A precipitous decline in eyelid movements (ELMs) has been shown to be a highly reliable indicator of sleep onset. While ELMs correlate well with eye movements during waking and rapid eye movement (REM) sleep, the eye sensor remains silent during the period of slow eye movements (SEMs) typical of sleep onset. If the ELM density (e.g. ELMs per minute) dropped simultaneously with the appearance of SEMs prior to sleep onset, it could be a promising tool for identifying decreases in alertness prior to overt sleep onset. The present study was designed to determine whether the presence of SEMs in the transitional period preceding stage 1 sleep is reflected in decreases in ELM density. ELM densities were computed for 2.5-s epochs with and without SEMs, as well as for 15-s epochs. Decreases in ELM density not only were an excellent correlate of the appearance of SEMs during wakefulness with closed eyes, but also a good predictor of their occurrence (c. 82% accuracy) at a time resolution of 2.5 s. Based on these results, we conclude that ELM density reliably predicts moderate changes in the level of alertness during quiet wakefulness.

**KEYWORDS** alertness, drowsiness, electro-oculography, eyelid movements, nightcap, slow eye movements

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**INTRODUCTION**

The dramatic increase in the number of accidents associated with sleepiness has stimulated research aimed at identifying behavioral and physiological correlates of alertness in different occupational settings (Hakkanen et al. 1999; Torsvall and Akerstedt 1987; Wright and McGown 2001). Variations in the electroencephalogram (EEG) have been traditionally considered as the ‘gold standard’ for identifying fluctuations in the level of alertness. However, changes in the electro-oculogram (EOG) have been demonstrated to be at least as good of indicators of sleepiness (De Gennaro et al. 2000; Hyoki et al. 1998; Akerstedt and Gillberg 1990).

The EOG activity prior to sleep onset, during the transition from wakefulness to drowsiness, is mainly characterized by the appearance of slow rolling eye movements (SEMs; Santamaria and Chiappa 1987). This EOG activity shows a linear increase before the onset of stage 1 sleep, continues to increase through stage 1, and then undergoes a gradual decline after the onset of stage 2 (De Gennaro et al. 2000). During wake, SEMs not only correlate negatively with performance and positively with subjective estimates of sleepiness (Akerstedt and Gillberg 1990; Torsvall and Akerstedt 1987), but also with changes in EEG activity (De Gennaro et al. 2000).

Physiological studies in monkeys have found that preoculomotor neurons in the medial paramedian pontine reticular formation (pause neurons) show continuous, regular discharge, that is only interrupted prior to and during eye blinks and saccades typical of wakefulness. However, the activity of these neurons ceases simultaneously with the appearance of SEMs at the onset of light sleep (Henn et al. 1984). These premotor neurons innervate motoneurons in brainstem motor nuclei which not only control fixation and compensatory eyeball movements but which are also responsible for eyelid movements (ELM). We have recently shown that a decline in
ELMs identifies sleep onset with a mean difference of 45 s compared with traditional polysomnography (PSG; Cantero et al. 2002), and a 93% agreement in wake–sleep scores for 30-s epochs. In addition, ELM density was a better predictor of sleep onset than changes in the time course of either theta or alpha power. Based on these findings, we hypothesized that during normal transitions from wake to sleep, eyelid behavior may be a more sensitive indicator of changes in arousal systems than are EEG power fluctuations.

To detect ELMs, we use a piezoelectric film sensor. Tonic levator activity during wake, as well as active movements of the lid produced by contraction of the orbicularis oculi and levator palpebrae superioris muscles. While sensitive to blinking and rapid eye movements (REMs) during wake and REM sleep, as well as the tonic levator activity during wake, there is no ELM activity coincident with SEMs during stage 1 sleep (Ajilore et al. 1995). If changes in ELM density can predict the appearance of SEMs not only during sleep but also during wakefulness, it might be a valuable tool to measure decreases in alertness prior to sleep onset, and to alert individuals in potentially dangerous situations. Thus, the goal of the present study was to determine whether the appearance of SEMs during quiet wakefulness preceding the onset of stage 1 sleep could be reliably predicted by a decline in ELM density.

