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ORIGINAL ARTICLE

The Effects of Sleep Deprivation on Oculomotor Responses

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ABSTRACT

Purpose: Fatigue due to sleep deprivation is one of the main causes of accidents. An objective and efficient method for determining whether the person is tired could provide a valuable tool in accident prevention. In this study, we evaluated whether oculomotor responses related to pupillary light reflex and saccadic velocity can identify subjects with sleep deprivation and whether these objective values correlate with subjective feeling of sleepiness.

Methods: Thirteen normal subjects (5 male, 8 female) participated in a 4-day study. During the first two days following a full night's (8 hr in bed) sleep, they underwent baseline automated oculomotor testing using the FIT-2500-Fatigue-Analyzer. Following a third full night's sleep, participants were then sleep-deprived for 28 hr. Ten measurements of automated oculomotor tests were performed during the sleep deprivation period. Visually-guided saccadic velocity (SV), initial pupil diameter (PD), pupillary constriction latency (CL), and amplitude of pupil constriction (CA) were assessed using the FIT-2500-Fatigue-Analyzer. The FIT-index, which expresses the deviation of the ocular parameters from the baseline measurements, was calculated. Correlation of oculomotor parameters with the subjective Stanford Sleepiness Scale (SSS) was performed.

Results: We found that oculomotor measures showed a significant increase in CL (298.6 to 308.4 msec, $P < 0.05$) and calculated FIT index (3.4 to 16.8, $P < 0.05$) and a significant decrease in SV (64.8 to 59.6 deg/sec) during sleep deprivation. The SSS was found to significantly increase over the sleep deprivation period (2.05 to 5.05, $P < 0.05$) and was significantly correlated with the FIT-index ($r > 0.66$, $P < 0.02$).

Conclusion: Evaluation of oculomotor responses, particularly CL and SV together with the FIT-index, might have practical applications for the assessment of an individual's state of alertness or fatigue. Correlation of the FIT-index to the SSS provides evidence for the potential usefulness of oculomotor function measurements in the detection of subjective sleepiness.

KEYWORDS: Fatigue; Oculomotor responses; Pupil; Pupillography; Sleep deprivation

INTRODUCTION

In our modern technological society, fatigue caused by sleep deprivation has become a problem of central importance in occupational activities that require vigilance and attention over an extended period of time, often involving late evening and night shifts. Fatigue due to sleep deprivation is considered to be one of the main causes of work, air, and surface traffic accidents.[1–6]

Although levels of fatigue can be subjectively assessed, it has been shown that this does not reflect the objective, physiological status of the tired person, mainly because subjective reports are biased by motivation, personal factors, experience, training etc. Hence, it is obvious that fatigue must be measured with objective methods. There are several autonomic parameters that are influenced by fatigue, and indeed several methods have been suggested, such as electrocardiogram, electroencephalogram,[7,8] rectal

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temperature,[9,10] blood pressure,[7] etc. However, none of these assessment methods has gained popular acceptance. This is likely due to inconvenience of use, difficulties in data accumulation, impractical use in field settings, and other causes that eventually rendered all these methods to be not cost-effective. Thus, there is an evident need to find practicable, non-invasive, yet reliable tools to measure sleep-related fatigue, and especially in subjects at high risk for accidents.

Pupillary activity is one of the most observable indicators of autonomic nervous system balance, and thus, was considered to have potential as a fatigue parameter. Pupillary constriction during fatigue was first described by Crawford in 1936;[11] however, the pioneers in recording pupil activity in total darkness during alertness and fatigue were Lowenstein et al.,[12] who described the so-called fatigue waves—slow oscillations in pupil size with high amplitude. Yoss et al. studied pupillary activity in total darkness in normal subjects and in narcoleptics, describing several stages of vigilance reflected in the pupillogram, ranging from full alertness to extreme drowsiness.[13–15] They noted that as the subject becomes sleepier, the pupil becomes smaller and starts to oscillate at a higher amplitude and slower frequency. Dark room pupillograms were subsequently used to study alertness in patients with sleep disorders and in healthy subjects.[16–19] More recent studies used computerized analyses to interpret the pupillogram.[20,21] Another oculomotor function, saccade velocity, was also shown to be influenced by sleep deprivation and fatigue.[22,23]

The use of ocular parameters as an indicator for fatigue is, however, limited by the inter-person variability in pupil size, amplitude, etc. Therefore, the use of these parameters could only be feasible by comparing the same parameter in the same person in different examinations. The purpose of this study was to evaluate the change in a variety of ocular parameters during sleep deprivation and to try to establish a uniform factor that takes into account the change in these parameters and, therefore, will be sensitive to fatigue.

