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Distinct pattern of oculomotor impairment associated with acute sleep loss and circadian misalignment

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Key points

- Inadequate sleep and irregular work schedules have not only adverse consequences for individual health and well-being, but also enormous economic and safety implications for society as a whole.
- This study demonstrates that visual motion processing and coordinated eye movements are significantly impaired when performed after sleep loss and during the biological night, and thus may be contributing to human error and accidents.
- Because affected individuals are often unaware of their sensorimotor and cognitive deficits, there is a critical need for non-invasive, objective indicators of mild, yet potentially unsafe, impairment due to disrupted sleep or biological rhythms.
- Our findings show that a set of eye-movement measures can be used to provide sensitive and reliable indicators of such mild neural impairments.

Abstract Sleep loss and circadian misalignment have long been known to impair human cognitive and motor performance with significant societal and health consequences. It is well known that human reaction time to a visual cue is impaired following sleep loss and circadian misalignment, but it has remained unclear how more complex visuomotor control behaviour is altered under these conditions. In this study, we measured 14 parameters of the voluntary ocular tracking response of 12 human participants (six females) to systematically examine the effects of sleep loss and circadian misalignment using a constant routine 24-h acute sleep-deprivation paradigm. The combination of state-of-the-art oculometric and sleep-research methodologies allowed us to document, for the first time, large changes in many components of pursuit, saccades and visual motion processing as a function of time awake and circadian phase. Further, we observed a pattern of impairment across our set of oculometric measures that is qualitatively different from that observed previously with other mild neural impairments. We conclude that dynamic

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vision and visuomotor control exhibit a distinct pattern of impairment linked with time awake and circadian phase. Therefore, a sufficiently broad set of oculometric measures could provide a sensitive and specific behavioural biomarker of acute sleep loss and circadian misalignment. We foresee potential applications of such oculometric biomarkers assisting in the assessment of readiness-to-perform higher risk tasks and in the characterization of sub-clinical neural impairment in the face of a multiplicity of potential risk factors, including disrupted sleep and circadian rhythms.

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Introduction

Neuro-functional impairment associated with sleep loss and circadian misalignment (SLCM) is a major cause of motor vehicle crashes (Lee *et al.* 2016), industrial accidents (Akerstedt and Wright, 2009) and catastrophic events, such as the Chernobyl disaster (Mitler *et al.* 1988). Although such accidents are attributed to SLCM, the exact nature of the impairment leading to bad outcomes has been difficult to characterize, because of the complex coordination of perceptual, cognitive and motor resources that is generally required to perform many tasks. Prior research has demonstrated that sustained attention fluctuates with SLCM, and as a result, simple reaction time tests are often used to estimate that component of performance impairment due to decreased vigilance (Lim and Dinges, 2008). Furthermore, eyelid drooping/closures and slow ocular drift have been shown to increase with SLCM (Anderson *et al.* 2013); these involuntary ocular behaviours are immediate precursors to sleep and thus strong predictors of falling-asleep accidents (Lee *et al.* 2016). However, these two passive ocular phenomena are likely independent of any active mistakes caused by degraded visuomotor function. Visual and oculomotor impairment with SLCM could account for some of the human errors that occur when individuals perform tasks while drowsy, yet not on the verge of falling asleep. There is, therefore, an acute need to fully understand how dynamic visual processing and coordinated oculomotor control are affected by SLCM.

There is also a need for reliable biomarkers that detect and characterize the broad gamut of performance impairments that manifest themselves when sleepy. Unfortunately, it is not possible to predict impairment simply by noting the amount of sleep loss or the time of day, because there are large inter-individual differences in sleep need (Klerman and Dijk, 2008) and in resilience to sleep loss (Van Dongen *et al.* 2004; Van Dongen *et al.* 2006) and to shifts in circadian phase (Czeisler *et al.* 1999; Wyatt *et al.* 1999; Gronfier *et al.* 2007). Furthermore, individuals appear unable to assess subjectively the magnitude of their impairment due to sleep loss (Van Dongen *et al.*

2003), which is one of the reasons individuals engage in activities when they are too impaired to perform them appropriately. Although reaction time measures have proven valuable for objective detection of compromised vigilance (Lim and Dinges, 2008), there is still an ongoing need for reliable and objective tests that can characterize the complex, multi-dimensional nature of the functional impairments, beyond vigilance loss, caused by SLCM.

Human ocular tracking, which combines continuous smooth eye movements (pursuit) with intermittent ballistic jumps (catch-up saccades) to follow a moving object of interest (Orban de Xivry and Lefèvre, 2007), reflects both low-level quasi-reflexive sensori-motor processes (Robinson, 1981; Lisberger *et al.* 1987; Gellman *et al.* 1990; Ilg *et al.* 1993; Ilg, 1997; de Brouwer *et al.* 2002*b*; Konen *et al.* 2005) and higher-order perceptual, cognitive and attentional processes (Heywood and Churcher, 1971; Steinbach, 1976; Khurana and Kowler, 1987; Kowler, 1990; Butzer *et al.* 1997; Beutter and Stone, 1998; Stone *et al.* 2000; Krauzlis and Adler, 2001; Barnes, 2008), mediated by multiple neural pathways across cortical, cerebellar and brainstem circuits (for a review see Krauzlis, 2004). Oculomotor behaviour therefore offers a quantitative window onto multiple functional characteristics of potential impairments (Diefendorf and Dodge, 1908) across a wide array of neural pathways. Previous literature has documented snapshots of rather modest sleep-deprivation effects on disparate aspects of oculomotor behaviour (e.g. decreased saccadic velocity, binocular gaze disconjugacy, decreased pursuit gain, increased positional errors). Here we used unpredictable dynamic stimuli to examine systematically a wide constellation of open- and closed-loop response characteristics of both the saccadic and smooth-pursuit components of ocular tracking to characterize more comprehensively the effects of time since awakening and circadian phase on dynamic visual processing and visuomotor control. More specifically, we tracked the changes in 14 oculomotor metrics that efficiently capture distinct aspects of dynamic vision and visuomotor function (Liston and Stone, 2014) using a well-established sleep-deprivation protocol (Duffy and Dijk, 2002).

Methods

Ethical approval

The study conformed to the standards set by the latest revision of the *Declaration of Helsinki*, except for registration in a database, with each participant providing their informed, written consent. This study was conducted at the National Aeronautics and Space Administration, Ames Research Center, and was reviewed and approved by the Human Research Institutional Review Board (HRIRB) under protocol HRI-325.

Overview

We used an efficient and randomized oculomotor behavioural task (Krukowski *et al.* 2003; Liston and Stone, 2014) based on the classic Rashbass step-ramp paradigm (Rashbass, 1961) adapted to visual polar coordinates. We applied established and novel oculomotor analyses (Westheimer, 1954; Robinson, 1965; Bahill *et al.* 1975; Lisberger and Westbrook, 1985; Robinson *et al.* 1986; Krukowski and Stone, 2005; Liston and Stone, 2014) to generate 14 measures of oculomotor performance within a 10–15 min test using a video-based, table-mounted, pupil-tracking system with an accuracy of 0.5 deg and a precision of 0.2 deg (Liston *et al.* 2016). Using a chin and forehead rest to minimize head movements, seated participants performed the test repeatedly over a 24 h period to probe the behavioural effects of acute sleep deprivation and circadian phase on the wide array of neural processes known to underlie voluntary oculomotor control, in particular key spatio-temporal parameters of the pursuit and saccadic responses and of the visual processing of direction and speed information.

Selection/exclusion criteria

Thirteen human participants, whose prior informed consent was obtained in writing, completed the study. Data from one participant were excluded, because his melatonin acrophase occurred after his habitual wake time, indicating circadian misalignment and the possibility that he had an undiagnosed sleep disorder or was non-compliant with the pre-testing sleep regime.

Participants were required to be healthy (i.e. certified to participate in the study by their primary care physician) non-smokers, between 18 and 40 years old, with normal sleep habits defined as Pittsburg Sleep Quality Index (PSQI) scores <5, and Morningness–Eveningness Questionnaire (MEQ) scores >42 and <58. Potential participants were excluded from the study if they had experienced acute total sleep deprivation any time in the prior 12 months, or if they travelled across one or more time zones in the prior 3 months. Participants were also excluded if they consumed excess alcohol (>14 standard drinks/week for males, and >7 standard drinks/week for females), or if they reported illicit drug use. Similarly, participants were excluded if they scored >70 on the Minnesota Multiphasic Personality Inventory (MMPI-2) Depression scale, >75 on the Psychopathic Deviance, Schizophrenia and Hypomania State scale, >10 on the Beck Depression Inventory (BDI), or >40 on the State Trait Anxiety Inventory. Additionally, participants were excluded if they scored below any of the following criteria on the scales of the Symptom Checklist 90-R: >1.25 on Depression, >1 on Hostility, >0.75 on Phobic Anxiety, >1.25 on Paranoid Ideation, >1 on Psychoticism, and >1.25 on Anxiety. Participants were also excluded if their corrected binocular visual acuity was worse than 20/40 (> +0.30 logMAR).

