Increased spontaneous eye blink rate following prolonged wakefulness

Article *in* Physiology & Behavior · February 2007

DOI: 10.1016/j.physbeh.2006.09.023 · Source: PubMed

6 authors, including:

Giuseppe Barbato
Università degli Studi della Campania "Luigi Vanvitelli
42 PUBLICATIONS **1,171** CITATIONS
SEE PROFILE

Antonella Raffaella Paolillo
Centro di Psicoterapia Analitico Transazionale ad orientamento Psicodinamico
2 PUBLICATIONS **46** CITATIONS
SEE PROFILE

Gianluca Ficca
Università degli Studi della Campania "Luigi Vanvitelli
70 PUBLICATIONS **1,503** CITATIONS
SEE PROFILE

Journal of Sleep Research

Increased spontaneous eye blink rate following prolonged wakefulness.

Journal:	*Journal of Sleep Research*
Manuscript ID:	JOSR-06-062
Manuscript Type:	Regular Research Paper
Date Submitted by the Author:	30-Mar-2006
Complete List of Authors:	Barbato, Giuseppe; Second University of Naples, Psychology De Padova, Vittoria; Second University of Naples, Psychology Paolillo, Antonella; Second University of Naples, Psychology Arpaia, Laura; Second University of Naples, Psychology Russo, Eleonora; Second University of Naples, Psychology Ficca, Gianluca; Second University of Naples, Psychology
Keywords:	blink rate, dopamine, sleep deprivation, wakefulness

Increased spontaneous eye blink rate following prolonged wakefulness.

Giuseppe Barbato* , Vittoria De Padova, Antonella Raffaella Paolillo, Laura Arpaia, Eleonora Russo, Gianluca Ficca.

Department of Psychology, Second University of Naples, Italy

* Corresponding author :

Giuseppe Barbato, MD, PhD
Department of Psychology.
Second University of Naples.
Via Vivaldi 43. 81100 Caserta. ITALY
Phone : 0039-0823-274790
FAX : 0039-0823-274792
E-mail : Giuseppe.Barbato@unina2.it

SUMMARY

Spontaneous eye blink rate provides a non invasive measure of central dopamine activity. To analyze the role of dopamine activity in sleep deprivation, we assessed eye blink rate throughout prolonged wakefulness (from 10:00 a.m. to 07.00 a.m.) in 25 young normal subjects. Eye blink rate increased troughout the wakefulness period (repeated ANOVA df=7,168; F=2.9, p=0.007). Blink rates during the wakefulness period paralleled increases in sleepiness, suggesting that increased blink rate might reflect a dopamine mediated activation that counteracts rising sleep drive. These results suggest that antidepressant effects of sleep deprivation might be attributed to activation of the physiological mechanisms which regulates wake maintenance.

.

Key Words: eye blinking, dopamine, sleepiness, sleep drive, sleep deprivation

INTRODUCTION

Sleep deprivation (SD) is a consolidated technique of sleep-wake manipulation which has been used as an antidepressant treatment in depressed patients. It was firstly described by Pflug and Tolle in1971, who successfully treated with such procedure a depressed patient with severe insomnia. Since that first patient, several independent groups have used sleep deprivation to treat patients with major depression (Leibenluft and Wehr, 1992, Wirz-Justice and Van den Hoofdakker, 1999). Although rapid, the clinical improvement lasts one or few days, thus antidepressant effects are time limited, and in most cases, relapse occurs after recovery sleep.

The rapid onset of the clinical changes induced by sleep deprivation, and the rapid offset induced by the subsequent sleep recovery, has provided a model to investigate the pathophysiological mechanisms of affective disorders.

Changes in circadian and sleep-wake dependent phase relationships have been suggested as possible mechanisms for SD antidepressant effects. According to the "internal coincidence hypothesis" (Wehr and Wirz Justice, 1981), in depressive patients the circadian pacemaker is phase advanced, thus patients sleep at a wrong biological clock time, at a time when sleep is depressogenic. SD avoids the coincidence of sleep with this critical phase.

