

Conditioned taste aversion and motion sickness in cats and squirrel monkeys^{1,2}

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The relationship between vomiting and conditioned taste aversion was studied in intact cats and squirrel monkeys and in cats and squirrel monkeys in which the area postrema was ablated by thermal cautery. In cats conditioned 7-12 months after ablation of the area postrema, three successive treatments with xylazine failed to produce either vomiting or conditioned taste aversion to a novel fluid. Intact cats, however, vomited and formed a conditioned aversion. In squirrel monkeys conditioned 6 months after ablation of the area postrema, three treatments with lithium chloride failed to produce conditioned taste aversion. Intact monkeys did condition with these treatments. Neither intact nor ablated monkeys vomited or evidenced other signs of illness when injected with lithium chloride. When the same ablated cats and monkeys were exposed to a form of motion that produced vomiting prior to surgery, conditioned taste aversion was produced and some animals vomited. These findings confirm other studies indicating motion can produce vomiting in animals with the area postrema destroyed and demonstrate that motion-induced conditioned taste aversion can be produced after ablation of the area postrema. The utility of conditioned taste aversion as a measure of subemetic motion sickness is discussed by examining agreement and disagreement between identifications of motion sickness by conditioned taste aversion and vomiting. It is suggested that a convincing demonstration of the utility of conditioned taste aversion as a measure of nausea requires the identification of physiological correlates of nausea, and caution should be exercised when attempting to interpret conditioned taste aversion as a measure of nausea.

Key words: area postrema, conditioned taste aversion, motion sickness, nausea, emesis.

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On a étudié la relation entre le vomissement et l'aversion gustative conditionnée chez des chats et des singes écureuils intacts et chez des chats et des singes écureuils dont l'area postrema avait été détruite par thermocautérisation. Chez les chats conditionnés 7-12 mois après l'ablation de l'area postrema, trois traitements successifs à la xylazine n'ont pu provoquer de vomissement ni d'aversion conditionnée à un nouveau liquide. Les chats intacts, toutefois, ont eu des vomissements et ont développé une aversion gustative conditionnée. Chez les singes écureuils conditionnés 6 mois après l'ablation de l'area postrema, trois traitements au chlorure de lithium n'ont pu provoquer d'aversion conditionnée. Les singes intacts ont développé un conditionnement avec ces traitements. Ni les singes ayant subi une ablation ni les singes intacts n'ont eu de vomissement ou montré d'autres signes de maladie après avoir reçu une injection de chlorure de lithium. Lorsque les chats et singes ayant subi une ablation ont été exposés, avant l'opération, à une forme de mouvement provoquant le vomissement, une aversion gustative conditionnée a été observée et certains animaux ont eu des vomissements. Ces résultats confirment d'autres études indiquant que le mouvement peut provoquer des vomissements chez les animaux dont l'area postrema a été détruite, et démontrent que l'aversion gustative conditionnée induite par le mouvement peut être produite après l'ablation de l'area postrema. On discute de l'utilité de l'aversion gustative conditionnée en tant que mesure de mal des transports sous-émétique, en examinant les points communs et divergents en ce qui a trait à l'identification du mal des transports par le biais de l'aversion gustative conditionnée et des vomissements. On suggère qu'une solide démonstration de l'utilité de l'aversion gustative conditionnée en tant que mesure de la nausée requiert l'identification de corrélats physiologiques de la nausée. L'aversion gustative conditionnée en tant que mesure de nausée doit être interprétée sous réserve.

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Introduction

The conditioned taste aversion (CTA) procedure was introduced and studied extensively by Garcia (1981) and his col-

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leagues as a unique example of classical conditioning in animals. Although the various toxic treatments used to produce CTA are referred to as unconditioned stimuli (USs), Garcia and Ervin (1968) proposed that malaise or disruption of the "mileau interne" was the stimulus that effectively served as the US to produce conditioning. Thus, they proposed that the internal consequences of toxic treatments ("illness") are associated with recently ingested novel food substances (i.e., with foods ingested contiguously with those internal consequences). In this scheme, the obvious biological utility of CTA is that it protects animals from repeated exposure to toxic foods that threaten survival.

Following Garcia's argument and various forms of empiri-

cal evidence, there has been a persistent acceptance of the concept that illness serves as the proximal US producing CTA. Many nauseogenic drugs and procedures that produce internal malaise also produce CTA. For example, food aversions may be formed in humans during the course of medical regimens, as in chemotherapy (Bernstein 1985) or alcohol aversion therapy (Logue 1985), further supporting the concept that illness serves as the US in the production of CTA.

On the other hand, illness and CTA are not related in a predictable manner in all instances. Treatment with some drugs (e.g., amphetamine, scopolamine) can produce CTA even though the drugs are administered at doses that produce no other signs of sickness (see Ashe and Nachman, 1980, and Gamzu et al., 1985, for reviews of this issue). In addition, certain agents known to be toxic, and known to produce illness, apparently cannot be used to produce CTA (Riley and Tuck 1985). Reconciliation of these inconsistencies between illness and CTA is difficult because the physiological and neural events that underlie illness (e.g., the nausea-emesis syndrome) have not been precisely specified. Furthermore, objective measures of illness are limited. Emesis is generally identified objectively, although exact identification by observation may be difficult in animals (and not all animals have a complete emetic reflex). Nausea, however, typically is identified by self-report, and there are few techniques available for directly assessing its presence or degree. Plasma vasopressin is elevated (Rowe et al. 1979) and tachygastria has been reported during nausea in man (Stern et al. 1985), but these measures are not well documented for animals. Plasma vasopressin is elevated for 3–6 min after vomiting in cats, but its level before vomiting when nausea is expected has not been identified because the precise time of vomiting cannot be anticipated (Fox et al. 1987). We are unaware of documentation of tachygastria associated with vomiting in animals.