Prior to testing, participants maintained static individually selected sleep–wake schedules, with 8.5 h of time in bed for 14 days. To ensure compliance, each participant wore an actigraph (Actiwatch Spectrum, Respironics Inc., Bend, OR, USA) on their non-dominant wrist, recorded daily time stamped voicemails at their sleep and wake times, and maintained a sleep diary.

Laboratory procedures

We conducted a constant-routine protocol (Duffy and Dijk, 2002) to minimize the influence of external factors on our measures of interest. Participants arrived at the NASA sleep laboratory 1–2 h after their habitual wake time. Following orientation and initial acuity testing, participants were placed in an environment without access to time cues and instructed to lie semi-prone on a bed with the head elevated at a 45° angle. In order to maintain a regulated physiological state, participants were prohibited from removing blankets and clothing, and from crossing their legs above the knee or elevating their torso or back (except when running the oculomotor test battery). To reduce the influence of metabolism on alertness, meals were divided into hourly isocaloric snacks based on the participant's body weight. Ambient light was maintained at a constant illuminance of <15 lux and all extraneous lighting sources were prohibited, although participants were exposed to up to 23 melanopic lux during oculomotor testing. Tympanic temperature was measured every 30 min using a Braun ThermoScan® (Braun GmbH, Frankfurt, Germany) to provide a real-time estimate of circadian phase. Participants were required to stay awake for the duration of the laboratory experiment, which lasted until the participant's tympanic temperature returned to baseline levels to ensure that we captured the circadian trough and recovery for each participant (between 24 and 26 h since awakening). To ensure compliance with the protocol and to administer the test batteries, a staff

member remained in the room with the participant at all times. Participants remained in private rooms and were isolated from other participants. A study staff member remained in the room to monitor them and to keep them awake. Participants were allowed to read and play games with study staff, but were not allowed to use any illuminated devices during the study.

Saliva samples were collected hourly and immediately frozen and stored at $\leq -17.8°C$. Participants did not consume any solid foods or liquids 45 min prior to the collection of each sample and were required to rinse their mouths with water 5 min prior to every sample. Salivary melatonin and cortisol concentrations were measured by radioimmunoassay by Stockgrand, Ltd, University of Surrey (Guildford, UK), using the methods of Aldhous and Arendt (1988).

Binocular visual acuity was measured using the Freiburg test (Bach, 1996) when the participant arrived at the laboratory. Oculomotor testing was performed at that time and one to four additional times during the daytime phase of the study (to quantify baseline performance) and then seven to nine times (hourly) during the night-time phase.

Rhythm analysis

Salivary melatonin values in pg/mL of each individual participant were subjected to best-fit cosine analysis (SAS software, version 9.2, SAS Institute, Cary, NC, USA). A cosine transformation was applied to the time variable using 24 h as the default circadian cycle; the PROC NLIN procedure in SAS was used to estimate the acrophase (peak time, circadian nadir) of the melatonin rhythm. All participant melatonin curves showed a significant cosine fit at the $P < 0.05$ level allowing us to estimate each individual's acrophase with a 95% confidence interval of approximately ± 17 deg (68 min).

Oculomotor task

Data were collected 2–5 times during the day and then hourly throughout the night, beginning approximately 1 h after each participant's habitual bedtime. The oculomotor task has been described previously (Liston and Stone, 2014). In brief, we used a behavioural oculomotor task based on the classic Rashbass (1961) step-ramp paradigm modified to accommodate a full sampling of the polar angles (Lisberger and Pavelko, 1989; Krukowski *et al.* 2003; Krukowski and Stone, 2005) using 180 trials corresponding to a trial along every even angle around the clock. Each trial started with a red target in the middle of the screen. The participant was instructed to initiate the trial by a manual button press on a game controller when they were ready after fixating the central target. After a random amount of time between 200 and

5000 ms (truncated exponential distribution), the target would jump 3.2–4.8 deg away from the fixation point, immediately move back at a constant speed (16, 18, 20, 22 or 24 deg/s) towards the fovea, and then onwards for a random amount of time from 700 to 1000 ms before disappearing. Participants were instructed to keep their eyes on the target in the centre without blinking and then to follow it as best they could once it started moving until it disappeared. The target would then reappear in the central location, awaiting the initiation of the next trial by the participant. We calibrated the eye tracker by having the subjects fixate nine locations on a 3×3 Cartesian grid in order to derive a six-parameter affine transformation from camera to world coordinates (Beutter and Stone, 1998).

Oculometric analyses

We analysed data largely as described previously (Liston and Stone, 2014), but we computed 14 different oculometric measures (as opposed to the 10 described originally) and we refined a number of the computations (see below). Prior to any analysis, we detected and removed saccades using a method described in detail elsewhere (Liston *et al.* 2013), modified to apply a bi-phasic saccade template appropriate for the higher spatio-temporal fidelity of our 250-Hz eye tracker, and were able to reliably detect and remove saccades down to approximately one-eighth of a degree in amplitude (limited by tracker noise). We then computed the following oculometric measures using MATLAB^{TM} (R2017a, The MathWorks, Natick, MA, USA):

- Latency (see, Lisberger and Westbrook, 1985; Tychsen and Lisberger, 1986) was defined as the median across trials of the time between target motion onset and the initiation of pursuit. The trial-by-trial latencies were localized objectively using a hinge function, least-square best-fit to the eye-velocity trace searching for latencies between 90 and 300 ms, with an added *prior probability* bias that assumes a reci-normal distribution of latencies (Oswal *et al.* 2007) with a mean of 5.95/s (corresponding to the inverse of the median latency, 168 ms, of our prior population of 41 normal human subjects (Liston and Stone, 2014)) and standard deviation of 6/s, which biases fits towards those expected from our population of normal subjects. We used a much weaker prior than the narrow one used previously (2/s in Liston and Stone, 2014; Liston *et al.* 2017) to allow for greater sensitivity to the *a posteriori* data, while still preventing spurious fits that can often result from any blind least-squares mini-mization. Trials for which the fixation baseline data were not stable (SD >3 deg/s) or for which there was less than 28 ms of saccade-free data in either the 100 ms baseline or the initial 100 ms pursuit acceleration interval were

excluded from the computation of latency, acceleration and direction (13.9% of trials).

- Acceleration (see, Lisberger and Westbrook, 1985; Tychsen and Lisberger, 1986) was defined as the median initial open-loop eye acceleration across trials. The value for each trial was computed as the mean radial acceleration of the saccade-free component of the tracking response in the 100-ms interval immediately following pursuit onset.

- Steady-state gain (Robinson *et al.* 1986) was defined as the median across trials of the mean eye-speed of the saccade-free component of tracking response in the interval 400–700 ms after motion onset, projected along the target direction and divided by the target speed. This geometric approach of combining the horizontal and vertical eye-velocity traces avoids the problem of generating large non-zero fixation speed biases due to the rectification of noise that results when using the standard Cartesian-to-polar transformation, and emphasizes the component of eye velocity that is correctly directed to minimize retinal slip. Trials for which steady-state velocity was negative, or for which there was less than 80 ms of saccade-free pursuit in the steady-state interval, or for which there was a blink during the steady-state interval, or for which the steady-state eye speed was unstable (SD >8 deg/s) were excluded from the computation of gain and proportion smooth (10.1% of trials), independent of any culling used for the initiation metrics above.

- Proportion smooth (e.g. von Hofsten and Rosander, 1997) was defined as the median across trials of the proportion of time that tracking within the steady-stated interval was smooth, as a metric of how much pursuit is contributing to steady-state tracking. This approach is different from how we computed proportion smooth in previous studies (Liston and Stone, 2014; Liston *et al.* 2017), where we used the ratio of distance travelled. We abandoned this previous method as it is biased upward by backward saccades (when present) or downward by hypermetric forward saccades (when present).

- Saccadic rate was defined as the total number of forward or backward catch-up saccades divided by the total steady-state tracking time (i.e. 300 ms per trial plus any added lead time if the saccade onset preceded and the saccade spanned the interval boundary). Trials with blinks in the steady state were excluded, but this occurred rarely.

- Saccadic amplitude was defined as the median amplitude of the forward (positive) catch-up saccades occurring in the steady-state tracking interval 400–700 ms after motion onset. Our prior published saccadic amplitude data (Liston and Stone, 2014; Liston *et al.* 2017) did not restrict the metric to those saccades made during the 400–700 ms steady-state

period and did not correct for the significant change in eye position due to the ongoing pursuit displacement occurring in concurrence with the saccade. As such, the values reported here are smaller than previously reported by us, but correspond to the true amplitude of the underlying catch-up saccades (de Brouwer *et al.* 2002*a*,b; Blohm *et al.* 2003). Backward saccades (often observed during high-gain pursuit) were not included in the computation of the median 'catch-up' saccade amplitude. Lastly, for the saccadic amplitude and dispersion calculations, we excluded those saccadic events with durations above 120 ms as they include head-movement, other artifacts, or large re-orienting saccades unrelated to the tracking task.