Neuroimaging studies have proposed that SD might work throughout decrease of a state of hyperarousal (Wu *et al.,* 1999). PET and SPECT studies have showed that patients with higher metabolic rates in limbic areas are more likely to improve after sleep deprivation (Ebert *et al.,* 1991). High metabolism in the ventral anterior cingulate Appears to predict those patients who improve after SD, while a decreased metabolism in the medial prefrontal cortex characterizes clinical improvement (Wu *et al.,* 1999). According to Van den Burg et al., 1992, sleep deprivation by inducing cerebral fatigue might break the distressing hyperarousal state of depressives patients, resulting in feelings of relief and tiredness.

Hypotheses on major neurotransmitters modification induced by SD have been also proposed to explain its therapeutic effect.

Since serotonin is implicated both in sleep and mood regulation, several studies have addressed its role in SD, providing however conflicting results. Sleep deprivation enhances serotonin turnover in animals, increases the firing rate of serotonin neurons in the dorsal raphe nuclei, down regulate presynaptic 5HT1A receptors (Prevot et al., 1996). Therapeutic response to SD has been associated with a functional polymorphism within the promoter of the 5-HT transporter gene (Benedetti et al., 1999). On the other hand, brain 5-HT levels do not significantly changes either after 24 hours (Borbely et al., 1980) or 72 hours of SD (Wesemann et al., 1983), neither significant changes of extracellular 5-Ht occur after SD (Bjorvatn et al., 2002). Furthermore, tryptophan depletion does not reverse sleep deprivation antidepressant effects but rather prevents depressive relapse after the recovery night (Neumeister et al., 1998), suggesting that SD does not exert its effects troughout serotonin system. It appears however that serotonin could have a role in the prolongation of the SD effects. Pindolol, a 5ht1A autoreceptor antagonist which augments serotonin release, prevents the short term relapse which follow SD (Smeraldi et al.,1999).

Since the therapeutic effect of sleep deprivation is acute and transient and the antidepressant effects normally involved in serotonin function are gradual and stable, it should be considered that SD mechanisms are different from those mediating the improvement obtained with antidepressant drugs.

Neuroendocrinological studies have suggested a possible role for dopamine function in the antidepressant SD effect. Calil and Zwicker (1986), found a decrease of plasma prolactin level, which is regulated by dopaminergic systems, in normal controls following SD. After SD, the prolactin response to sulpiride, a D2 receptor antagonist, resulted greater in depressed patients responder to SD compared to non responder, suggesting a altered receptor sensitivity possibly due to increased dopamine release in responders (Ebert et al., 1993). A higher striatal dopamine release in responders to sleep

deprivation has been shown using 123-iodobenzamide IBZM-SPECT (Ebert et al., 1994). Ebert et al., (1998) have hypothesized that the antidepressant effect of sleep deprivation is mediated by an enhanced dopamine release resulting in an amphetaminlike action of SD. Data from animal studies suggest that most of the behavioural changes induced by SD (hyperactivity, irritability, aggressiveness, hypersexuality, stereotypy, decreased need of sleep) might be mediated by changes in the sensitivity of D1 and D2 dopamine receptors.

Two studies have used spontaneous blink rate (BR), a non invasive measure considered an indicator of central dopamine activity, to test dopamine function after sleep deprivation. Barbato et al. (1995) reported increased blink rate following one night of total sleep deprivation in eight normal subjects. They also reported an inverse correlation between eye blink rate and alpha EEG power, with decreased power of the alpha -1 (8.0-10 Hz) EEG band and increased power of beta (12.25-16 Hz) band following sleep deprivation Ebert et al., (1998) reported that only depressed patients had a significantly higher increase of blink rate after SD. Sleep deprivation increased blink rate in the group of twelve depressed patients but not in the group of twelve healthy controls. The blink rate increase was proportional to improvements in depressive state after sleep deprivation.

To study the possible role of dopamine in sleep deprivation effects, we studied blink rate troughout a prolonged period of wakefulness. To investigate the role of vigilance factors, possibly implicated in blink rate regulation, and the effect on mood, subjective measures of sleepiness and mood were also assessed.