Using the rationale that the neural pathways important to nausea/vomiting should mediate CTA if illness is the proximal US for conditioning, two recent articles have investigated the neural mechanisms important to motion-induced CTA in rats. Because the area postrema (AP) is crucial to CTA induced by blood-borne toxins such as lithium chloride (LiCl) (Ritter et al. 1980) and intravenous copper sulfate (Coil and Norgren 1981) in rats, and the AP also serves as a chemoreceptive site of action for emetic effects of several drugs, including xylazine in cats (Borison et al. 1984) and X-irradiation in dogs (Wang et al. 1958) and the squirrel monkey (Brizzee et al. 1955), the possible role of the AP in motion-induced CTA in rats has been investigated. Ossenkopp (1983) reported that motion-induced CTA was enhanced in rats with the AP ablated. Sutton et al. (1988) did not find direct enhancement of CTA in AP-ablated rats but did report slower extinction of motion-induced CTA in rats with the AP ablated. In both studies, destruction of the chemoreceptive function of AP was demonstrated by the ineffectuality of drugs (scopolamine methyl nitrate by Ossenkopp, 1983, and LiCl by Sutton et al., 1988) for producing CTA in these same ablated rats. Thus, both of these studies show that motion-induced CTA in the rat can occur when the AP is destroyed. No objective measures of illness were reported in either study, however, so any possible relationship between illness and CTA could not be assessed directly in these experiments.

Because the relationship between illness and CTA was crucial to our interest in using the CTA paradigm to study motion sickness, we conducted similar experiments using the cat and

squirrel monkey so that vomiting could provide an objective measure of illness. By studying CTA in species with a complete emetic reflex, we hoped to make a more direct investigation of the relationship between illness and CTA. In addition, we ablated the AP in both species to investigate further the role of this structure in motion-induced CTA and vomiting.

General methods

Subjects

Twenty-three adult male squirrel monkeys and 26 adult female cats were selected from the pool of animals used in motion sickness research. All animals were housed either in individual cages or in runs at the Ames Research Center Animal Care Facility on a 14-h light – 10-h dark cycle (monkey) or an 8.5-h light – 15.5-h dark cycle (cat). For 4 h (monkey) or 22 h (cat) prior to each conditioning session, the animals were deprived of food and water.

Surgical procedures

Bilateral ablation of the AP was carried out in 7 adult monkeys and 10 adult cats. Aseptic precautions were employed in all surgical procedures. The trachea was intubated with a plastic tracheal tube (2.5 mm for monkeys and 3.5 mm for cats) and pulmonary ventilation was supported artificially. Halothane inhalation anesthesia was used. The neck was extended and strongly ventroflexed by the use of a head holder to give good access to the foramen magnum. The occipital bone and first cervical vertebra were exposed by lateral retraction of the nuchal muscles. An opening was made in the lower portion of the occipital bone to expose the cerebellar area and lower medulla. A midline sagittal incision was made in the dura mater and cerebellomedullary pia-arachnoid. The cerebellum was then gently displaced upward by means of a small paraffin-coated spatula. The medullary velum was also incised and the floor of the fourth ventricle was exposed to direct vision.

During the AP ablation operation, the operative field was kept dry and free of CSF by continuous aspiration rostral to the operative area. The AP was ablated by free-hand thermocoagulation with the aid of an operating microscope at 6× magnification. The cautery tip, a 42-gauge stainless steel wire loop inserted into a pen-type handle, was energized with three AAA batteries operated by a foot switch to a level below red heat. Because three different neurosurgeons indicated during consultation that the dura heals and closes a surgical opening very rapidly without being sutured, the dura was not sutured following the ablation. Rather, the edges of the sagittally incised pia-arachnoid and dura mater were brought into approximation and the neck muscles were sutured together over the dura, thus holding it in place. The skin was then closed by interrupted sutures with 3-0 silk.

During recovery, animals were treated during the 1st week with analgesics as deemed necessary by the attending veterinarian. For variable periods after surgery, animals showed a sharp decrease in voluntary movement, and initially both cats and monkeys typically refused food. Normal feeding and activity returned after 10–15 days. After recovery, the lesioned animals could not be distinguished from intact animals.

Conditioning was conducted 6 months (monkeys) and 7–12 months (cats) following surgery. These lesioned animals were used in other studies of motion sickness before and after the CTA experiments were conducted.

Histological procedure

Following completion of this and the other experiments, the animals were deeply anesthetized with sodium pentobarbital and perfused transcardially with saline, followed by a solution of Formalin (and acetic acid and methanol for monkeys). Blocks of tissue were stored in Formalin for 2–3 weeks before being prepared for light microscopy. Brainstems were embedded in paraffin and 10- μ m serial coronal sections were cut at the level of the AP. Sections were mounted on microscope slides, stained with hematoxylin and eosin, and evaluated for completeness of AP ablations and for any damage to adjacent structures. Monkeys were perfused 1 year after ablation

of the AP, and cats were perfused 8–12 months after ablation of the AP.

Conditioning procedures

Conditioned taste aversion was studied using a "one-bottle" conditioning paradigm. A 30-min drinking period in which animals had access to a novel fluid (the CS) was immediately followed by the experimental treatment (injection of a drug or exposure to motion) or a control treatment (injection of saline). Conditioning sessions occurred every 3 days.

Conditioning was accomplished in two phases, with different treatments used as the US in the first and second phase. All animals had three conditioning sessions in phase I (days 1, 4, and 7). On day 10, animals being conditioned only in phase I (i.e., conditioned with only one US) had the 30-min drinking period only, while animals being conditioned in both phases were exposed to the second treatment immediately after the drinking period on day 10. For those monkeys conditioned in phase II, two more conditioning sessions occurred (on days 13 and 16) followed by an additional drinking session on a final day (day 19) to assess the effects of the sixth conditioning session. For those cats conditioned in phase II, one more conditioning session occurred (on day 13) followed by a final drinking session (day 16).