- Saccadic velocity slope and intercept, key measures of the 'main sequence' (Bahill *et al.* 1975), were defined as the linear regression parameters of the plot of peak saccadic velocity (corrected for the ongoing pursuit speed) as a function of saccadic displacement (corrected for the displacement due to pursuit) for all forward catch-up saccades.

- Saccadic dispersion was defined as the standard deviation of the distribution of directions across the distribution of forward catch-up saccades. This value combines the directional variability caused by noisy saccade generation (variability in saccadic end points – saccadic directional precision) with that caused by initial pursuit directional error (offsets from the target trajectory of the saccadic starting points – pursuit directional precision).

- Direction noise (Liston and Stone, 2014) was defined as the average across trials of the local standard deviations taken across the measured pursuit directions at a given direction and its two nearest neighbour directions (corrected for the 2 deg expected differences). This is slightly different from the method we used previously, which just used direction differences between two adjacent points.

- Direction asymmetry and anisotropy, more specifically up–down asymmetry and oblique-effect anisotropy (Krukowski and Stone, 2005), were defined, respectively, as the best-fitting first and second polar harmonic modulations of the direction gain, i.e. the local linear-regression slope of the pursuit-versus target-direction curve within a 30° window (Liston and Stone, 2014).

- Speed noise (Liston and Stone, 2014) was defined as the standard deviation across trials of pursuit speed at a given target speed divided by that speed (Weber fraction reported as a percentage of target speed), averaged across the five target speeds. In previous studies, we merely reported the average un-normalized speed threshold.

- Speed responsiveness was defined as the best-fitting linear regression slope of the mean radial pursuit speed

(independent of direction) *versus* target speed. This is slightly different from the method we used previously (Liston and Stone, 2014; Liston *et al.* 2017) as we now use raw radial speed (as opposed to projected speed along the direction of target motion), which makes this metric more uncorrelated with pursuit gain. In addition to those trials culled for the computation of gain (see above), those trials with very low gains (for which pursuit was <4 deg/s) were excluded from the computations of speed responsiveness and speed noise (11.7% of trials). This additional culling was designed to more cleanly segregate the question of how vigorous the pursuit response is in general (captured by its gain) from the question of how well pursuit can discriminate between small differences in speed (captured by its speed responsiveness and uncertainty).

Blinks were also recorded when the eye-position values defaulted to −1 during the steady-state analysis window.

Experimental design and statistical analysis

We used a within-subject and repeated-measures design to test for any adverse effects of extended time awake and circadian phase on 14 measures of ocular tracking performance. First, we computed baseline characteristics for our participants. We averaged each of the oculomotor metrics collected during the daytime for each subject to yield a distribution of 'baseline' values. We then computed the Pearson correlation, r, across subjects between all possible pairs of baseline oculomotor metrics to determine to what extent these metrics are independent of each other. Only one of the 91 pairs of baseline metrics was found to be significantly correlated across subjects (proportion smooth and saccadic rate, $P = 0.044$, Bonferroni corrected t test), extending prior findings (Liston & Stone, 2014) that our 14 metrics represent largely mathematically independent measures of visuomotor performance within the context of our study (i.e. on average, only 20% of their across-subject variance is shared and therefore at least some of the information they carry about performance is not redundant). The distributions of baseline values across participants were also used to perform the receiver operating characteristic (ROC) analysis described below.

To systematically analyse changes in oculomotor metrics across the biological night, we took advantage of our within-subject design to reduce the impact of inter-subject variability and increase our statistical power by subtracting each subject's individual baseline from each of their individual measures before binning and averaging the deviations from baseline across participants. We tested for changes in each oculomotor metric as distinct hypotheses (and not as multiple attempts to support a single hypothesis) so no correction was needed for the independent testing of each metric.

To evaluate the impact of time awake on each of the oculomotor metrics, we conducted two analyses. First, we conducted a linear regression analysis to evaluate cumulative changes over a full 24-h cycle. Significance of linear trends was determined by a two-tailed Student's t test based on r (Excel^{TM} formula tdist[abs(r)/(1-r^2)/df,df,2]) using the 11 binned values plotted in the figures with the degrees of freedom (df) equal to 9, or using all the individual time points (df = 127). Significance was confirmed using a commercial linear regression package and its F-test reported here (GraphPad Prism, GraphPad Software Inc., La Jolla, CA, USA) yielding nearly identical results. For those metrics with significant linear across-subject trends of time awake, we performed two *post hoc* one-tailed tests of the *a priori* expected signed effects: (1) multiple Bonferroni–Holm corrected t tests, for each of the binned repeated measures separately across the night-time runs (with those individual points found to be significant shown in red in Figures 2–4) and (2) uncorrected t tests of the within-subject linear trends based on r. Second, we also performed a ROC analysis (MATLAB) on the raw non-normalized metrics (i.e. using raw values in each of their respective units) comparing the distributions of the baseline and the sixth night-time run values across the 12 subjects to determine the detectability of impairments due to SLCM at the performance nadir, with significance determined using a one-tailed Wilcoxon rank-sum test of the *a priori* hypothesized signed effect based on the significant changes observed with the across-subject regression analysis. Significance was confirmed using a commercial ROC package (SigmaPlot, Systat Software, Inc., San José, CA, USA) yielding nearly identical results. Given that for any metric to have practical utility as a biomarker, it must provide reliable detectability from a single test measure without requiring the existence of a paired baseline, our ROC analysis was used to simulate the detectability of such a single potentially impaired run within the context of a future across-subject test paradigm with a prior hypothesis (i.e. comparison of the results of a given run with those of a population baseline).

To assess effects of circadian phase, we shifted each participant's measures relative to his or her melatonin acrophase and then combined data across all participants in bins aligned with respect to circadian degrees, with 0 degrees marking the time of the melatonin peak. To determine to what extent the oculomotor responses modulate sinusoidally with circadian phase (goodness of fit), we found the best least-squares fit to a cosine function with a period of 24 h and compared the reduced chi-square of that fit to that of the null model (the constant baseline value). We also computed r^2 values to estimate the percentage of variance accounted for. To determine significance of the fit, we performed a two-tailed t test based on the r between each of the metrics and their

best-fitting cosine reported here (df = 9) and confirmed significance using the correlation analysis in GraphPad Prism. To compare how the different eye-movement metrics fluctuate relative to internal biochemical markers of circadian phase, we also plotted the mean modulation in melatonin and cortisol, and computed the r^2 between them and certain metrics to highlight special cases.

Caveats

Although we conducted a controlled experiment to evaluate changes in eye movements over time, our study has certain limitations. To fully separate the homeostatic and circadian influences, we could have used a forced-desynchrony protocol; however, such a protocol takes approximately 25–30 days to fully separate circadian and homeostatic processes and we did not have the capacity to conduct such a study. Another potential concern is that, while we conducted our experiments under constant low lighting conditions, the stimulus display that we used for our eye-tracking task periodically exposed participants to light throughout the night. Although light exposures as short as 2 ms have been shown to affect circadian rhythm (Zeitzer *et al.* 2011), we do not believe that the episodic light exposure in our study exerted more than a minimal influence on our findings because the measured melatonin rhythms appeared well preserved for all participants. Lastly, although we did not find clear learning effects in our prior oculometric study (Liston & Stone, 2014) nor did we observe the consistent improvement across repeated daytime measures that would be expected from learning, we cannot entirely rule out the possibility that learning influenced our results to some small degree. However, it should be noted that any performance improvement over time due to learning could not have generated the time-awake trends we observed and would have had no net effect on the fitted circadian modulation, but could potentially have concealed small time-awake impairment trends that then failed to reach significance.

Results

Baseline and demographic characteristics from the final cohort of 12 participants are presented in Table 1.