MATERIALS AND METHODS

Twenty-five young subjects 17 females, 8 males, age 18-23 years, (22,2 ± 1,9), were recruited for the experiment. All provided their informed consent. All subjects had no history of Axis I psychiatric illnesses, had normal physical examinations before the study and were not affected by any significant medical, neurological or ophtalmological illness. To exclude subjects with relevant sleep impairments and with any kind of substance abuse, a questionnaire assessing life and sleep habits was administered to all subjects.

To get accustomed to instruments, protocol and environment, subjects underwent a habituation session in the week preceding the day of the experiment. Subjects who were wearing contact lenses or who were suffering at the time of testing from a cold, flu, headache, or any condition interfering with visual sensitivity were excluded. No naps could be taken during the whole period of the experiment, and neither coffee nor alcoholics were allowed across the whole day and night sessions.

Vertical and horizontal electro-oculograms (EOGs) were recorded on a Grass Model 78 polygraph. Gold skin electrode were placed 3.0 cm above and 2.0 cm below the left eye as measured from the center of pupil to the center of the electrode (vertical EOG), and at the outer canthi (orizontal EOG). Eye blink was defined as a sharp high amplitude wave > = 100 microV and < 400 msec in duration. EOG records were obtained in an air conditioned room with indoor light of 150 lux at the level of the subject's eye.

During the eye blink recording, each subject sat silently in front of a blank, neutral wall. The subject was asked to remain awake, so that we could study basal ocular activity.

None of the subjects fell asleep during the recording sessions. Eye blink rate was taken as the mean number of blinks which occurred during the first 2 consecutive minutes after a 3 minute accommodation period, subjects were unaware of the accommodation period.

Subjects also performed a blink suppression time (BST) test, trying to avoid blinking for the longer time possible. This time interval was defined by the number of seconds from the end of eye blink to the first eye movement occurring during the suppression task.

Eye blink rate (BR) and blink suppression time were measured at eight points throughout a 24 hours period : 10 :00, 13 :00, 16 :00, 19:00, 22 :00, 1:00, 4:00, 7:00. Before each recording session, subjects were administered the Karolinska sleepiness Scale (KSS) (Akerstedt and Gillberg, 1990), and the visual analogue scale for mood.

To evaluate changes across time of blink parameters and sleepiness, statistical analysis was conducted through a one-way ANOVA for repeated measures, having time of day as factor. In case of significant results, post-hoc contrasts were performed in order to check the exact measures generating the difference. A Spearman analysis of correlation was used to assess correlations between the eye blink rate and the eye blink suppression time.

RESULTS

Blink rate increased significantly across the 24 hours period, (fig.1), (N= 25 ; df=7,168; F=2.9, p=0.007); as shown by post-hoc contrasts, at 7:00, after sleep deprivation, blink rate was significantly higher than at 10:00 (HSD Tukey p=0.014).

A similar pattern was shown by the sleepiness scores according to the Karolinska Sleepiness Scale, (fig.2), (N=25 ; df = 7,168 ; F = 19,1 p=0.0001)

No significant changes in eye blink suppression time (N= 22; df= 7,147 ; F=1.45, p=0.19) and in self evaluation of mood (N=19 ; df=7,126, F=1,7, p= 0.10) were found. For the eye blink suppression time a decreasing trend at the evening recording was recognizable.

A significant negative correlation between eye blink rate and the ability to suppress eye blink was found only at five (10:00, 13:00, 1:00, 4:00, 7:00) of the eight time points examined, (table 1).

DISCUSSION

In the present study, spontaneous eye blink rate showed a progressive increase troughout the wake prolongation, higher values were found at the last recording, at 7:00 A.M., following a whole night of sleep deprivation. The result confirm and extend our previous findings that eye blink rate increases following sleep deprivation (Barbato *et al.,* 1995), while a stable pattern is present in morning, midday and afternoon sessions (Barbato *et al.,* 2000) .
Using a constant routine protocol, Cajochen et al. (1998) have shown that blink rate yielded peak levels after 16 hours of sustained wakefulness and declined thereafter.
Considering that blink rate is considered an indicator of central dopamine activity (Karson et al., 1990), our findings are in favour of a progressive increase of dopamine activity during wake prolongation, and suggest a dopamine activation following sleep deprivation. It is interesting that usually the time course of a positive response to SD in depressed patients begins in the second half of the night, at a time when the rise on eye blink rate occurred.
The increase in subjective sleepiness across the night suggests that dopamine mechanisms may counteract the somnolence and allow the subject to stay awake despite the concomitant increase on sleep pressure.
Previous studies have suggested that physiological arousal and sleep drive are relatively independent processes (Sangal et al., 1994; Jones, 1994). Bonnet and Arand (1998) have found that sleepiness as measured by the Multiple Sleep Latency Test (MSLT) varies as a function of preceding activity. Compared to watching television for 15 minutes, a 5 minute walk, by inducing an increase in physiological arousal, increases sleep latency.
Objectively measurable sleepiness appears as the result of the combination of sleep drive and arousal (Bonnet and Arand, 1998). Physiological arousal may mask sleepiness by override a cumulated sleep drive.