METHODS

Subjects and procedure

Ten paid subjects (five women; 20–25 years) with regular sleeping habits and apparent good health were recruited and signed consent forms prior to the study. The Massachusetts Mental Health Center’s Human Studies Committee approved the study. Four nap trials were routinely performed in an acoustically isolated bedroom at 2-h intervals (09:30, 11:30, 13:30 and 15:30 hours). Subjects were asked to rest lying in the bed with their eyes closed and to fall asleep if they wished. Each trial was terminated after 20 min of either PSG-identified sleep or wake.

PSG recordings

The EEG recordings were performed using two derivations (C3 and O1 referred to the ipsilateral mastoid). EOG electrodes were placed 1 cm lateral to the outer canthus of each eye and referred to the contralateral mastoid. Bipolar electromyography (EMG) was recorded from two submental electrodes. Electrode impedance was kept below 10 kΩ. All electrophysiological signals were amplified on a Grass Model 8–10 polygraph (Grass Instruments, Quincy, MA, USA), digitized (200 Hz, 12-bit resolution), filtered (EEG and EOG: 0.3–35 Hz; EMG: 5–70 Hz), and stored digitally on a Macintosh computer for subsequent offline analysis.

ELM recordings

The ELMs were recorded and analyzed with the Nightcap® sleep monitoring system, which uses an adhesive-backed, 25 mm x 7 mm piezoelectric film attached to the upper eyelid. An ELM was automatically identified whenever the output of the piezoelectric film, filtered between 3 and 20 Hz, exceeded 10 mV during a 250 ms epoch. Analog outputs from the Nightcap were digitized and stored along with the polysomnographic data, permitting precise temporal alignment of the two systems.

Quantitative analysis of EOG and ELMs

Stage 1 sleep was scored as the first of four consecutive 15-s epochs in which occipital alpha rhythm either was absent or was present in <50% of the epoch. This is in keeping with the criteria used in clinical practice (1 min of continuous stage 1 is the minimum required; see Carskadon et al. 1986). EOG recordings were visually inspected from lights-out to the onset of stage 1 sleep. Analyses of EOG and ELM activity were limited to epochs preceding the onset of stage 1 sleep.

The transition from wakefulness to sleep is not only characterized by the appearance of SEMs, but also by a progressive decrease in fast eye movements and eye blinks as well (Santamaria and Chiappa 1987). We therefore scored the EOG for each 2.5-s epoch as follows: (i) ‘FEM’ epochs – fast eye movements lasting more than 250 ms and <1 s; (ii) ‘SEM’ epochs – SEMs lasting more than 1 s; and (iii) ‘NEM’ epochs – no detectable eye movements. FEMs and SEMs were scored regardless of their amplitude, except that eye movements that occurred coincident with body movements were excluded from analysis. As eye blinks appeared primarily at the beginning of trials, coincident with body movements, they were largely excluded from analyses, and accounted for only a small proportion of FEM epochs.

RESULTS

Correspondence between ELM and SEMs

The number of ELMs was calculated for each 2.5-s epoch and averaged separately for epochs scored as FEM, SEM and NEM. The results for each subject were then averaged across the four naps, as no significant differences were detected between naps. On average, 0.7 ± 0.1 (mean ± SEM) ELMs were recorded in SEM epochs, compared with 2.3 ± 0.3 in NEM epochs and 4.9 ± 0.2 in FEM epochs (Newman–Keuls post hoc test: F(2,26) = 75.9, P < 10–10).

Based on this high correspondence between ELMs and SEMs on a time resolution of 2.5 s, we predicted that longer epochs would show a decrease in ELM density as the time spent in SEMs increased. To test this hypothesis, the density of ELMs was calculated for 15-s epochs which were themselves placed into three conditions: (i) ‘high SEM’, when SEMs were present in at least 50% of the epoch; (ii) ‘low SEM’, when...
SEMs were present, but in <50% of the epoch; (iii) ‘NSEM’, when the epoch showed no slow eye movements. Less than 2% of epochs with SEMs contained other eye movements (i.e. eye blinks and saccades) and were excluded from analyses. ELM densities were then averaged across subjects for each condition. Instances where a subject had <5 epochs in a given condition were excluded.