Animals were observed continuously for 1 h after injections to determine whether vomiting occurred. In the event vomiting had not occurred within the 1st h after injection, periodic checks of the cage were conducted at intervals of approximately 10 min for evidence of vomitus. Similarly, periodic checks of the cage of each animal were conducted at 10-min intervals for 1 h after motion was terminated. The animals typically appeared relaxed and normal as evidenced by voluntary locomotion by the end of this observation period.

Experiment 1: Monkeys

Method

Yellow, sweet, almond-flavored water (50 g sucrose, 0.2 mL food color, and 1.5 mL almond flavor in 1.0 L of water) was used as the CS. During each conditioning session, the CS was available in standard drinking bottles mounted on the side of a ventilated, clear Plexiglas cage of the same size as the cage used for rotation as described below. Animals were transferred to these cages 10 min before the beginning of the 30-min drinking period to permit acclimation to the test room. The amount of fluid consumed in each drinking period was determined by weighing drinking bottles, and the latencies of retches and vomits during treatments were recorded. Monkeys were observed for 30 min after treatments to determine whether vomiting occurred. No animal vomited during this observation period, and no evidence of vomiting was detected in periodic checks over the following hour.

Monkeys were assigned to four groups defined by the treatments used as USs in conditioning sessions as follows.

Group 1: Conditioned with motion in phase I only ($n = 5$). These animals were individually exposed to counterclockwise rotation about the vertical axis for 30 min at 150°/s in a ventilated, clear Plexiglas cage (52 × 23 × 30 cm) within 5 min after removal of the CS at the end of the drinking period.

Group 2: Conditioned with LiCl in phase I only ($n = 6$). These animals were injected intraperitoneally with 0.3 M LiCl (5 mL/kg) within 5 min after removal of the CS.

Group 3: Conditioned with saline in phase I followed by motion in phase II ($n = 5$). In phase I, animals were injected intraperitoneally with 0.9% NaCl (5 mL/kg) within 5 min after removal of the CS. In phase II (beginning on day 10), the animals were exposed to rotation as described for group 1.

Group 4: AP-lesioned animals conditioned with LiCl in phase I followed by motion in phase II ($n = 7$). In phase I, animals were injected with LiCl as described for group 2

above. In phase II, these animals were exposed to rotation (as described for group 3).

Results

Histology of AP ablations

Sections through the caudal medulla of the AP of an unoperated control (right column) and a lesioned monkey (left column) are shown in Fig. 1 to illustrate the general extent of the lesions. The AP was destroyed in all animals and limited damage occurred to peripostremal structures with varying amounts of damage occurring in different animals. The tractus solitarius was intact in all animals.

Phase I conditioning

All of the rotated monkeys vomited during each of the conditioning sessions, but no monkey vomited after injection with LiCl or NaCl. For the rotated monkeys, the latencies to vomiting ranged from 1 to 8 min. The average consumption of the CS for the four groups of monkeys is shown in Fig. 2. In the first conditioning session, the CS was consumed before exposure to the US; thus, consumption of the CS in this period serves as a baseline for intake before any conditioning occurred.

Overall, analyses of effects of the treatment variables on consumption of the CS were assessed by computing a 4 (groups) × 4 (sessions) mixed unweighted means analysis of variance (ANOVA) with repeated measures on the sessions variable. There was no reliable effect for groups ($F(3,19) = 1.49, p > 0.25$), but there were reliable effects for sessions ($F(3,57) = 20.98, p < 0.001$) and for the interaction of sessions with groups ($F(9,57) = 5.57, p < 0.001$).

The simple effects of the groups × sessions interaction were computed to analyze these effects further. The simple effects of groups in the first session reflected there was no reliable difference in fluid consumption by the four groups prior to conditioning ($F(3,19) = 2.29, p > 0.11$). The simple effects for each group across the four sessions were computed to clarify interpretation of the sessions × groups interaction. Consumption decreased dramatically for intact animals rotated ($p < 0.001$) or injected with LiCl ($p < 0.001$) reflecting the formation of CTA. However, there was no change in consumption across conditioning sessions for intact animals injected with saline ($p > 0.78$) or AP-lesioned animals injected with LiCl ($p > 0.61$).

These findings indicate that LiCl is an effective US for producing CTA in the squirrel monkey as it is in numerous other species. However, CTA was formed even though no monkey vomited after treatment with this US, confirming that emesis is not necessary for the production of CTA in the monkey. The failure to produce CTA with LiCl in monkeys with AP ablated implies that the AP serves as a chemoreceptive site of action for systemically injected LiCl in the squirrel monkey as it does in rats (Rabin et al. 1983; Ritter et al. 1980; Sutton et al. 1988).

Phase II conditioning

Intact animals injected with saline and AP-lesioned animals injected with LiCl in phase I were both conditioned with motion serving as the US in phase II. Neither of these groups of animals formed CTA in phase I. Of the five intact monkeys previously injected with saline, all but one (which failed to vomit during any of these tests) vomited during each exposure to rotation (latencies to vomit ranged from 4 to 22 min). Three of the seven AP-lesioned monkeys never vomited during con-