Folkard and Akerstedt (1991) have proposed a three process model for the regulation of sleepiness/alertness. The changes of the daytime alertness resulting by the combined action of a homeostatic process, a circadian process and a sleep inertia. Edgar et al. (1993) have also proposed that the build-up of daytime sleep drive is usually unexpressed because it is opposed by an alerting process generated in the SCN.

The dopaminergic activation reported in the present study might be responsible for an increase in arousal levels which could overpower the rising sleep drive, in accordance with the sleep opponent process identified by Edgar et al.(1993). In a previous study (Barbato et al., 1995) we found that blink rate increased and relative power of alpha EEG decreased following one-night sleep deprivation. Post SD changes of blink rate and alpha activity resulted inversely correlated.

Dumont et al. (1998) have reported that the waking EEG between 18.00-24.75 Hz was correlated with subjective sleepiness and may reflect the increasing effort made by subjects to perform the task as sleep deprivation lengthened.

This view appears also in accordance with the changes in blink rate as a function of time on task (Morris and Miller, 1996; McGregor and Stern, 1996, Brookings et al., 1996), dopamine activity may increase to sustain the effort of the subject to cope with the task despite increasing levels of fatigue.

A second eye blink parameter that was analyzed in the present study was the duration of voluntary suppression of eye blinking. Few authors have analyzed this parameter. Bracha and Karson have reported (unpublished report cited in Karson et al., 1990) that blink voluntary suppression in schizophrenic patients was shorter than in normal subjects. This variable appears inversely correlated to blink rate, being shorter when the blink rate is higher. The duration of blink suppression showed a “U” shape profile across time: at the first four points it was specular to the increasing profile of blink rate, while at the last three points it returned to morning and afternoon levels, also the two measures did not show consistent levels of negative correlations, suggesting that different factors could contribute to the control of the two parameters. Subjective levels of cooperativeness and motivation may specifically

interfere with the task of suppressing blink rate. Furthermore, the ability to suppress blink may more closely reflect the tendency of sleep to overpower wakefulness (i.e.: manifest sleepiness), while blink rate, as previously discussed, may reflect arousing processes.

The present findings are consistent with the hypothesis that sleep deprivation might produce a central dopamine increase as suggested by previous studies. These results also suggest that antidepressant effects of sleep deprivation might be attributed to an activation of physiological mechanisms which regulates wake maintenance.

REFERENCES

Akerstedt, T., Gillberg, M. Subjective and objective sleepiness in the active individual. *International Journal of Neuroscience,* 1990, 52: 29-37.

Barbato, G., Ficca, G., Beatrice, M., Casiello, M., Muscettola, G., Rinaldi, F. Sleep deprivation effects on eye blink rate and alpha EEG power. *Biological Psychiatry,* 1995, 38: 340-341.

Barbato G, Ficca G, Muscettola G, Fichele MT, Beatrice M, Rinaldi F. Diurnal variation in spontaneous eye-blink rate. *Psychiatry Res,* 2000, 93: 145-151.

.

Benedetti, F., Serretti, A., Colombo, C., Campori, E., Barbini, B., Di Bella, D., Smeraldi E. Influence of a functional polymorphism within the promoter of the serotonin transporter gene on the effects of total sleep deprivation in bipolar depression. *Am J Psychiatry,* 1999,156:1450-2.