The ELM density varied significantly with the amount of SEMs within 15-s epochs [Fig. 1a; repeated measures ANOVA, \( F(2,14) = 44.5; P < 10^{-6}; \varepsilon = 0.77 \)], with lower ELM densities correlating with longer times spent in SEMs (\( P < 10^{-8} \)). This result was observed in each of the 10 subjects (Fig. 1b). The inverse relationship between ELMs and SEMs (\( r = -0.78; P < 10^{-10} \)) is shown in Fig. 1c for both the group and individual subjects.

**ELM density as a predictor of SEMs**

To estimate the ability of ELM recordings to predict the appearance of SEMs, we calculated the percent of 2.5 s EOG-scored SEM and NSEM epochs with and without ELMs. Across subjects, 71.5% of epochs with no ELMs were accompanied by SEMs, while 86.4% of epochs containing ELMs showed no SEMs. As FEMs were usually coincident with higher ELM densities, they had the potential of inflating the actual predictive power of ELM density. However, the prediction of SEMs was equally accurate when FEMs were excluded from analyses (\( P > 0.2 \) for comparison of accuracy with and without FEMs). Indeed, 73.2% of epochs without ELMs contained SEMs, while 76% of epochs with ELMs, showed no evidence of FEM or SEM in the EOG channel. ELM density predicted the presence or absence of SEMs correctly in 81.9% of all epochs (3408 of 4161 epochs), and in 75% of epochs (2448 of 3265) without FEMs. The results are shown in Fig. 2 for each individual subject.

**DISCUSSION**

The aim of this study was to test the hypothesis that the previously observed dramatic drop of ELMs to zero at sleep onset (Cantero et al. 2002) paralleled the appearance of SEMs, which typically heralds the onset of stage 1 sleep. If this were so, the occurrence of SEMs in the transitional period preceding stage 1 would be accompanied by a concomitant decline in ELM density. This prediction was confirmed in the present study. The ELM density in 2.5-s epochs was an excellent correlate and predictor of SEMs in quiet wakefulness. Three lines of evidence support this conclusion: (i) 2.5 s SEM epochs contained only one-seventh as many ELMs as FEM epochs, and one-third as many ELMs as seen in NEM epochs; (ii) the number of ELMs in 15-s epochs decreased linearly as the percentage of time spent in SEMs within the epoch increased; and, most importantly (iii) ELM density could reliably (\( c. 82\% \) of the time) predict the presence or absence of SEMs in 2.5-s epochs, suggesting that it can predict changes in SEM frequency with a temporal resolution of 2.5 s.

Decreases in alertness which typically signal transition to sleep are characterized by numerous changes in central and peripheral activity. However, most of these changes are too slow to permit identification of losses of alertness with a resolution of <1 min. This is prohibitively long for such potentially dangerous situations as driving a car or operating dangerous equipment, which require sustained vigilance.

**Figure 1. Correlation of ELMs with SEMs.**

(a) Mean ELM density (ELMs per 15-s epoch) in epochs without slow eye movements (NSEM), with SEMs in <50% of the epoch (low SEM), and with SEMs in more than 50% of the epoch (high SEM); subject mean values (\( n = 10 \)); error bars = SEM; (b) individual data. (c) Changes in ELM density in 15-s epoch, as a function of time spent in SEMs. Individual (open circles) and grand average (filled circle) data are presented.
Previous studies have reported a high correspondence between changes in EOG activity and level of alertness. Thus, spontaneous eye blinking decreases before sleep onset (De Gennaro et al. 1996), and SEM activity shows a linear increase from wakefulness to sleep (De Gennaro et al. 2000).

To date, only spontaneous eye blinks had been recorded by procedures other than conventional EOG techniques, such as photo, video or reflecting techniques (e.g. Caffier et al. 2003; Hanowski et al. 2003). These recording procedures make spontaneous eye blinks a reliable tool to measure losses of alertness in typical work settings, different from those in the laboratory. Indeed, a recent study has reported that the duration of the eye blink measured by an infrared sensor correlates well with subjective drowsiness (Caffier et al. 2003). The main advantage of such procedures is their use of contact-free sensing. However, they are unable to provide an alerting signal with the temporal resolution of the ELM sensor (2.5 s).