METHODS

Subjects

We examined 13 healthy student volunteers. There were eight females and five males, aged 26 ± 2.4 (mean ± SD) years. Participants were recruited by notices posted on a university bulletin board. This study was approved by the Institutional Ethics Committee of Assaf Harofeh Medical Center, and a written informed consent was obtained from each subject after the nature and intent of the study was fully explained. The study protocol was consistent with the tenets of the Declaration of Helsinki for trials in human subjects. Potential subjects were initially screened by telephone to fulfill the inclusion criteria of being in a good mental and physical health without a history of sleep disorders. Subsequently, all subjects underwent a complete medical history interview and completed the Mini Sleep Questionnaire,[24] which is designed to screen for sleep disorders. A complete ophthalmologic examination including visual acuity, slit lamp, and fundus examination was performed. Exclusion criteria were: suspected sleep or other medical disorder as apparent from the sleep and general health questionnaires, ocular pathology, previous ocular surgeries, and current use of any medications.

Instruments

Subjective Sleepiness Assessment

The Stanford Sleepiness Scale (SSS),[25] a self-rating scale, was used to assess the participant's feeling of sleepiness. The scale contains seven statements describing a gradually increasing feeling of sleepiness (Table 1). Participants were asked to choose the statement from 1 to 7 that fully expressed their feeling of vigilance.

Objective Fatigue Measurements

The FIT 2500 Fatigue Analyzer (FIT, Pulse Medical Instruments, Inc., Rockville, Maryland, USA) was used for objective assessment of fatigue. This is a self-contained, fully automated, computer-controlled, commercially available optical tracking and recording system, which contains an infra-red pupillometry device together with an eye movements tracking system. Applicability of the device for assessment of oculomotor changes during partial and total sleep deprivation has been previously evaluated.[26,27]

Examination commenced as follows: subjects focused with their dominant eye on a low brightness

TABLE 1 Stanford Sleepiness Scale

Rating	Degree of sleepiness
1	Feeling active and vital; alert; wide awake
2	Functioning at a high level, but not at peak; able to concentrate
3	Relaxed; awake, responsive, but not at full alertness
4	A little foggy; let down; not at peak
5	Sleepy; woozy; prefer to be lying down; fighting sleep
6	Foggy; slowed down; beginning to lose interest in remaining awake
7	Almost in reverie; sleep onset soon; losing struggle to remain awake

light visible through a round opening in the device. When ready, the subject pressed a button to start the sequence. After 1 sec the center light extinguished while left- and right-side lights were alternately illuminated, and the subject was instructed to shift their gaze between them (total visual angle 26.8°). Saccade velocity was calculated at a sampling rate of 500 Hz with a calculated resolution of 0.6°. The subject then focused his gaze on a center fixation light and pupillary diameter was measured at a rate of 60 samples per sec. A flash of high-intensity bright light (0.2 sec duration) then stimulated the pupillary light response, and pupillary constriction latency was measured (time from flash to onset of pupil constriction). Pupillary constriction amplitude was derived from the difference between the pupillary diameter and the smallest after-flash diameter. If eye responses were not captured, as would occur with excessive blinking, head movement, or failure to direct gaze appropriately, the FIT issued an error message. The time for each test session was approximately 30 sec.

Participants were required to avoid caffeine, alcohol, and strenuous physical activity on the day preceding and during the study.

Examination in Alertness

Following a full night's sleep, measurements of the above parameters were recorded 12 times for each subject on Day 1 and Day 2 from 8:00 till 13:00 at 1-hr intervals.

Examination during Sleep Deprivation

On Day 3 following a full night's sleep (8-hour sleep, as monitored by an ActiGraph device; ActiGraph, Pensacola, Florida, USA), the subjects underwent the sleep deprivation evaluation. Ocular parameters and the subjective feeling of fatigue scale were recorded at: 08:00, 10:00, 12:00, 23:00, 01:00, 03:00, 05:00, 08:00, 10:00, and 12:00. Thus, each subject was sleep-deprived for at least 28 hr.