Bjorvatn, B., Gronli, J., Hamre, F., Sorensen, E., Fiske, E,. Bjorkum, A.A., Portas, C.M., Ursin, R. Effects of sleep deprivation on extracellular serotonin in hippocampus and frontal cortex of the rat. *Neuroscience,* 2002, 113: 323-30.

Bonnet, M.H., Arand, D.L. Sleepiness as measured by modified multiple sleep latency testing varies as a function of preceding activity. *Sleep*, 1998, 21: 477-483.

Borbely, A.A., Steigrad, P., Tobler, I. Effect of sleep deprivation on brain serotonin in the rat. *Behav Brain Res*, 1980 1: 205-10.

Brookings, J.B., Wilson, G.F., Swain, C.R. Psychophysiological responses to changes in workload during simulated air traffic control. *Biological Psychology* , 1996, 42: 361-377.

Cajochen, C., Khalsa, S.B.S., Czeisler, C.A., Dijk, D.J. Circadian variation of slow eye movements during sustained wakefulness. *6th Meeting of the Society for Research on Biological Rhythms*, 1998 Abstract #1, page 33.

Calil, H.M., Zwicker ,A.P. Effects of desipramine and total sleep deprivation on hormonal levels of healthy subjects. *Psychiatry Res*, 1986, 2: 337-348.

Dumont, M., Macchi, M.M., Carrier, J., Lafrance, C., Hebert, M. Time course of narrow frequency bands in the waking EEG during sleep deprivation. *Neuroreport*, 1999, 10: 403-407.

Ebert, D., Kaschka, W.P, Stegbauer,P., Schrelll, U. Prolactin response to sulpiride in depression before and after sleep deprivation. *Biol Psychiatry,* 1993, 35: 880-885.

Ebert, D., Feistel, H., Barocka, A., Kaschka, W. Increased limbic blood flow and total sleep deprivation in major depression with melancholia. *Psychiatry Res.* 1994, 55: 101-9.

Ebert, D., Feistel, H., Barocka, A. Effects of sleep deprivation on the limbic system and the frontal lobes in affective disorders: a study with Tcggm HMPAO SPECT. *Psychiatry Res*, 1991, 40: 247-251.

Ebert, D., Berger, M. Neurobiological similarities in antidepressant sleep deprivation and psychostimulant use: a psychostimulant theory of antidepressant sleep deprivation. *Psychopharmacology (Berl),* 1998, 140: 1-10.

Edgar, D.M., Dement, W.C., Fuller, C.A. Effect of SCN lesions on sleep in squirrel monkeys. *Neuroscience,* 1993,13: 1065-1079.

Folkard, S., Akerstedt, T. A three process model of the regulation of alertness and sleepiness. In: Ogilvie, R., Broughton, R. (Eds.). Sleep, arousal and performance: problems and promises. *Birkhauser, Boston*, 1991, 11-26.

Jones, B.E. Basic mechanisms of sleep-wake states. In: Kryger, M., Roth, T., Dement, W.C. eds. Principles and practice of sleep medicine. Saunders,Philadelphia, 1994, 145-162.

Karson, C.N., Dykman, R., Paige, S.R. Blink rates in schizophrenia. Schizoprenia *Bullettin,* 1990, 16: 345-354.

Lavie, P. Ultrashort sleep waking schedule.III. ”Gates” and “Forbidden zones” for sleep. *Electroncephalography Clinical Neurophysiology*, 1986, 63: 414-425.

Leibenluft, E., Wehr, T.A. Is sleep deprivation useful in the treatment of depression? *Am J. Psychiatry*, 1992, 149: 159-168.

McGregor, D.K., Stern, J.A. Time on task and blink effects on saccade duration. *Ergonomics*, 1996, 39: 649-60.

Mitler, M.M., Gujavarty, K.S., Browman, C.P. Maintenance of wakefulness test: a polysomnographic technique for evaluating treatment efficacy in patients with excessive somnolence. *Electroencephalography Clinical Neurophysiology*, 1982, 53: 658-661.

Morris, T.L., Miller, J.C. Electrooculographic and performance indices of fatigue during simulated flight. *Biological Psychology*, 1996, 42: 343-60.