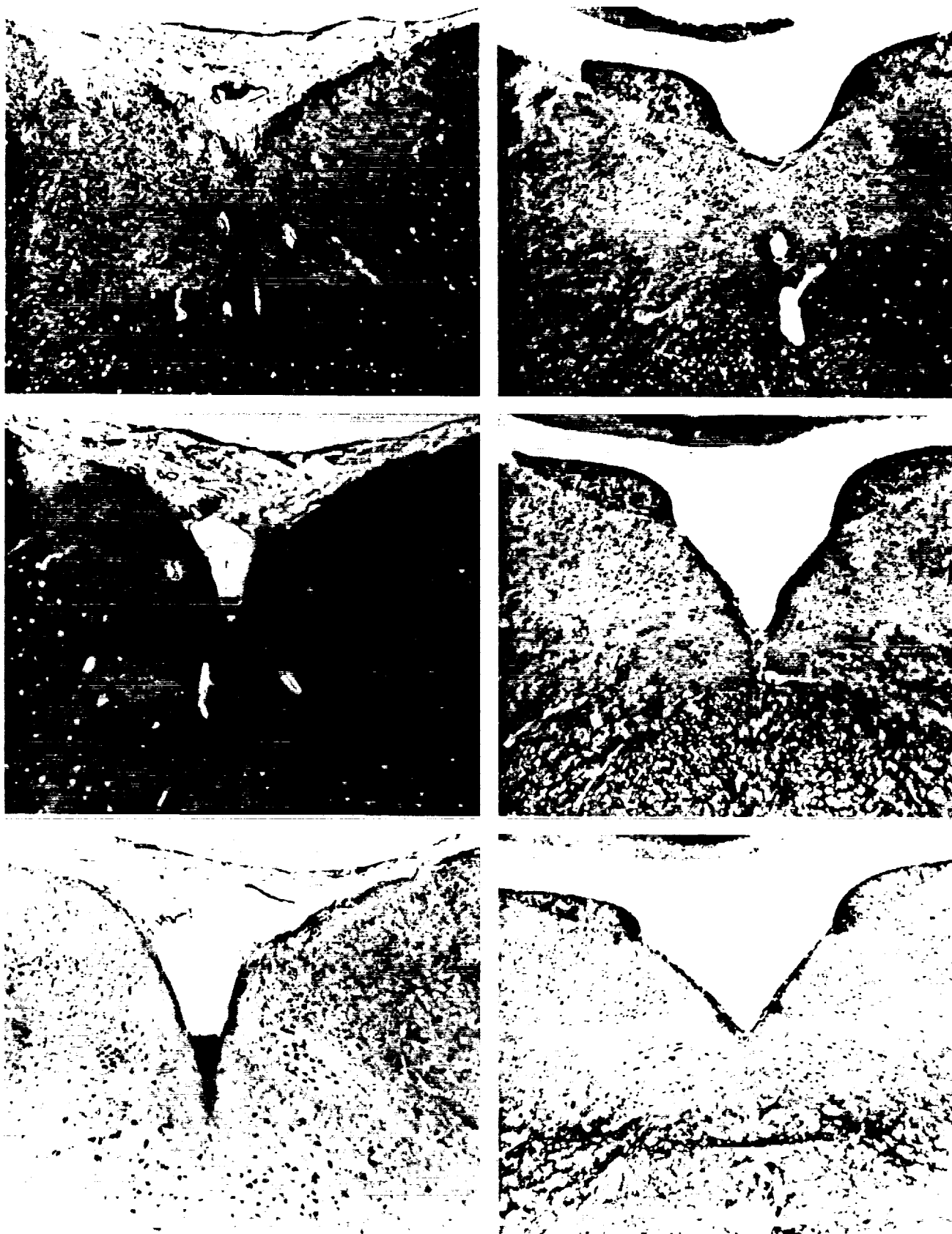


FIG. 1. Sections at three levels of the caudal medulla of squirrel monkeys. Photographs in the right column are for an unoperated control monkey, while those in the left column illustrate the extent of damage in a lesioned monkey.

PHASE I : MONKEYS

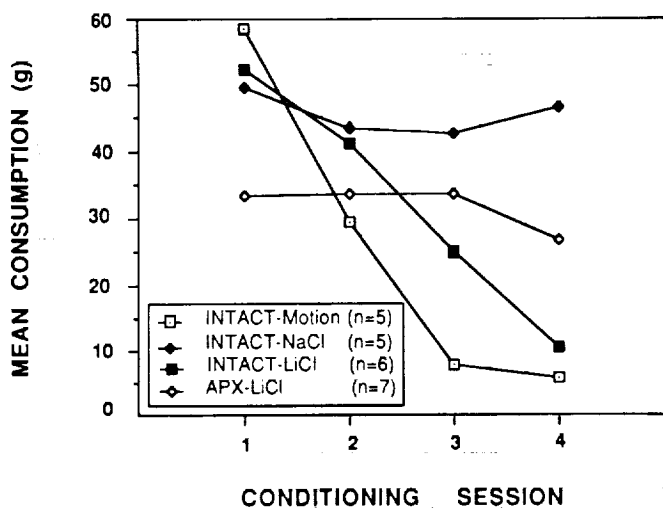


FIG. 2. Average consumption of flavored fluid (CS) by the four groups of monkeys during the first phase of conditioning. Consumption of fluid in conditioning session 1 serves as a baseline measure because fluid was consumed prior to the first treatment with the US. The formation of CTA in intact animals conditioned either with motion or with LiCl is reflected in the progressive decrease in fluid intake in sessions 2 through 4.

ditioning sessions with rotation as the US, and three vomited during at least two of the conditioning sessions (latencies ranged from 6 to 30 min).

The effects of conditioning with motion in phase II are shown in Fig. 3. The consumption reported for session 4 is the same data shown for session 4 in Fig. 2. These data comprise the appropriate comparison to evaluate conditioning with motion (reflected in sessions 5, 6, and 7) because they reflect the average consumption immediately before motion was used as the US.