Data Analysis

Measurements done on the first two days were averaged and served as individual baseline parameters for each subject. In addition, the overall change in the combination of factors recorded was calculated as a FIT index using the equation as proposed by the manufacturer:

$$\text{FIT index} = \left((\text{PD} - \mu\text{PD})/\sigma\text{PD}\right)^2 + \left((\text{CA} - \mu\text{CA})/\sigma\text{CA}\right)^2 + \left((\text{CL} - \mu\text{CL})/\sigma\text{CL}\right)^2 + \left((\text{SV} - \mu\text{SV})/\sigma\text{SV}\right)^2$$

The values of μ and σ are the baseline mean and baseline standard deviation of each parameter for the individual. The FIT index takes into account changes in all four measured oculomotor parameters and expresses the deviation of these parameters from their calculated baseline.

The ten measurements taken during the sleep deprivation stage were compared to the baseline measurement recorded at the alertness stage. Comparison was performed by way of ANOVA for repeated measures using the Mixed model. The same analysis was carried out for the SSS. Whenever a significant time trend was found, pair-wise comparisons between each time point and baseline were conducted using Hochberg's method for significance level adjustment. The association between the recorded pupillary parameters and the SSS were evaluated using a two-tailed Spearman rank correlation coefficient. In addition, in order to avoid the calculation of multiple correlation coefficients, the Mixed model was applied to evaluate the association between the SSS and each one of the parameters.

All statistical analyses were performed using SAS for Windows version 9.1.3 (SAS Institute Inc., NC, USA). The Distribution of FIT index scores was skewed. The application of logarithm transformation to this parameter resulted in a fairly normal distribution as presented in the following Stem and Leaf, Boxplot, and Q-Q graphs. The same analysis (repeated measures analysis of variance using the Mixed model) was then performed on the transformed variable and similar results were obtained. An overall significant difference between time points and, in particular, the significant difference between baseline and 17, 19, 21, 24, 26 and 28 hours ($p = 0.0004$, 0.0054, 0.0003, 0.0228, 0.0128, and <0.0001, respectively) was seen. Applying the same transformation to all other variables did not result in any significant time trend.

RESULTS

Table 2 presents the mean values of evaluated papillary parameters during baseline and sleep deprivation assessments.

The FIT index showed the most robust and significant changes during sleep deprivation (Figure 1) Following 15 hr of sleep deprivation, FIT index's values were statistically significantly higher as compared to the measured baseline. Of the individual parameters, latency of pupillary constriction and saccadic velocity changed most significantly and consistently during sleep deprivation. During evaluations at sleep deprivation (hours 15, 21, 26, and 28) constriction latency values were significantly higher as compared to the baseline. Saccade velocity values were significantly decreased during sleep deprivation as measured at 24, 26, and 28 hr points. However, the changes in pupillary diameter and constriction amplitude values during

TABLE 2 Oculomotor parameters during alertness and sleep deprivation.

	PD	CL	CA	SV	FIT index
Baseline	5.9 ± 0.9	298.6 ± 22.4	1.3 ± 0.2	64.8 ± 5.7	3.4 ± 0.1
0	5.7 ± 0.8	301.5 ± 27.8	1.1 ± 0.3	63.6 ± 5.4	3.7 ± 3.0
2	5.8 ± 0.9	296.7 ± 27.2	1.2 ± 0.2	65.1 ± 8.6	3.7 ± 1.2
4	5.8 ± 0.9	296.4 ± 25.8	1.1 ± 0.2	65.3 ± 8.6	3.5 ± 1.7
15	6.0 ± 0.9	307.0 ± 27.4*	1.2 ± 0.4	63.6 ± 9.7	12.3 ± 10.8*
17	6.1 ± 0.8	306.9 ± 26.9	1.2 ± 0.3	61.1 ± 10.8	18.9 ± 17.0*
19	6.1 ± 0.9	302.1 ± 29.0	1.3 ± 0.3	63.6 ± 9.6	13.9 ± 11.7*
21	6.0 ± 0.7	304.4 ± 25.4*	1.3 ± 0.3	63.3 ± 9.2	16.9 ± 9.6*
24	6.1 ± 0.7	303.0 ± 24.3	1.2 ± 0.3	59.8 ± 8.3*	11.8 ± 5.9*
26	6.0 ± 0.9	306.1 ± 20.5*	1.2 ± 0.4	59.4 ± 8.3*	13.8 ± 13.5*
28	6.0 ± 0.9	308.4 ± 23.0*	1.0 ± 0.1	59.6 ± 8.0*	16.8 ± 10.1*

CA = amplitude of pupil constriction (mm); CL = pupillary constriction latency (msec); PD = initial pupil diameter (mm); SV = saccadic velocity (deg/sec).
*Significantly different from baseline ($P < 0.05$).