Neumeister, A., Praschak-Rieder , N., Hesselmann, B., Vitouch, O., Rauh, M., Barocka, A, Tauscher, J. Kasper S.Effects of tryptophan depletion in drug-free depressed patients who responded to total sleep deprivation. *Arch Gen Psychiatry*, 1998, 55: 167-72.

Pflug, B., Tolle, R. Therapie endogener Depressionen durch Schlafentzug. *Nervenarzt,* 1971, 42: 117-124.

Prevot, E., Maudhuit, C., Le Poul, E., Hamon, M., Adrien, J. Sleep deprivation reduces the citalopram-induced inhibition of serotoninergic neuronal firing in the nucleus raphe dorsalis of the rat. *J Sleep Res*., 1996, 5: 238-45.

Sangal, R.B., Thomas, L., Mitler, M.M. The maintenance of wakefulness test (MWT) and the multiple sleep latency test (MSLT) measure different abilities in patients with sleep disorders. *Chest,* 1992, 101: 898-902.

Smeraldi, E., Benedetti, F., Barbini, B., Campori, E., Colombo, C. Sustained antidepressant effect of sleep deprivation combined with pindolol in bipolar depression. A placebo-controlled trial. *Neuropsychopharmacology*. 1999, 20: 380-5.

Van Den Burg, W., Beersma, D.G., Bouhuys, A.L., Van Den Hoofdakker, R.H. Self-rated arousal concurrent with the antidepressant response to total sleep deprivation of patients with a major depressive disorder: a disinhibition hypothesis. *J Sleep Res.,* 1992 1: 211-222.

Wehr, T.A., Wirz Justice, A. Internal coincidence model for sleep deprivation and depression. *In Koella WP, editor. Sleep*, 1980, Basel:Karger 26-30.

Wesemann, W., Weiner, N., Rotsch, M., Schulz, E. Serotonin binding in rat brain: circadian rhythm and effect of sleep deprivation. *J Neural Transm Suppl.*, 1983, 18: 287-94.

Wirz-Justice, A., Van den Hoofdakker, R.H. Sleep deprivation in depression: what do we know, where do we go? *Biol Psychiatry* 1999, **46**: 445-53.

Wu, J., Buchsbaum, M.S, Gillin, J.C., Tang, C., Cadwell, S., Wiegand, M., Najafi, A., Klein, E., Hazen, K., Bunney, W.E.Jr, Fallon, J.H., Keator D.Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulate and medial prefrontal cortex. *Am J Psychiatry*, 1999, 156: 1149-58.

Table 1

Relationship between eye blink rate (BR) and blink suppression time (BST)

Time	BR	BST	rho	p
10 :00	18 ± 11	28.9 ± 20.4	-0.46	0.03
13 :00	20 ± 13	29.4 ± 28.0	-0.54	0.01
16 :00	19 ± 11	26.0 ± 29.2	-0.27	ns
19 :00	21 ± 12	16.0 ± 14.5	-0.19	ns
22 :00	21 ± 13	19.4 ± 20.4	-0.21	ns
01:00	23 ± 13	27.4 ± 33.5	-0.57	0.009
04:00	24 ± 14	24.0 ± 26.5	-0.54	0.02
07:00	25 ± 14	29.2 ± 29.3	-0.69	0.002

Eye blink rate (BR): mean number of blinks during 2 consecutive minutes.

Blink suppression time (BST): time interval from the end of eye blink to the first eye movement occurring during a blink suppression task.

