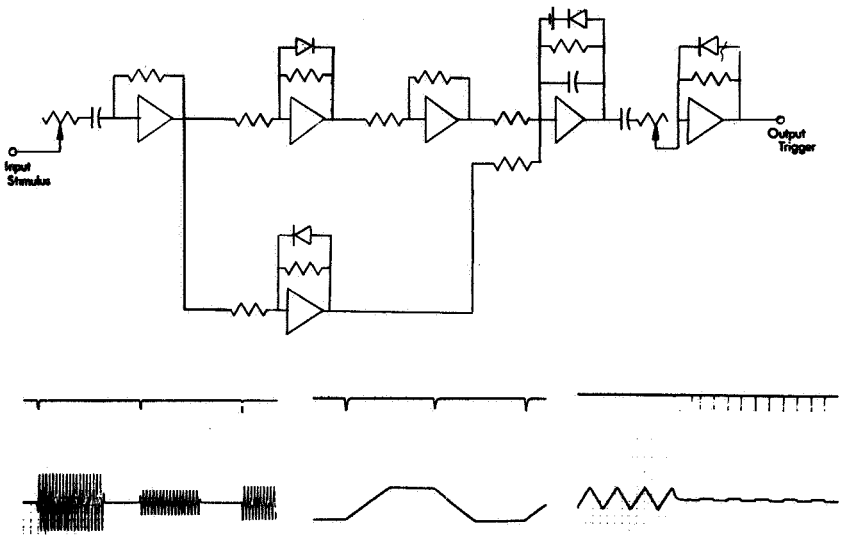

FIGURE F–9.—The inhibition of the R–M response by changes in another sensory variable. Left: R–M response to sound amplitude change is inhibited by an on-going sound frequency modulation (0.5 cycle per sec), sound modulated between 400 and 800 cps. Amplitude change step 15 db from 40 db basic level. (During control response FM modulation was zero—that means a tone of steady frequency was continuously heard in addition to the amplitude change. The masking effect thus was, if anything, greater during the control run than during inhibition.) Right: The R–M response to moving light circles is inhibited by amplitude modulating the same light source at the rate of 2 cycles per sec through the intensity modulation of the oscilloscope beam. (The movement was as clearly visible as before. Also the sound amplitude change was still clearly audible in spite of FM on-going sound modulation.) Center: The R–M response to expanding circles is not inhibited by on-going sound frequency modulation which was effective in inhibiting responses to sound amplitude change. This illustrates that a variable from a different sense does not inhibit the R–M response, but different variables in the same sense do.

behavior: unidirectional rate sensitivity between rest and motion. There is no response going from motion to rest but there is when proceeding from rest to motion, if the change is sufficiently rapid.[4]

The dynamic behavior of the R–M function has been simulated with an analog circuit on our analog computer. The analog displays the dynamic behavior as observed in data illustrated. It does not predict the shape of the response, but predicts under what dynamic stimulus conditions a response occurs, i.e. it predicts its dynamic behavior as a triggered function and the conditions under which it may be triggered (fig. F–9).

[4] It is different from a simple "on response" in that the response is inhibited by previous change in both directions.

The R–M function divides experience into sub-units. Each separate movement of a variable elicits an R–M response if it is separated by sufficient period of rest (0.5 second or more). If there is a continuum of changes, however, without sufficient separation of sensory rest, no R–M responses are produced. Sinusoidal stimulation will produce only one R–M response at the beginning of the first cycle regardless of frequency.

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