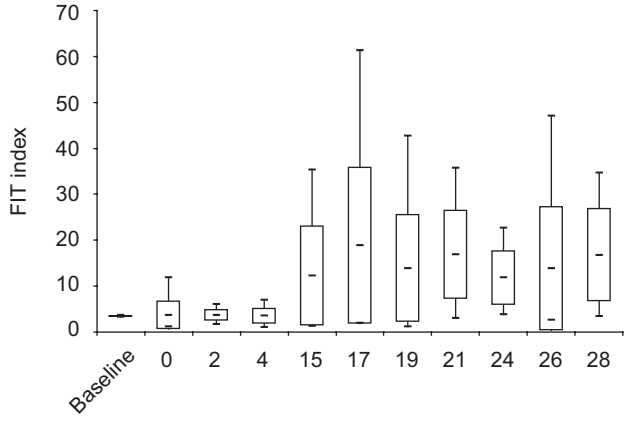

FIGURE 1 Box (mean ± SD) and whisker (smallest and largest values) plot showing distribution of FIT index at baseline and during the experiment.

sleep deprivation were not statistically significant in this study.

Subjective rating of sleepiness as assessed with the SSS showed an increase in sleepiness during sleep deprivation. This change was statistically significant from the 15-hr sleep deprivation time point and beyond (Table 3).

Significant positive correlation was found between the SSS and FIT index during alertness and fatigue ($r > 0.66$, $P < 0.02$) as measured at hour 0, 2, 19, 26, and 28 of sleep deprivation. Of the individual parameters, a significant negative correlation was found between Saccade velocity and SSS at alertness (hour 0, $r = -0.85$, $P < 0.001$) and at prolonged sleep deprivation (hour 28, $r = -0.74$, $P < 0.009$). Furthermore, SSS was positively correlated with pupillary constriction latency (hour 0, $r = 0.62$, $P < 0.05$) and negatively correlated with constriction amplitude (hour 0, $r = -0.66$, $P < 0.05$) and with pupillary diameter (hour 28, $r = -0.62$, $P < 0.05$). Using the Mixed model for evaluation of the association

TABLE 3 Stanford Sleepiness Scale score during sleep deprivation

Sleep deprivation (hours)	Score
0	2.05 ± 0.7
2	1.63 ± 0.5
4	2.46 ± 0.6
15	4.02 ± 0.4*
17	4.28 ± 0.4*
19	5.05 ± 0.6*
21	5.40 ± 0.9*
24	4.37 ± 0.6*
26	4.48 ± 0.8*
28	5.05 ± 0.7*

*Significantly different from baseline ($P < 0.05$).

between the SSS and each one of the parameters, we observed that only FIT index was significantly correlated with the SSS during the entire study period (Table 4).

The application of logarithm transformation to FIT index resulted in a normal distribution. The same analysis (repeated measures analysis of variance using the Mixed model) was then performed on the transformed variable and similar results were obtained. An overall significant difference between time points and, in particular, significant difference between baseline and 17, 19, 21, 24, 26, and 28 hr ($P = 0.0004$, 0.0054, 0.0003, 0.0228, 0.0128, and <0.0001, respectively).

DISCUSSION

The results of our study demonstrate a clear relationship between sleep deprivation, the subjective feeling of sleepiness, and changes in oculomotor function. Based on evaluation of these changes in individual oculomotor parameters, namely saccadic velocity, initial pupil diameter, pupillary constriction latency,

TABLE 4 Association between the Subjective Sleep Score and each one of the parameters using the Mixed model

Parameter	Time trend	*P*-value	Interaction with time
PD	0.024	0.90	0.73
CL	0.01	0.116	0.29
CA	-0.45	0.43	0.58
SV	-0.034	0.17	0.33
FIT index	-0.002	0.0036	0.095

CA = amplitude of pupil constriction (mm); CL = pupillary constriction latency (msec); PD = initial pupil diameter (mm); SV = saccadic velocity (deg/sec).

and amplitude of pupil constriction, the FIT index was calculated. This parameter showed the greatest magnitude of change during sleep deprivation and was highly correlated with a subjective feeling of sleepiness as expressed by the SSS. To the best of our knowledge this study is the first to utilize this index in assessment of sleep deprivation.