Baseline measures

We found that baseline oculomotor measures were largely consistent with normal performance by human participants from daytime assessments reported elsewhere. The average pursuit latency and initial acceleration ($\pm$ SD across 12 subjects) were 158.8 ± 9.7 ms and 103.5 ± 23.4 deg/s^2, respectively. The average

Table 1. Demographic characteristics of study participants ($\pm$ SD)

Characteristic	Value ($n = 12$)
Age (years)	24.8 ($\pm$ 5.4)
Sex	6 ♀
Sleep episode duration	7 hrs 48 min ($\pm$ 16 min)
Height (cm)	170.2 ($\pm$ 10.4)
Weight (Kg)	67.8 ($\pm$ 12.9)
BMI (kg/m^2)	23.3 ($\pm$ 3.0)
PSQI score	3.2 ($\pm$ 1.8)
MEQ score	50.9 ($\pm$ 5.4)

BMI, body mass index; MEQ, Morningness–Eveningness Questionnaire; PSQI, Pittsburgh Sleep Quality Index.

initial pursuit direction noise, anisotropy and asymmetry were $9.4 \pm 1.5°$, 0.31 ± 0.09 and 0.09 ± 0.17, respectively. These values are consistent with healthy pursuit initiation and perifoveal open-loop direction processing under high spatial, temporal and directional uncertainty (Watamaniuk and Heinen, 1999; Krukowski *et al.* 2003; Krukowski and Stone, 2005; Liston and Stone, 2014), although latency is shorter (Tychsen and Lisberger, 1986) and directional noise much lower (Stone and Krauzlis, 2003) when directional uncertainty is low. The average steady-state gain and proportion smooth were 0.76 ± 0.09 and 0.76 ± 0.06, respectively. The average steady-state pursuit speed responsiveness and speed noise were 0.37 ± 0.19 and $19.6 \pm 3.6\%$, respectively. These values are not inconsistent with healthy steady-state pursuit and foveal speed processing (Stone and Thompson, 1992; Watamaniuk and Heinen, 2003; Liston and Stone, 2014), although gain and speed slope (Robinson *et al.* 1986; Liston & Stone, 2014) are typically a little higher, and speed noise can be considerably lower under optimal conditions (Kowler and McKee, 1987; Gegenfurtner *et al.* 2003). The average catch-up saccade rate, amplitude and dispersion were 3.8 ± 0.5 Hz, 2.0 ± 0.6 deg and $17.2 \pm 3.9°$, respectively, which is not inconsistent with prior studies; however, amplitudes can be larger and more variable with faster ramp conditions (de Brouwer *et al.* 2002*a*). The average slope and intercept of the peak saccadic velocity *versus* displacement curves was 30.3 ± 4.5/s and 48.9 ± 13.1 deg/s, respectively. The former is consistent with previous findings, while the latter appears somewhat higher than typically observed previously, although the best-fitting linear descriptive parameters that we report here have not generally been reported in the past (Bahill *et al.* 1975; Harwood *et al.* 1999; de Brouwer *et al.* 2002*a*; Houben *et al.* 2006). Lastly, the number of blinks per 180-trial run was, on average, 1.8 ± 2.2 with four participants showing no blinks whatsoever in their baseline data.

Effects of time awake

Figure 1 illustrates example time sequences for two different metrics for a single participant. The raw measures for latency and initial acceleration are plotted as a function of time since awakening for three daytime measures and eight hourly night-time measures. Note that, for this participant, latency shows little or no systematic change over time, while acceleration decreases over time with an apparent superimposed modulation. To systematically analyse any such effects (or lack thereof) of time awake for all 14 metrics across our population and to allow
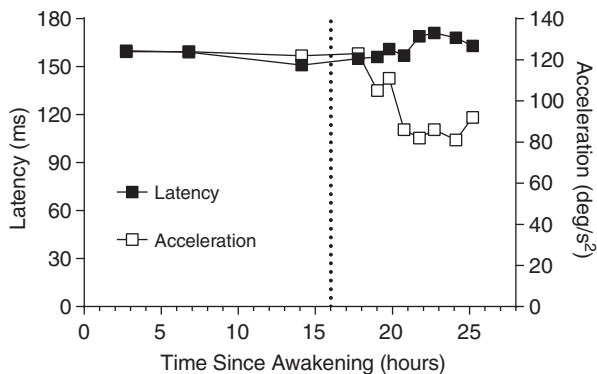

Figure 1. Example data from one participant
Plot of the repeated measures for two of the oculometrics, latency and initial acceleration, for one participant. The vertical dashed line separates the daytime (leftward symbols) and night-time (rightward symbols). Note that the temporal trends are well-behaved (i.e. not obscured by noise, even at the individual level).

for meaningful comparison across metrics in disparate raw units, we took each participant's deviation from their own baseline normalized with respect to that baseline (i.e. percentage change from their baseline, except for direction asymmetry where we used raw deviation from a near-zero baseline), aligned three daytime and eight night-time runs with respect to time since awakening, and averaged them across participants. We then found a clear pattern of cumulative changes in tracking performance as a function of time since awakening over one 24-h cycle for many of the metrics (Figs 2–4). Not shown in the figures, we also found, on average, a fourfold increase in the number of blinks after 24 h of sleep deprivation.

Pursuit behaviour shows systematic changes with increasing sleep deprivation captured in plots of percentage change in various measures of performance relative to baseline (within-subject mean of their daytime runs) averaged (±SD) across the 12 participants as a function of time since awakening (Fig. 2). Mean latency shows no significant overall trend ($F_{1,9} = 0.29$, $r^2 = 0.03$, $P = 0.61$) (Fig. 2A). Mean acceleration, however, shows a significant ($F_{1,9} = 13.9$, $r^2 = 0.61$, $P = 0.005$) linear decrease, indicating an average cumulative decrement in performance with sleep deprivation, peaking around −15% (Fig. 2B). Linear regression of individual data indicates that 6 of the 12 participants experienced a significant ($P < 0.05$) cumulative decrease in initial acceleration (e.g. see Fig. 1). Mean pursuit gain (Fig. 2C) and proportion smooth (Fig. 2D) both show highly significant ($F_{1,9} = 22.88$, $r^2 = 0.72$, $P = 0.001$ and $F_{1,9} = 29.1$, $r^2 = 0.76$, $P = 0.0004$, respectively) linear
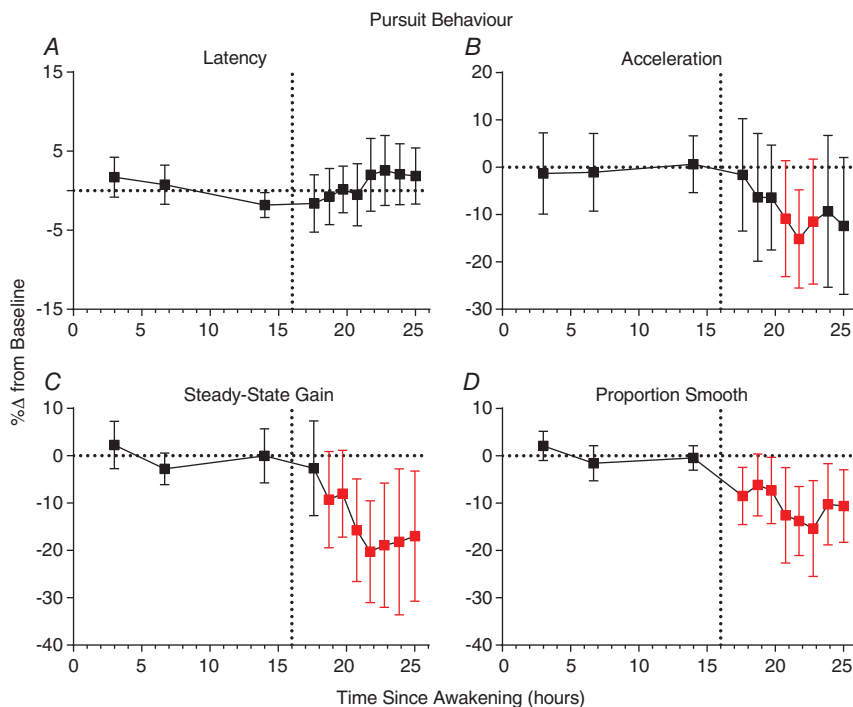

Figure 2. Effect of time awake on pursuit behaviour
The four panels plot mean oculometric measures (±SD across participants) of pursuit latency (A), initial pursuit acceleration (B), steady-state pursuit gain (C), and proportion of the tracking response that is smooth (as opposed to saccadic) (D) as a function of time awake over a 24-h cycle (3 daytime and 8 night-time measures). Night-time points showing significant impairment with respect to the daytime baseline ($P < 0.05$, *post hoc* 1-tailed *t* test, Bonferroni–Holm corrected for repeated measures) are shown in red.

decreases as a function of time awake peaking around −20% and −15%, respectively. Regression of the individual data indicates that 9 and 10 participants experienced a significant ($P < 0.05$) cumulative decrease in steady-state gain and proportion smooth, respectively.