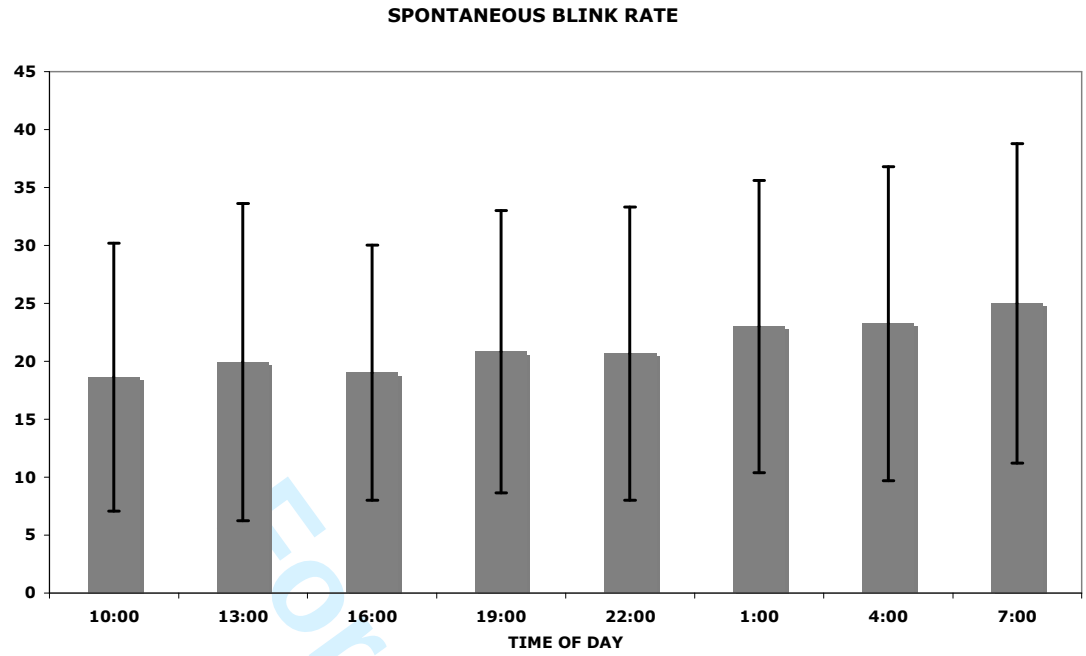

Figure 1. Average profiles of blink rate during the period of prolonged wakefulness

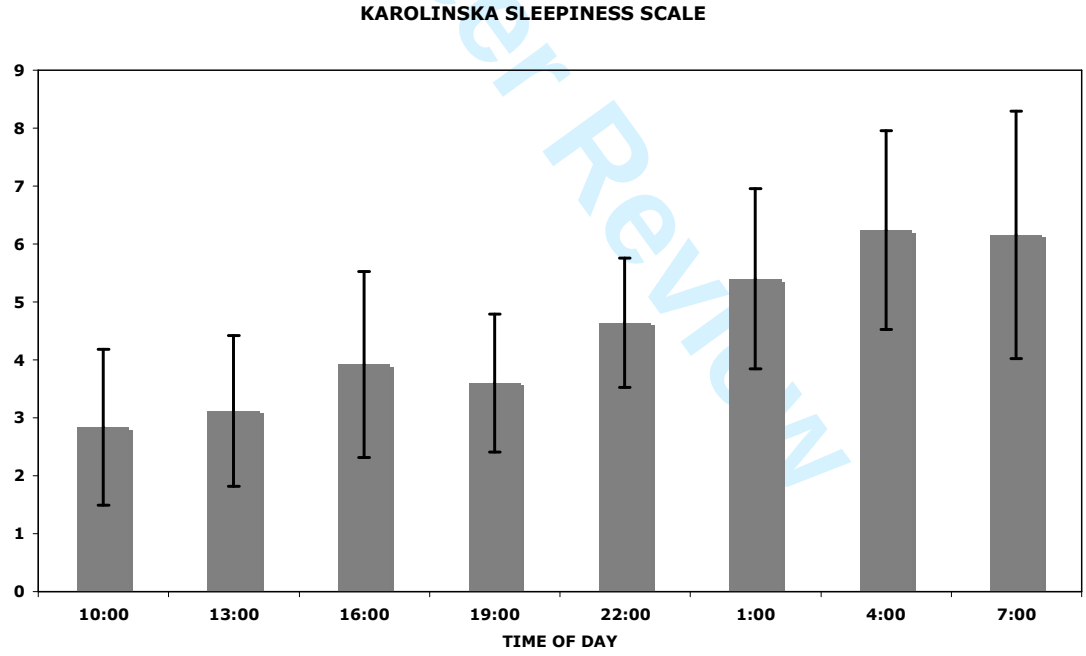

Figure 2. Average profiles of Karolinska Sleepiness Scale during the period of prolonged wakefulness