These optical sensing systems must compute parameters such as eye-closing and reopening times over several eye closures before changes in blink duration can be meaningfully identified. Similar problems are seen in video camera systems that capture approximate glance direction and approximate level of eye closure (e.g. Hanowski et al. 2003).

Like spontaneous eye blinks, the occurrence of SEMs has been found to be tightly correlated with the subjective experience of drowsiness, as well as changes in the EEG (Akerstedt and Gillberg 1990). However, our results indicate that the ELM density is a better predictor of presleep SEMs than is EEG activity. Indeed, a strong relationship between SEMs and EEG spectral power is only seen when the time period of analysis includes the entirety of stage 1 sleep (De Gennaro et al. 2000).

This strong correlation between presleep ELM and EOG activity can be explained by the physiology underlying these processes. Activity in motoneurons innervating the levator palpebrae superioris is tightly related to activity of the extraocular motor system responsible for eyeball movements (Porter et al. 1989; for a review see Delgado-Garcia 1999). With the onset of drowsiness, the phasic activity of extraocular motoneurons decreases in frequency as the duration of spontaneous saccades increases (Henn et al. 1984). This decrease is probably accompanied by a relaxation of the levator palpebrae (leading to the drooping of the lids, so evident with sleepiness) which could account, at least in part, for the significant decline in ELMs that is coincident with the appearance of SEMs.

The activity detected by the eyelid sensor when there are no eye movements is likely to be caused by the sustained firing of tonic levator palpebrae motoneurons even as activity in motoneurons controlling extraocular muscles decreases. The firing rate of these extraocular motoneurons decreases during light sleep compared with the wake state (Henn et al. 1984). But the sustained firing of levator palpebrae motoneurons in the period immediately preceding sleep onset, would lead to the relatively high ELM frequency seen before sleep onset, despite the absence of eye movements. With the appearance of SEMs at the onset of light sleep, extraocular motoneuron activity ceases (Henn et al. 1984), and we suspect that levator palpebrae motoneurons simultaneously become silent, explaining the absence of ELMs during NREM sleep, when REMs are not present.

Both extraocular and levator palpebrae motoneurons are innervated by premotor neurons in the reticular formation. The activity of these premotor neurons is also modulated by changes in alertness. Pause neurons reduce their average firing rate by almost half during drowsiness, while fixation is still maintained, drop to zero during sleep onset and immediately recover their normal levels of activity upon awakening (Henn et al. 1984). Such changes in the activity of premotor neurons in the reticular formation may be the first detectable sign of changes in alertness, changes that are reflected immediately in the frequency of ELMs.

We have previously observed that ELM counts are good correlates of other EOG phenomena such as eye blinks and saccades during wake, as well as REM during sleep (Stickgold et al. 1996). The present study demonstrates that ELM density is highest when FEMs are present, is significantly reduced in the absence of eye movements, and drops to near zero with the appearance of SEMs. To our knowledge, no other ambulatory system can predict moderate changes in alertness with a time resolution of <1 min. As ELM density can predict the
occurrence of SEMs with a time resolution of 2.5 s, it holds the potential of being a valuable marker for sudden drops in alertness. Based on the strong relationship between EOG and drowsiness reported in previous studies, and the high ELM–EOG correspondence reported in the present study, we suggest that ELM density can be a valuable tool for the identification of critical decreases in alertness in occupational settings where such changes must be identified within seconds.

CONCLUSIONS

Results from the present study suggest that ELM activity, quantified using the Nightcap eye sensor, can be reliably used to determine changes in alertness during quiet wakefulness in humans. Across 15-s epochs, ELM density decreased significantly with the appearance of SEMs, which have been found to be a quite good correlate of subjective and objective sleepiness. This decrease in ELM density was more pronounced as the amount of SEMs within the epoch increased. ELMs could further distinguish 2.5-s epochs with SEMs from epochs without SEMs with a relatively high accuracy (c. 82%). Whether changes in ELM counts can predict other EOG phenomena in wakefulness under conditions of sustained vigilance is still unknown. However, the present results should encourage further study of ELM density as a rapid measure of alertness in occupational environments.

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