Overall analyses of effects of motion on consumption of the CS were assessed by computing a 2 (groups) \times 4 (sessions) mixed ANOVA with repeated measures on the sessions variable. This analysis revealed a reliable effect for sessions ($F(3,30) = 3.05, p < 0.05$) indicating CTA was formed, but there was no difference between the two groups ($F(1,10) = 1.26, p > 0.29$) nor was there a reliable groups \times sessions interaction ($F < 1$). Thus, although motion serves as an effective US for conditioning in phase II, the magnitude and rate of formation of the aversion are less than seen with the intact animals in phase I. This apparent reduction in the effectiveness in producing conditioning may be due to repeated exposure to the CS in phase I (Braveman 1975; McLaurin et al. 1963).

These same AP-ablated animals, as a group, failed to form CTA in phase I when LiCl was used as the US indicating the chemoreceptive function of the AP was eliminated by the ablations. Because animals with AP ablated apparently form motion-induced CTA in a manner similar to intact animals, it is implied that the AP plays no crucial role in the formation of motion-induced CTA in the squirrel monkey.

Experiment 2: Cats

Method

Chocolate-flavored milk was used as the CS. During each

PHASE II : MONKEYS

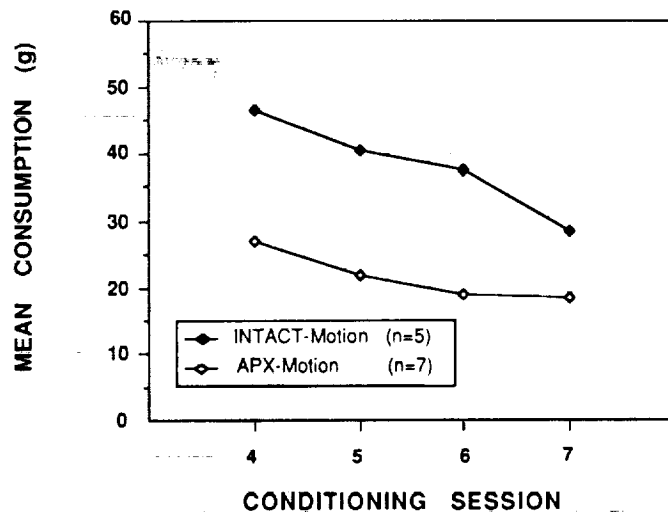


FIG. 3. Average consumption of flavored fluid (CS) by the two groups of monkeys transferred to the second phase of conditioning. Consumption of fluid in conditioning session 4 is reproduced from Fig. 2 and serves as a reference measure for conditioning with motion as the US in phase II. The formation of CTA in intact and lesioned animals conditioned with motion is reflected in the progressive decrease in fluid intake in sessions 5 through 7.

conditioning session, approximately 100 mL of the CS was available in Petri dishes placed on the floor of a ventilated, clear Plexiglas cage (52 \times 23 \times 30 cm). Animals were transferred to these cages 10 min before the beginning of the 30-min drinking period to permit acclimation to the test room. The amount of fluid consumed in each drinking period was determined by weighing the Petri dishes, and latencies to retches and vomits were noted.

Cats were assigned to three groups defined by the treatments used as USs in conditioning sessions as follows.

Group 1: Conditioned with xylazine in phase I only ($n = 8$). These animals were injected subcutaneously (s.c.) with 0.66 mg/kg xylazine within 5 min after removal of the CS.

Group 2: Conditioned with saline in phase I followed by xylazine in phase II ($n = 8$). In phase I, the animals were injected subcutaneously with saline (volume equivalent to that for xylazine as in group 1). In phase II (on days 10 and 13) they were injected with 0.66 mg/kg xylazine s.c. as described for group 1 in phase I.

Group 3: AP-lesioned animals conditioned with xylazine in phase I and with motion in phase II ($n = 10$ and $n = 8$, respectively). In phase I, lesioned cats were injected with 0.66 mg/kg xylazine s.c. In phase II (days 10 and 13), eight of the animals (those that did not condition in phase I) were placed in a ventilated Plexiglas cage (50 \times 18 \times 21 cm) and exposed to sinusoidal vertical linear acceleration (0.6 Hz with either a 30.5 or 61.0 cm excursion) for 60 or 5 min after the first retch/vomit occurred.

Cats were observed continuously for 1 h after injection with xylazine to determine whether vomiting occurred. In the event vomiting had not occurred within the 1st h after injection, periodic checks of the cage were conducted at intervals of approximately 10 min for evidence of vomitus. Similarly, periodic checks of the cage of each animal were made after