The SSS was shown previously to be a useful diagnostic tool in the assessment of sleepiness[25] and became widely adopted in neurophysiologic studies estimating subjective sleepiness.[28–32] We used this scale in our study for continuous assessment of feeling of sleepiness among participants during sleep deprivation. SSS scores were increased with prolonged sleep deprivation and were significantly different from alertness values.

Of the individual oculomotor parameters, saccade velocity decreased and constriction latency increased during sleep deprivation. These findings are in full agreement with reported results of other investigators.[26,27] Interestingly, pupillary diameter did not change with progressive sleep deprivation, a finding which is in agreement with some studies,[26,33] but at odds with some earlier studies.[19,34] Considering constant intensity of the ambient light and FIT's infra-red light illumination during measurement of pupillary diameter, plausibly that pupillary diameter is only dependent on the activity of the central nervous system. Similar observations of absence of significant change were found with pupillary constriction amplitude, consistent with previously published studies,[26,27,33] but in contrast to earlier studies such as the pioneer study of Lowenstein.[12] One explanation for these differences could be the difference in methodology. While studies showing consistent pupillary diameter and constriction amplitude changes during sleep deprivation were conducted under total dark adapted conditions,[19,35,36] the studies that did not show such correlation, including ours, were conducted under normal ambient light. Indeed, a recently published study of Yu et al.[37] showed high dependency of both pupillary diameter and constriction amplitude on the operational environment, including ambient luminance and time of day testing.

Visually-guided saccadic velocity was decreased during sleep deprivation, presenting an average of 8% decrease. Such a finding is consistent with the previously published observations of Thomas et al.,[38] who noted an 11% decrease in saccade velocity after a 24-hr sleep deprivation. This is also in close agreement with Rowland et al.[26] and De Gennaro et al.[23] who both demonstrated a significant decrease of 5–6% in saccadic velocity after one night of sleep deprivation. Moreover, saccade velocity was recently shown to be essentially resistant to the influence of environmental factors, such as changes in ambient light and time-of-day effects.[37]

An additional oculomotor parameter, pupillary constriction latency, was shown to be considerably influenced by sleep deprivation and increased from baseline. We measured a 3% increase of constriction latency time from alertness baseline, a finding highly consistent with a change of 2–3% following sleep deprivation as previously reported by Rowland et al.[26] Like saccadic velocity, constriction latency proved to be beyond influence of changes in ambient light levels and time-of-day measuring variations.[37]

Thus, we have demonstrated that using only one factor may not be reliable for the evaluation of vigilance. The FIT index, which takes into account changes in all four measured oculomotor parameters and expresses the deviation of these parameters from their calculated baseline, proved to be the most accurate and reliable parameter. Figure 1 graphically represents that during sleep deprivation, the FIT index was persistently increased as compared to values at baseline and alertness hours. The inter-person variability of FIT index was also increased during sleep deprivation. Such behavior of the FIT index may imply that during the alertness state oculomotor function of different subjects is similar, but reaction of the autonomic nervous system to prolonged sleep deprivation is very individual and some persons get "more tired" than others. Moreover, the FIT index was significantly positively correlated with the SSS through alertness and sleep-deprived hours. These properties of the FIT index suggest that it is the most reliable parameter in sleepiness evaluation. Interestingly, that similarly to subjective reports of sleepiness presented by the SSS score that was increased starting 11 p.m. till the end of the experiment, the FIT index values increased about the same time indicating objective fatigue. Both SSS and FIT index continued to be increased during the sleep-deprived night and the next morning, but no significant continuous elevation was noted during the prolonged sleep deprivation. Whether both of these indexes reach their saturation with night sleepiness due to circadian rhythms remains unclear from our

study and further research with a different design, specifically aimed to answer such questions, may be needed in this regard.

One of the possible limitations of our study was an age homogeneity and small sample size which did not account for sex differences during sleep deprivation. All of our subjects were young and healthy and this fact may be a potential drawback for generalization of our findings to the older population, as well as those with sleep disorders.

CONCLUSION

In conclusion, our study shows an alteration in a variety of oculomotor functions following sleep deprivation. By using different parameters of oculomotor response, the FIT index effectively presents neurophysiologic changes occurring during sleep deprivation. Thus, this parameter may be a useful objective tool in assessing sleepiness.

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