Saccade behaviour shows systematic changes with sleep deprivation captured in plots of percentage change in the various measures of performance as a function of time since awakening averaged across subjects (Fig. 3). Mean saccadic rate (Fig. 3A) shows a highly significant
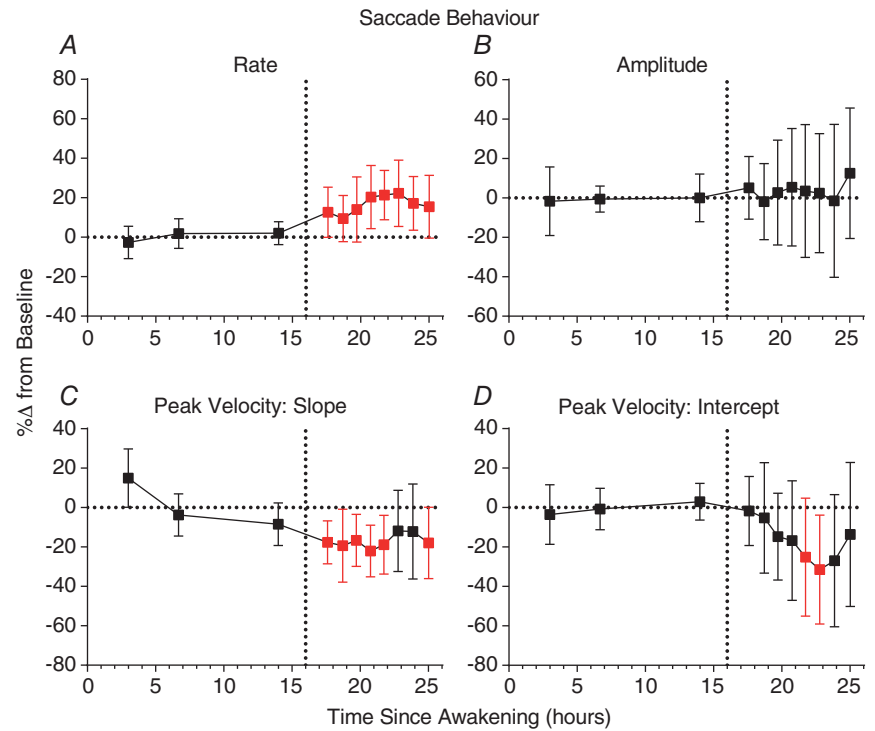

Figure 3. Effect of time awake on saccade behaviour
The four panels plot mean oculometric measures (±SD across participants) of saccadic rate (*A*), saccadic amplitude (*B*), peak saccadic velocity (slope) (*C*), and peak saccadic velocity (intercept) (*D*) as a function of time awake over a 24-h cycle (3 daytime and 8 night-time measures). Night-time points showing significant impairment with respect to the daytime baseline ($P < 0.05$, 1-tailed *t* test, Bonferroni–Holm corrected for repeated measures) are shown in red.
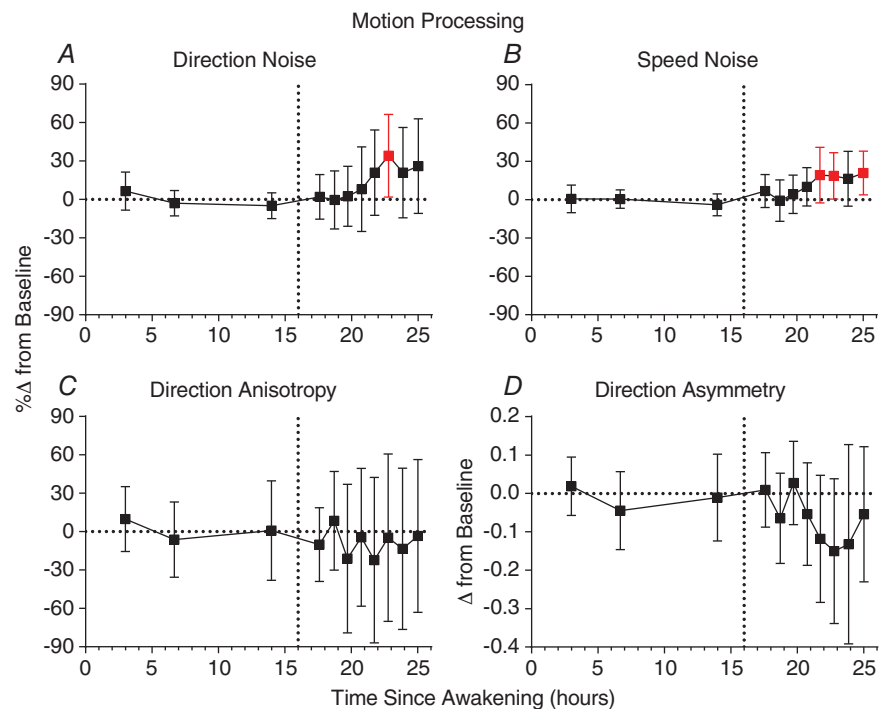

Figure 4. Effect of time awake on visual motion processing
The four panels plot mean oculometric measures (±SD across participants) of direction noise (*A*), speed noise (*B*), anisotropy (oblique effect) (*C*), and horizontal–vertical asymmetry (*D*) as a function of time awake over a 24 h cycle (3 daytime and 8 night-time measures). Night-time points showing significant impairment with respect to the daytime baseline ($P < 0.05$, 1-tailed *t* test, Bonferroni–Holm corrected for repeated measures) are shown in red.

Table 2. Oculometric sensitivity to time awake and circadian phase

	Time awake slope (%/h)	Detectability at nadir (%)	Circadian modulation (%)	Circadian phase (deg)
Pursuit latency	NS	NS	1.9	94
Open-loop acceleration	−0.60	71.5	11.4	224
Steady-state gain	−1.00	84.7	17.5	232
Saccadic amplitude	NS	NS	NS	NS
Saccadic dispersion	NS	NS	NS	NS
Saccadic rate	1.08	88.9	20.3	36
Proportion smooth	−0.70	89.6	12.8	219
Direction noise	1.14	83.3	24.9	83
Direction anisotropy	NS	NS	11.5	213
Direction asymmetry	−0.005[†]	NS	0.094[‡]	245
Speed noise	0.94	77.1	16.3	68
Speed responsiveness	NS	NS	NS	NS
Saccadic velocity (slope)	−1.24	76.4	20.8	201
Saccadic velocity (intercept)	−1.15	88.9	21.5	231

[†]Units are 1/h. [‡]Unitless. NS, not significant ($P > 0.05$).

($F_{1,9} = 34.9$, $r^2 = 0.80$, $P = 0.0002$) increase, peaking around 20%, presumably to compensate for the decrement in pursuit performance. Regression of the individual data indicates that 10 participants experienced a significant ($P < 0.05$) cumulative increase in saccadic rate. Mean saccadic amplitude (Fig. 3*B*) and dispersion (not shown) show no significant cumulative trend ($F_{1,9} = 3.58$, $r^2 = 0.28$, $P = 0.10$ and $F_{1,9} = 0.97$, $r^2 = 0.10$, $P = 0.36$, respectively). The mean slope (Fig. 3*C*) and intercept (Fig. 3*D*) of peak saccadic velocity *versus* displacement show significant decreases ($F_{1,9} = 20.95$, $r^2 = 0.70$, $P = 0.002$ and $F_{1,9} = 8.27$, $r^2 = 0.48$, $P = 0.02$, respectively), with regression of the individual data showing that seven participants experienced significant ($P < 0.05$) decreases for both.

Visual motion processing shows systematic changes, primarily in precision, captured in plots of percentage change in the various measures of performance as a function of time since awakening averaged across participants, except for asymmetry where we used absolute change from the near zero baseline value (Fig. 4). Mean direction (Fig. 4*A*) and speed (Fig. 4*B*) noise show significant ($F_{1,9} = 5.49$, $r^2 = 0.38$, $P = 0.044$ and $F_{1,9} = 10.47$, $r^2 = 0.54$, $P = 0.02$, respectively) linear increases, peaking around 30% and 20%, respectively. Regression of individual data shows that 5 and 7 participants experienced significant ($P < 0.05$) increases in direction and speed noise, respectively. Mean direction anisotropy (Fig. 4*C*) and asymmetry (Fig. 4*D*) show no significant trend ($F_{1,9} = 2.69$, $r^2 = 0.23$, $P = 0.14$ and $F_{1,9} = 4.09$, $r^2 = 0.31$, $P = 0.08$, respectively). Lastly, mean speed responsiveness shows no significant trend ($F_{1,9} = 3.45$, $r^2 = 0.28$, $P = 0.10$, not shown).

In addition to the above analysis, we also performed a linear regression on the entire scatter plot of the individual deviation-from-baseline *versus* time awake for all participants and all time points, for each of the 14 metrics. The same eight metrics (acceleration, gain, proportion smooth, saccadic rate, saccadic peak velocity slope and intercept, direction, and speed noise) retain their significant linear trends (with even lower *P*-values than reported above) without any binning or averaging prior to the regression. Furthermore, with the increased degrees of freedom, a linear decrease in direction asymmetry now reaches significance ($F_{1,127} = 6.97$, $r^2 = 0.05$, $P = 0.01$) with no additional metrics showing significant trends ($P > 0.16$). The findings of the linear-regression analysis of time-awake effects are summarized in the first column of Table 2.