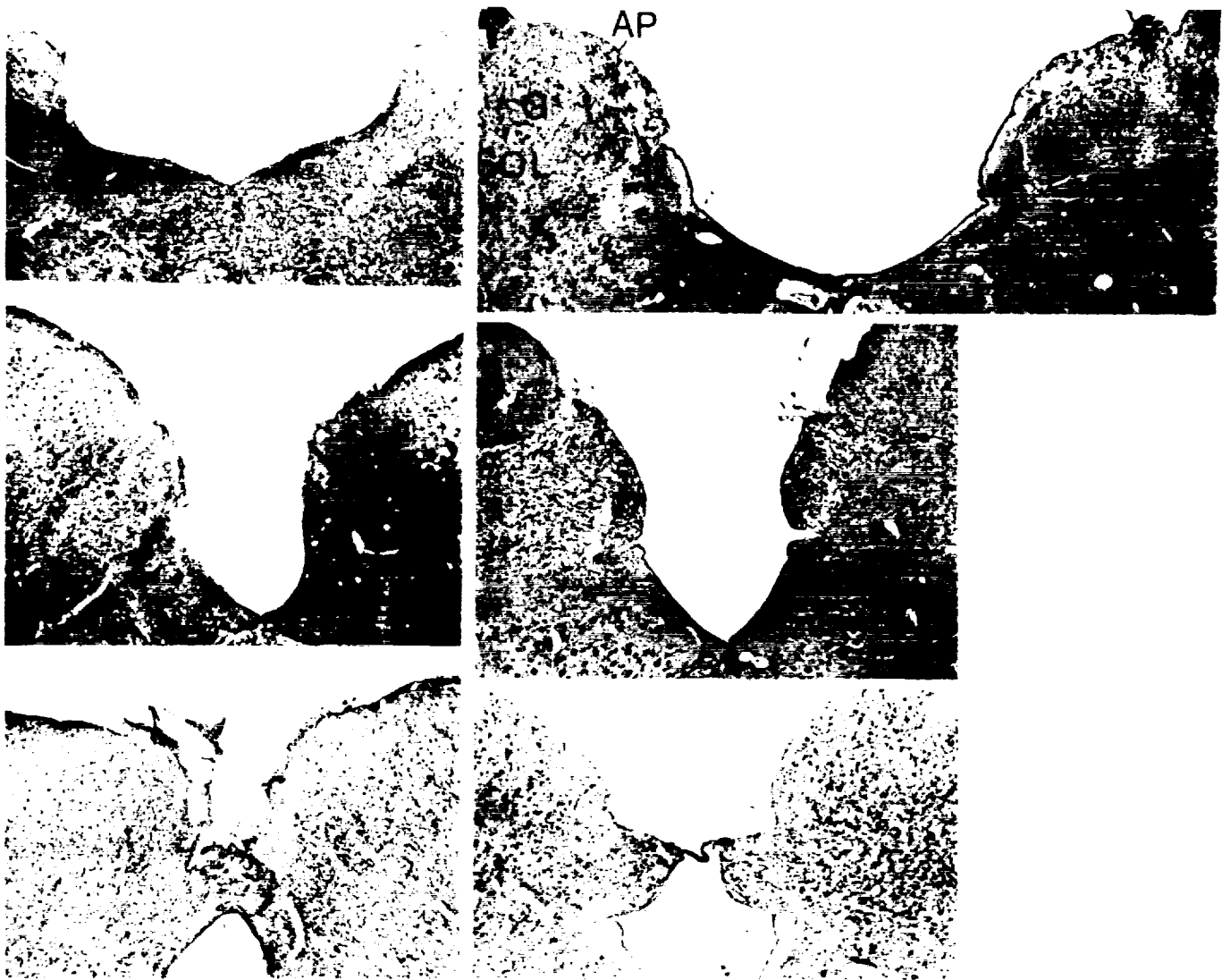


FIG. 4. Sections at three levels of the caudal medulla of cats. Photographs in the right column are for an unoperated control cat, while those in the left column illustrate the extent of damage in a lesioned animal.

motion was terminated. The animals typically appeared relaxed and normal as evidenced by voluntary locomotion by the end of the observation period.

Results

Histology of AP ablations

Sections through the caudal medulla of the AP of an unoperated control (right column) and a lesioned cat (left column) are shown in Fig. 4. As with the monkeys, the AP was destroyed in all animals and varying limited damage occurred to peripostremal structures in some animals. The tractus solitarius was intact in all animals.

Phase I conditioning

Each of the intact cats injected with xylazine vomited in at least one of the conditioning sessions. One cat vomited in one test, three vomited in two sessions, and four vomited in all sessions (latencies to first vomit ranged from 4 to 9 min). None of the AP-lesioned cats vomited when injected with xylazine, and none of the intact cats injected with saline vomited.

The average consumption of chocolate milk by the three groups of cats is shown in Fig. 5. Overall, analyses of effects

were assessed by computing a 3 (groups) \times 4 (sessions) mixed unweighted means ANOVA with repeated measures on the sessions variable. Reliable effects were indicated for groups ($F(2,22) = 8.42, p < 0.001$), sessions ($F(3,66) = 4.03, p < 0.01$), and the interaction of groups \times sessions ($F(6,66) = 10.12, p < 0.001$). Analysis of the simple effects of groups in session 1 reflected there was no reliable difference in the consumption of the CS prior to conditioning ($F(2,22) = 1.52, p > 0.24$).

Further analysis of the groups \times sessions interaction was conducted by computing the simple effects of sessions for each of the groups. Consumption of the CS decreased across conditioning sessions for intact cats when xylazine was the US ($p < 0.001$). However, there was no change in consumption of the US across sessions when xylazine was the US for lesioned cats ($p > 0.58$) or when intact cats were injected with NaCl ($p > 0.12$). Thus, the groups \times sessions interaction results from the failure of conditioning in intact animals injected with saline and AP-lesioned animals injected with xylazine, contrasted with the dramatic conditioning in intact animals injected with xylazine.

PHASE I : CATS

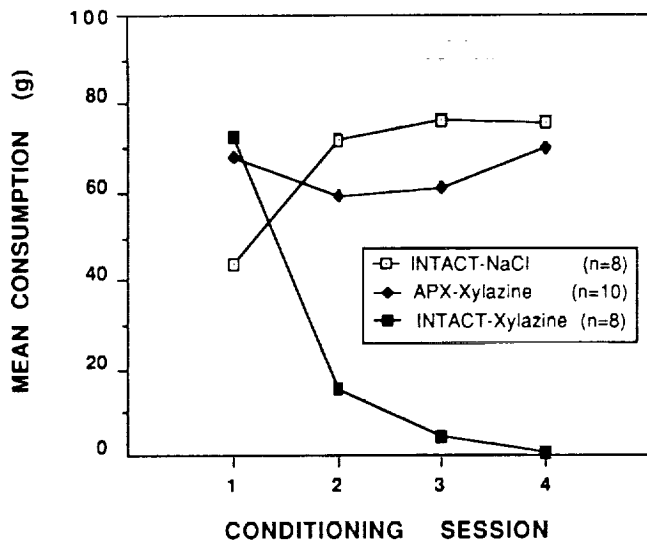


FIG. 5. Average consumption of chocolate milk (CS) by the three groups of cats during the first phase of conditioning. Consumption of fluid in conditioning session 1 serves as a baseline measure because milk was consumed prior to the first treatment with the US. The formation of CTA in intact animals conditioned with xylazine is reflected in the progressive decrease in the intake of milk in sessions 2 through 4.