To estimate the absolute detectability (sensitivity) to time awake and circadian timing of a single run of oculometric measures without assuming the existence of a within-subject (paired) baseline, we performed a ROC analysis on data from a single run near the nadir of performance (the time with the largest deficit averaged across metrics and participants), testing for the effects predicted by the above trend analysis (Fig. 5). Each panel of Fig. 5 shows the distribution of a particular metric across participants from their night-time run number 6 (on average, 22.8 h after awakening) and its Gaussian fit (blue), plotted alongside the Gaussian fit of the baseline measures (red). The area under the ROC curve (AUC), or the probability of correctly distinguishing a randomly selected run (from among the 12 participants) performed after acute sleep deprivation from a randomly selected baseline control run (from among the 12 participants) is as follows: 71.5% for initial pursuit acceleration (Wilcoxon

rank-sum test, 95% confidence interval: 50.1–92.9%, $z = 1.76$, $P = 0.04$), 84.7% for steady-state pursuit gain (67.2–100%, $z = 2.86$, $P = 0.003$), 89.6% for proportion smooth (77.2–100%, $z = 3.38$, $P = 0.0004$), 88.9% for saccadic rate (75.1–100%, $z = 3.20$, $P = 0.0007$), 83.3% for direction noise (66.6–100%, $z = 2.74$, $P = 0.004$), 77.1% for speed noise (57.0–97.2%, $z = 2.22$, $P = 0.02$), 76.4% for saccadic velocity slope (56.4–96.4%, $z = 2.17$, $P = 0.02$), and 88.9% for saccadic velocity intercept (75.8–100%, $z = 3.20$, $P = 0.0007$). The detectability using the other metrics was not significantly above chance (50%). While this detectability analysis shows that many oculometrics are sensitive enough to detect an effect of time awake with reasonable reliability by comparing a single run with an unpaired population of baseline runs, it does not distinguish between effects of sleep loss and circadian phase, nor does it address the issue of specificity (i.e. the probability of detecting impairments unrelated to sleep loss or circadian timing). The findings of the ROC analysis are summarized in the second column of Table 2.

Effects of circadian phase

Most of the oculomotor measures that we evaluated showed significant modulation as a function of circadian phase when averaged across participants. To systematically assess such effects (or lack thereof) for all 14 metrics across our population, we used a cosine function to fit the modulation around baseline, averaged across participants after binning with respect to circadian phase, to yield a least-squares best estimate of amplitude and phase of modulation (Table 2) as well as statistical measures of goodness of fit.

Pursuit behaviour shows systematic changes with biological time captured in plots of percentage modulation in performance as a function of circadian phase averaged ($\pm$SD) across the 12 subjects, along with the average measured melatonin (blue) and cortisol (red) modulation profiles (Fig. 6). Both mean latency (Fig. 6*A*) and initial acceleration (Fig. 6*B*) show a clear modulation that is reasonably well fit by a cosine function (the reduced χ^2 is 2.1 and 4.1 times better than the null model, respectively) accounting for 48.3% and 44.6% of the
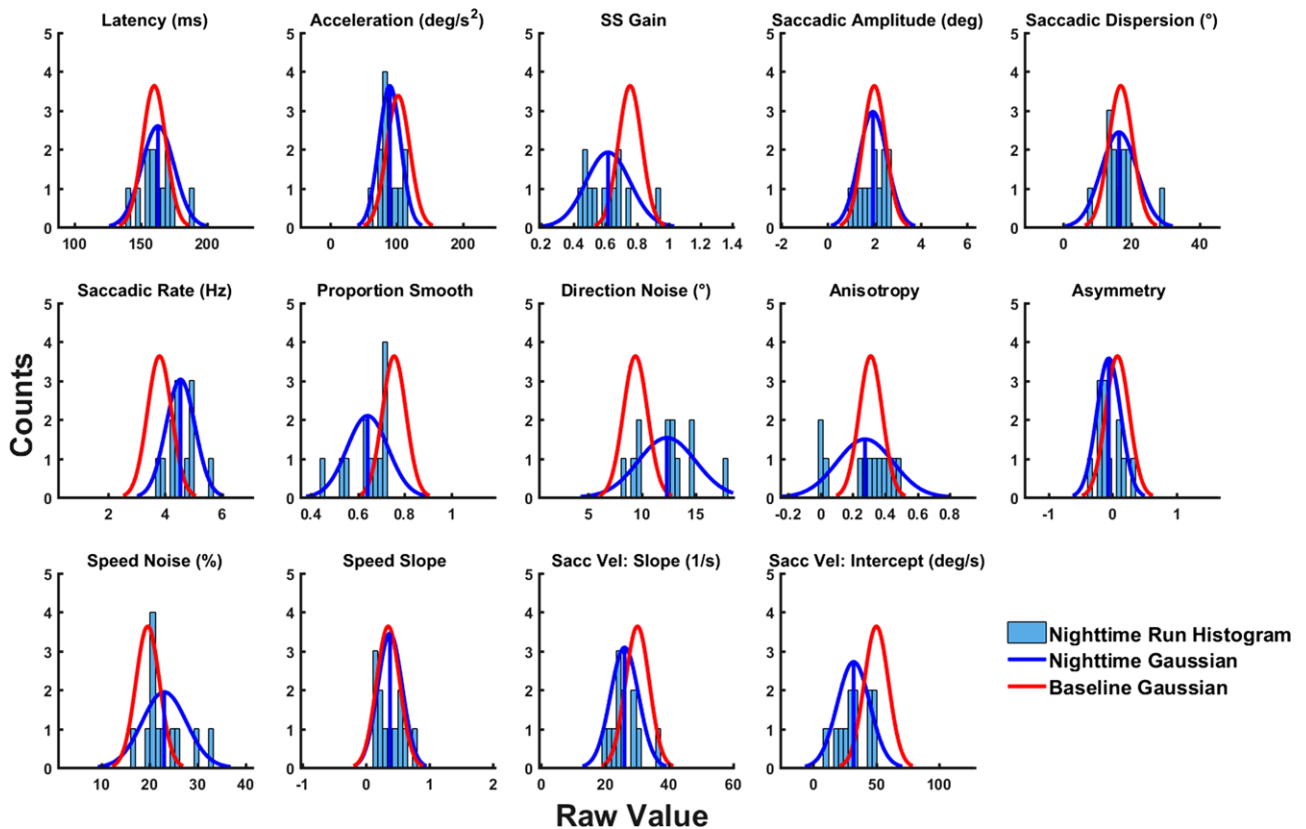

Figure 5. Receiver operating characteristic (ROC) analysis at the nadir of performance
The panels plot the histogram of the night-time run no. 6 measures from 12 participants, for each of the 14 different oculometrics, and their best fitting Gaussian (blue), along with best-fitting Gaussian to the 12 baseline measures (red). The area under the curve (AUC) indicates the accuracy of a two-alternative forced choice in distinguishing between randomly selected samples from the affected and baseline distributions. Although Gaussian fits are provided for visual insight, the ROC test is non-parametric, acting directly on the measured values. [Colour figure can be viewed at wileyonlinelibrary.com]

variance ($t(9) = 2.90$, $P = 0.02$; $t(9) = 2.69$, $P = 0.03$), respectively. Both mean gain (Fig. 6C) and proportion smooth (Fig. 6D) show a pronounced modulation that is well fit by a cosine (reduced χ^2 9.7 and 10.9 times better than the null model, respectively), accounting for 84.3% and 83.2% of the variance ($t(9) = 6.95$, $P = 0.0007$; $t(9) = 6.69$, $P = 0.0009$), respectively.

Saccade behaviour shows systematic changes with biological time captured in plots of percentage change in performance as a function of circadian phase averaged across subjects (Fig. 7). Mean saccadic rate (Fig. 7A) shows a clear modulation that is well fit by a cosine function (reduced χ^2 16.5 times better than the null model), accounting for 87.8% of the variance ($t(9) = 8.05$, $P = 0.00002$). Mean saccadic velocity slope (Fig. 7C) and intercept (Fig. 7D) again show a clear modulation that is well fit by a cosine function (reduced χ^2 14.3 and 5.5 times better than the null model, respectively), accounting for 76.7% and 59.2% of the variance ($t(9) = 5.44$, $P = 0.0004$; $t(9) = 3.61$, $P = 0.006$), respectively. Lastly, mean saccadic amplitude (Fig. 7B) and saccadic dispersion (not shown) do not show significant sinusoidal modulation ($t(9) = 1.26$, $P = 0.24$; $t(9) = 1.62$, $P = 0.14$, respectively).

Visual motion processing shows systematic changes with biological time captured in plots of performance

as a function of circadian phase averaged across subjects (Fig. 8). Both mean direction (Fig. 8A) and speed noise (Fig. 8B) show pronounced modulation that is reasonably well fit by a cosine (reduced χ^2 2.1 and 4.7 times better than the null model, respectively), accounting for 75.6% and 79.6% of the variance ($t(9) = 5.28$, $P = 0.0006$; $t(9) = 5.93$, $P = 0.0003$), respectively. Mean direction anisotropy (Fig. 8C) and asymmetry (Fig 8D) also shows significant sinusoidal modulation (reduced χ^2 1.9 and 2.8 times better than the null model), accounting for 39.2% and 68.2% of the variance ($t(9) = 2.41$, $P = 0.04$; $t(9) = 4.40$, $P = 0.002$), respectively, but the modulation of mean speed responsiveness (not shown) did not quite reach significance ($t(9) = 1.94$, $P = 0.09$). Lastly, while most metrics show peak/trough modulation somewhere between the melatonin and cortisol peaks albeit closer to cortisol, the modulation in mean direction and speed noise appears particularly tightly synchronized with the cortisol modulation ($r^2 = 95.7\%$ and 82.6% corresponding to $P = 0.00001$ and $P = 0.0002$, respectively), providing an even better fit than a simple cosine function, yet with no parametric freedom. The findings of the sinusoidal analysis of circadian-phase effects are summarized in the third and fourth columns of Table 2.
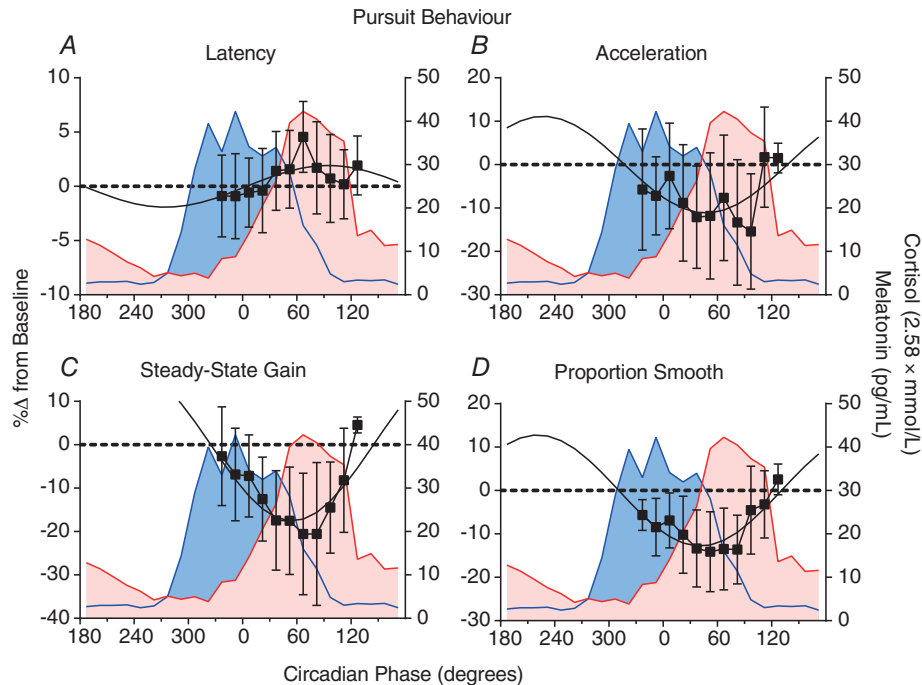

Figure 6. Effect of circadian phase on pursuit behaviour
The four panels plot mean oculometric measures (±SD across participants) of pursuit latency (A), initial pursuit acceleration (B), steady-state pursuit gain (C), and proportion smooth (D) as a function of circadian phase over a 24 h cycle along with the best-fitting sinusoid. The mean modulation of melatonin (blue) and cortisol (red) are superimposed here and in Figs 7 and 8. The SD of acrophase across participants was 13.9 deg. Note expanded scale for panel A.

Discussion

We found that the majority of our oculomotor measures show significant impairment with extended time awake and modulate with circadian phase. For those showing a linearly increasing impairment over a 24 h cycle (acceleration, gain, proportion smooth, saccadic rate, direction noise, speed noise, and the slope and intercept of saccadic velocity), we infer that there is a homeostatic component to the impairment and estimate its magnitude as the slope of the performance decline (Table 2). For those showing a significant sinusoidal modulation over a 24 h cycle (latency, acceleration, gain, proportion smooth, saccadic rate, direction noise, speed noise, direction anisotropy, direction asymmetry, and the slope and intercept of saccadic velocity), we conclude that there is an effect of circadian phase and estimate its magnitude and phase as the scale factor and phase of the best-fitting cosine model to the data (Table 2).

Physiological implications

We found no significant effect on pursuit latency (as did Fransson *et al.* 2008) suggesting that the shortest pathways from peripheral retina, either through direct brainstem visual pathways or through the lateral geniculate nucleus, primary visual cortex, and the middle temporal area (MT) to brainstem motor circuits, driving the earliest component(s) of ocular tracking (Lisberger and Westbrook, 1985; Tychsen and Lisberger, 1986; Rodman and Albright, 1989; Ilg *et al.* 1993; Stone *et al.* 2000; Pack and Born, 2001; Masson and Stone, 2002; Krauzlis, 2004; Konen *et al.* 2005), are more resistant to homeostatic effects. Conversely, the large effects on pursuit response dynamics suggest that the higher-order extrastriate and frontal circuits necessary for achieving and sustaining accurate steady-state foveal tracking and motion perception, in particular the medial superior temporal (MST) area and frontal pursuit area (FPA) (Newsome *et al.* 1985; Dürsteler *et al.* 1987; Newsome and Paré, 1988; Keating, 1991; Morrow and Sharpe, 1993, 1995; Heide *et al.* 1996; Shi *et al.* 1998) are more vulnerable to sleep loss. Although the observed decrement in initial acceleration could be due in part to changes within bottom-up visual pathways (e.g. V1 to MT; Newsome *et al.* 1985; Movshon and Newsome, 1996; Lisberger and Movshon, 1999), our observation of reduced initial acceleration *and* steady-state gain is more parsimoniously consistent with a similar dual effect of reversible lesions of FPA (Shi *et al.* 1998) presumably through disruption of its top-down influences on pursuit (Tanaka and Lisberger, 2001; Mahaffy and Krauzlis, 2011) or of MST (e.g. Dürsteler *et al.* 1987). Lastly, our observed impairment of saccadic velocity is likely mediated by changes in the
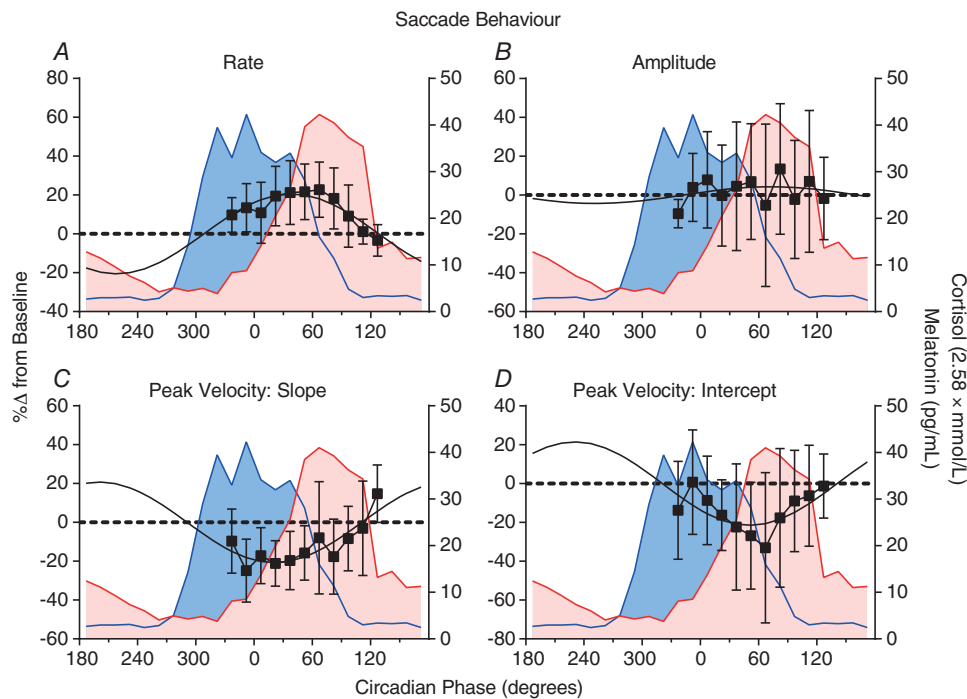

Figure 7. Effect of circadian phase on saccade behaviour
The four panels plot mean oculometric measures (±SD across participants) of saccadic rate (*A*), saccadic amplitude (*B*), peak saccadic velocity (slope) (*C*), and peak saccadic velocity (intercept) (*D*) as a function of circadian phase over a 24 h cycle along with the best-fitting sinusoid. [Colour figure can be viewed at wileyonlinelibrary.com]

responsiveness of brainstem pre-motor 'burst' neurons (Henn *et al.* 1984). While human imaging studies have found that sleep deprivation changes activation within frontal, parietal and to a lesser extent occipital cortex during cognitive tasks (e.g. Thomas *et al.* 2000; Chee and Choo, 2004; Drummond *et al.* 2004), the extent to which any of these sleep-modulated areas overlap with those activated during motion-perception and sensorimotor-control tasks (e.g. Barton *et al.* 1996; Petit and Haxby, 1999; Rosano *et al.* 2002; Tanabe *et al.* 2002) and the specific nature of the altered neural processing associated with sleep/circadian disruption remain fruitful areas for future research.