Phase II conditioning

All of the intact animals injected with saline in phase I (none vomited) and the eight AP-lesioned animals that did not form aversions when injected with xylazine in phase I were conditioned in phase II. Intact animals were injected with xylazine in phase II and lesioned animals were exposed to motion. Seven of the eight intact cats vomited on both conditioning sessions when injected with xylazine, while the remaining cat vomited only following the first injection with xylazine (vomit latencies ranged from 2 to 9 min). Of the eight cats with AP lesions, four failed to vomit during either of the tests when exposed to motion, three vomited during one of the two tests, and one cat vomited during both tests (latencies ranged between 3 and 4 min).

The effects of conditioning with these USs are shown in Fig. 6. The consumption reported for the intact animals in session 4 in this figure are the same data shown for this day in Fig. 5. The data shown in session 4 for lesioned animals report the average for the 8 cats transferred to phase II rather than the 10 cats conditioned in phase I.

A 2 (groups) \times 3 (sessions) mixed ANOVA with repeated measures on the sessions variable was used for an overall analysis. Reliable effects were reflected for sessions ($F(2,28) = 21.87, p < 0.001$), indicating aversion was produced, and for groups ($F(1,14) = 8.75, p < 0.01$), indicating stronger aversion in cats injected with xylazine. The interaction of groups \times sessions was not reliable ($F(2,28) = 2.42, p > 0.11$). The simple effects of sessions were computed to analyze the main effect for groups further. There was no difference in the consumption of the groups on day 4 ($p > 0.35$), but consumption by intact cats injected with xylazine was less than consumption by lesioned cats rotated on both day 5 ($p < 0.02$) and day 6

PHASE II: CATS

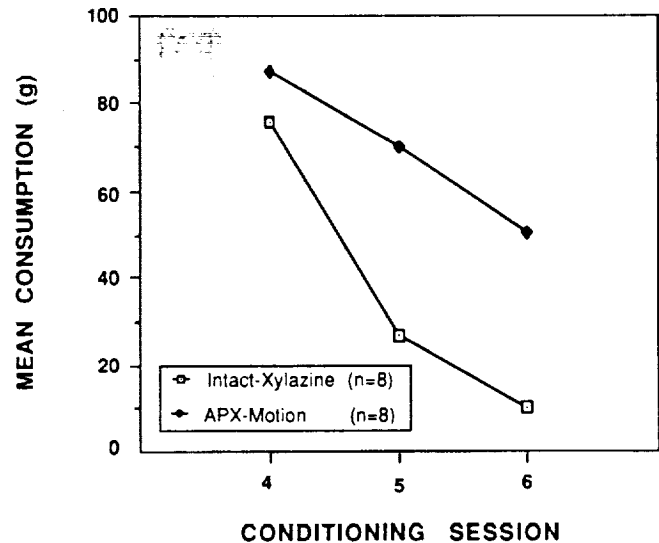


FIG. 6. Average consumption of chocolate milk (CS) by the two groups of cats transferred to the second phase of conditioning. Consumption of milk in conditioning session 4 is reproduced from Fig. 5 and serves as a reference measure for conditioning with the two USs in phase II. The formation of CTA in intact and lesioned animals is reflected in the progressive decrease in fluid intake in sessions 5 through 7.

($p < 0.007$). Thus, the stronger aversion for the cats injected with xylazine was present on the first conditioning trial.

Little difference is apparent in the magnitude of xylazine-induced aversions in intact animals conditioned in phases I and II. Thus, no CS preconditioning exposure effect occurred when multiple injections of xylazine served as the US for cats. No appropriate control group was included to evaluate a potential CS preconditioning exposure effect when motion was used as the US with cats. It is apparent, however, that elimination of the chemoreceptive function of the AP in cats as evidenced by failure of xylazine to produce CTA in phase I did not prevent the production of motion-induced CTA. Thus, as in squirrel monkeys, integrity of the AP is not necessary for the production of either vomiting or CTA in cats.

Discussion

The results of this study confirm a chemoreceptive function of AP for xylazine-induced vomiting in cats (Colby et al. 1981). In addition, a chemoreceptive function for the AP in the production of pharmacologically induced CTA is indicated for both monkeys and cats. After ablation of the AP, xylazine was not an effective US for inducing CTA in 8 of the 10 cats tested. The occurrence of CTA in two of the AP-ablated cats indicates a disassociation of CTA from vomiting, because neither of these cats vomited in response to the xylazine injections, which served as the US to produce CTA. In squirrel monkeys, CTA was not produced by injections of LiCl after the AP was destroyed. Thus, the well-documented role of AP in lithium-induced CTA in the rat (Rabin et al. 1983; Ritter et al. 1980; Sutton et al. 1988) is extended to the squirrel monkey.

TABLE 1. Possible outcomes when two criterion measures of illness are compared. In this example, criterion measure 1 is vomiting and criterion measure 2 is conditioned taste aversion (CTA). "Decision" labels in the table indicate the validity of measurement based on criterion measure 2 alone

Criterion measure 1 (vomiting)	Criterion measure 2 (CTA)	
	Present (+)	Absent (-)
Present (+)	Both measures + Decision: correct detection ("hit")	Measure 1 + Measure 2 - Decision: false rejection ("miss")
Absent (-)	Measure 1 - Measure 2 + Decision: false detection ("false alarm")	Both measures - Decision: correct rejection

Motion-induced vomiting was produced in both squirrel monkeys and cats after ablation of the AP confirming previous reports by Wilpizeski et al. (1986) for the squirrel monkey and Borison and Borison (1986) for the cat. The production of motion-induced CTA in AP-ablated cats and squirrel monkeys shown not to condition with pharmacological agents functioning via the AP demonstrates that this form of CTA can occur in the absence of the chemoreceptive function of the AP. Thus, it appears that neither vomiting nor CTA induced by motion depend on a humoral factor operating via a system requiring an intact AP (Crampton and Daunton 1983; Contrucci and Wilpizeski 1985).

Because CTA and vomiting can be elicited in cats and squirrel monkeys following elimination of the chemoreceptive function of AP for pharmacological agents, it appears that motion-induced vomiting and CTA can occur independently of the chemoreceptive function of the AP. Both responses can be produced by two (or more) systems, but it is not clear from our present knowledge whether they are produced by the same system. It has been suggested from a review of pharmacological studies that vomiting may be a sufficient but not a necessary condition for the production of CTA (Gamzu et al. 1985). However, it has been shown that CTA may not occur in some squirrel monkeys when rotation is terminated immediately after vomiting occurs (Wilpizeski and Lowry 1987; Wilpizeski et al. 1987, Figure 4B). Thus, vomiting is not a sufficient condition for the development of CTA in the squirrel monkey.

Disassociation of vomiting from CTA has been interpreted to indicate that nausea is the putative US producing CTA. Roy and Brizzee (1979) proposed using CTA to assess subemetic symptoms of motion sickness in the squirrel monkey. Wilpizeski and Lowry (1987) proposed that nausea and vomiting are independent processes, and they developed a two-factor theory of motion sickness in squirrel monkeys where CTA is used to assess the presence of nausea. They assume that (i) nausea produces CTA and (ii) vomiting is not a sufficient condition for producing CTA. If nausea and vomiting are independent, then animals can theoretically be categorized into one of the following four possible combinations: (i) nauseous and vomiting, (ii) nauseous without vomiting, (iii) vomiting without nausea, and (iv) not nauseous and not vomiting.

Riley and Tuck (1985) have addressed the interpretation of studies using CTA to assess drug toxicity by using the signal detection framework. To do this, individual instances of the presence or absence of illness assessed by two independent

measures (i.e., CTA and vomiting) are categorized into a 2 × 2 contingency table (see Table 1). When results of these measures agree, each case is scored as either a "hit" (correct identification) or a "correct rejection." When results of these measures disagree, each case is scored as either a "false alarm" (false detection) or a "miss" (false rejection).

According to this contingency table analysis, the possible combinations of nausea and vomiting are categorized as hit (nauseous and vomiting), false alarm (nauseous without vomiting), miss (vomiting without nausea), and correct rejection (not nauseous and not vomiting).

To apply this analysis to these data, animals were categorized based on their CTA/vomiting responses. Contingency table percentages were computed on data from these experiments using all of the AP-lesioned animals. CTA was scored as having been produced when consumption of fluid on the test day was <75% of consumption on the initial (baseline) day. Percentages of animals in a category were computed for the first and last conditioning sessions to evaluate whether the ratio of animals in each category changed as more conditioning sessions were used. Percentages computed from combined data in phases I and II ($n = 32$) are shown in Table 2. The increase in hit rate and decrease in miss rate from the first to the last conditioning test reflects the greater agreement of the two measures for predicting motion sickness as more conditioning tests are used. If nausea is estimated as the percentage of animals in the false alarm and hit categories, it increases from 34 to 50% by the final assessment. Notice, however, that the percentage of cases reflected by false alarms (animals assumed to be nauseated only) is invariant.

Percentages based on data for phase I and phase II separately are shown in Table 3. Hits and misses could not occur in the analysis for phase I because no animal vomited when injected with drugs. Some animals vomited in phase II when exposed to motion, so all possibilities can occur when phase II data are categorized. The false alarm rate is again invariant from the first to the last conditioning test in data for both phases. However, when the US elicited vomiting on some tests in phase II, the miss rate decreased from the first to the last conditioning test accompanied by an increase in the hit rate, again indicating improved agreement between the measures.

Interpretation of the sum of hits and false alarms as an accurate measure of nausea is based on the assumption that nausea is reliably and accurately reflected by CTA. This may be so, but skepticism has been proposed (Gamzu et al. 1985),

TABLE 2. Percentages of animals in the four possible categories defined by agreements and disagreements when the results of CTA and vomiting are used to identify motion sickness. Percentages computed on combined data ($n = 32$) from the two conditioning phases

Category	Conditioning test	
	First	Last
Miss	23	3
False alarm	27	27
Correct rejection	43	47
Hit	7	23

TABLE 3. Percentages of animals in the four possible categories defined by agreements and disagreements when the results of CTA and vomiting are used to identify motion sickness. Percentages for the two conditioning phases are computed separately

Category	Conditioning test	
	First	Last
Phase I ($n = 17$)		
Miss	0	0
False alarm	35	35
Correct rejection	65	65
Hit	0	0
Phase II ($n = 15$)		
Miss	47	7
False alarm	20	20
Correct rejection	20	27
Hit	13	47

and it remains to be tested directly. The apparently invariate rate of false alarms may indicate one way to perform such a test. If animals that are nauseous only are in fact identified as cases of false alarms, then those animals would form an appropriate subgroup for testing the correlation of CTA with an independent measure of nausea. No reliable measure of nausea for conducting such an analysis has been demonstrated. Tachygastria may be one candidate for such an analysis. Because tachygastria appears to precede nausea in humans, a perfect correlation between the production of motion-induced CTA in animals identified as nauseous (i.e., false alarm cases) and tachygastria in those same animals would imply nausea is the putative US for CTA. Another possible measure is the disruption of electrical control activity cycling associated with retrograde contractions of the gut, which has been shown to be associated with vomiting in dogs (Lang et al. 1986). If either of these measures should prove to be appropriate, however, it may prove to be more useful than CTA for assessing nausea.

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