Relationship to prior literature

Prior studies have shown that eyelid-closure/blink dynamics (e.g. Federal Highway Administration, 1998; Anderson *et al.* 2013) and binocular gaze coordination (Horne, 1975; Tong *et al.* 2016) are affected by fatigue or sleepiness, and that slow ocular drift accompanies the transition from wakefulness to sleep (Henn *et al.* 1984; Santamaria and Chiappa, 1987; Ferrara *et al.* 2000).

Prior studies have also found altered saccadic eye movements associated with sleep deprivation. Several groups have reported a significant decrease (5–10%) in the velocity of large (10–60 deg), voluntary, visually driven, horizontal saccades after 24 h of acute sleep deprivation (e.g. De Gennaro *et al.* 2000, 2001; Quigley *et al.* 2000; Rowland *et al.* 2005; Zils *et al.* 2005; Goldich *et al.* 2010; McClelland *et al.* 2010) or after chronic partial sleep deprivation (Russo *et al.* 2003), along with significant variance across time of day (De Gennaro *et al.* 2000; Fransson *et al.* 2008). Furthermore, Fransson and colleagues (2008) found a 5% decrement in the ratio of peak saccadic velocity to saccadic amplitude, indicating a change in the so-called 'main sequence' (Bahill *et al.* 1975; Otero-Millan *et al.* 2008; Di Stasi *et al.* 2012, 2013). Our results confirm and extend these findings to small (~1–3 deg), automatic catch-up saccades during steady-state tracking in all directions. In particular, we examined two saccadic-velocity metrics, one (slope) capturing the sensitivity of peak velocity to changes in amplitude as well as a second (intercept) capturing the asymptotic value of velocity as amplitude goes to zero, more fully characterizing changes to the main sequence. We found decrements in both saccadic-velocity metrics ranging from 10 to 30% after 20–25 h of sleep deprivation, larger than the 5–10% typically reported previously, perhaps due to the enhanced eye-tracking methodology/analysis used here or to a difference between large voluntary and small involuntary catch-up saccades. We also found a sinusoidal modulation of ~20% with circadian phase for both saccadic velocity metrics.

Prior studies have also found altered smooth pursuit eye movements associated with sleep deprivation. Several
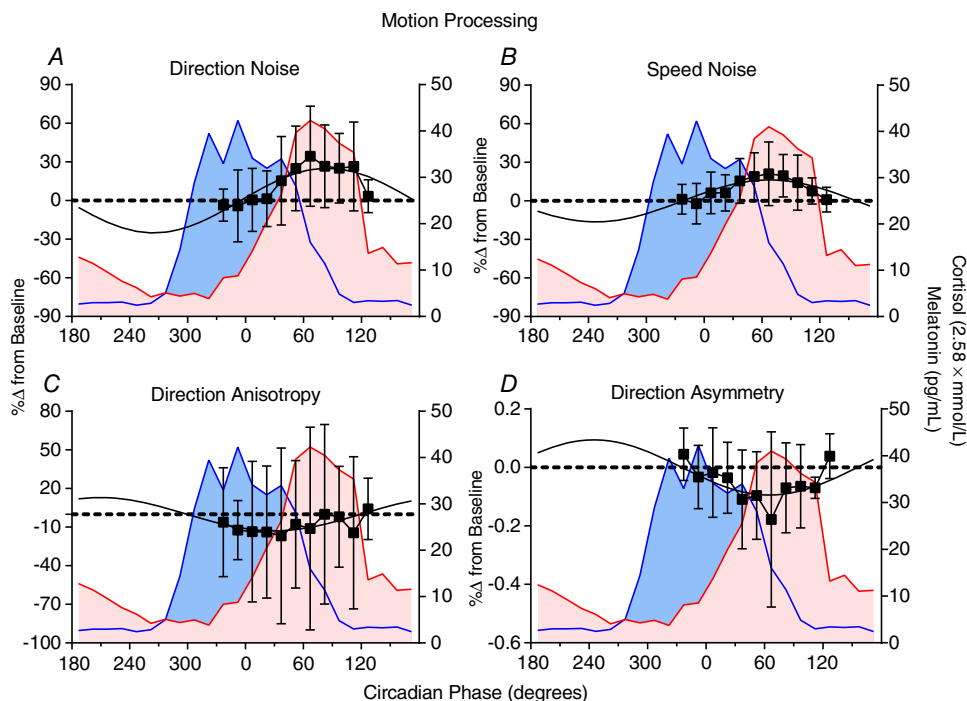

Motion Processing

Figure 8. Effect of circadian phase on visual motion processing
The four panels plot mean oculometric measures (±SD across participants) of direction noise (*A*), speed noise (*B*), anisotropy (oblique effect) (*C*), and horizontal–vertical asymmetry (*D*) as a function of circadian phase over a 24 h cycle along with the best-fitting sinusoid. [Colour figure can be viewed at wileyonlinelibrary.com]

groups found a small decrease in pursuit gain during tracking of predictable target motion after 24 h of sleep deprivation. Using a sinusoidal tracking task, DeGennaro and colleagues (2000) found a ∼7% decrement and significant variance across time of day. Using extended constant-velocity ramp stimuli, Fransson and colleagues (2008) found no significant change in gain for 20 deg/s motion (same speed as here), albeit they did find a 4% decrement after 36 h. The small magnitude of these effects was perhaps due to the predictability of their stimuli or because they did not remove saccades with velocities up to 50 deg/s (∼0.5 deg) and rejected data when the gain was below 0.5. Here we found significant impairment only a few hours into night-time.

Specificity

It is important to know to what extent our findings are specific to sleep and circadian manipulations. A prior study (Maruta *et al.* 2014) compared oculomotor effects of sleep deprivation with those of mild traumatic brain injury (mTBI). Using predictable two-dimensional target trajectories (Leung and Kettner, 1997), they examined the effects of sleep deprivation or mTBI using their 'indices' of oculomotor performance (Maruta *et al.* 2013) defined in motor coordinates (i.e. with respect to the movement trajectory). They found a largely similar qualitative pattern of impairment in both cases. Their two indices of positional precision (standard deviation of position error along the radial and tangential directions) and of pursuit performance (horizontal and vertical gains) showed changes following 26 h of sleep deprivation (+36.5%, +28.6%, −4.0% and −3.2% ($P = 0.11$), respectively). These same indices showed similar changes with mTBI albeit larger (+55%, +108%, −15% and −31%). The fact that they found significant *quantitative* differences in the two scenarios led them to suggest that the ratio of tangential to radial error might allow one to distinguish sleep deprivation from mTBI.

In the current study, the motion-processing metrics are defined in sensory coordinates (i.e. with respect to visual space in polar coordinates). In our recent study of TBI (Liston *et al.* 2017), we found a different qualitative pattern of effects than those presented here. In particular, we found significant impairment in speed responsiveness (accuracy) without significant changes in speed and direction noise (precision) associated with TBI, yet the opposite pattern here. In addition, a preliminary study of low-dose alcohol (Tyson *et al.* 2018) found that catch-up saccadic amplitude increases dramatically with blood alcohol level, while here we found no systematic change with time awake. Thus, the diverse nature of our ensemble of metrics provides *qualitative* specificity that could be harnessed to distinguish sleep/circadian impairment from that associated with mTBI or alcohol consumption.

A suitably broad suite of eye-movement metrics could therefore provide a sensitive and specific biomarker of SLCM. Furthermore, one could combine the metrics responsive to time awake and circadian phase (ROC AUC: 72–90%) to generate a single metric with even greater sensitivity (e.g. Goldich *et al.* 2010; Anderson *et al.* 2013; Liston *et al.* 2017). Additionally, one could capitalize on the multi-dimensionality to compare the pattern of effects (or lack thereof) observed after extended time awake to that associated with other neural stressors not only to detect neural impairment, but also classify it as likely due to SLCM or to other potential causes.

Conclusion

Our findings demonstrate that many features of human eye movements are dramatically impaired during an acute sleep-deprivation protocol. While previous studies found only modest or insignificant effects on pursuit gain (<10%) using completely predictable target motion, we found large effects on gain (∼20%) and other measures of visual and oculomotor performance (up to 30%) using motion stimuli with unpredictable onset, direction, speed and starting location. It would seem that tracking predictable target motion is easy enough to effectively perform nearly in one's sleep, while tracking target motion that is unpredictable across a number of spatial and temporal dimensions requires vigilance, attention and active visual processing, and thus is more sensitive to sleep/circadian disruption.

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Additional information

Competing interests

L.S.S. is listed as an inventor on NASA's U.S. patent no. 9,730,582 awarded 8/15/17 and three pending NASA patent applications on oculometric techniques for detecting neural impairment, but he has no role in any commercialization.

Author contributions

L.S.S. and E.E.F.-E. conceived and designed the study. L.S.S., P.F.C., N.H.F. and E.E.F.-E. performed the experiments and collected the data. L.S.S., T.L.T., E.E.F.-E. analysed the data. All authors contributed to the writing of the paper and approved the final version.

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