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# Diurnal variation in spontaneous eye-blink rate

Giuseppe Barbato[a,b,*], Gianluca Ficca[b], Giovanni Muscettola[a], Mariateresa Fichele[a], Michele Beatrice[a], Franco Rinaldi[a]

[a] *Department of Neuroscience and Behavioral Science, Section of Psychiatry, University Federico II, Naples, Italy*
[b] *Department of Psychology, Second University of Naples, Via Vivaldi, 43, 81100 Caserta, Italy*

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**Abstract**

The daily pattern of spontaneous eye-blink rate (BR), a non-invasive peripheral measure of central dopamine activity, was investigated in 24 healthy subjects. The spontaneous eye-blink rate showed a stable pattern in morning, midday and afternoon hours. A significant increase was found at the evening time point (20.30 h). The finding is suggestive of a late evening increase of central dopamine activity. An increased level of subjective sleepiness was also found at the same evening point, at a time corresponding to the 'evening wake maintenance zone' or the 'forbidden zone for sleep'. A possible hypothesis is that the 'forbidden zone for sleep' may reflect a dopamine-mediated activation that counteracts a rising sleep drive. The role of diurnal variation of dopamine function should be considered both in the choice of the drug treatment regimen, and in the evaluation of biological and neuropsychological parameters. 

*Keywords:* Eye movements; Dopamine; Circadian rhythms; Sleepiness

## 1. Introduction

Clinical studies on patients with dopamine-related illnesses suggest a diurnal variation of dopamine activity. Patients with hereditary progressive dystonia (Segawa syndrome) show a remarkable diurnal fluctuation of symptoms, which become more severe towards the evening (Wang et al., 1994). An afternoon worsening of tardive dyskinetic symptomatology has been described in neuroleptic-treated patients (Hyde et al., 1995).

* Corresponding author. Department of Psychology, Second University of Naples, Via Vivaldi, 43, 81100 Caserta, Italy. Tel.: +39-0823-274790; fax: +39-0823-282320.
*E-mail address:* md1006@mclink.it (G. Barbato)

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The number of acute dystonic reactions following neuroleptic administration shows a significant distribution across the day: 80% of the episodes occurring between 12.00 and 23.00 h (Mazurek and Rosebush, 1996).

Previous studies on daily variations of dopaminergic activity in humans have mainly relied on plasma levels of the major dopamine metabolite, homovanillic acid (HVA). Doran et al. (1985) reported the highest levels of plasma HVA at night. In contrast to control subjects, schizophrenic patients did not show such a significant variation. Sack et al. (1988) found a diurnal rhythm of plasma HVA in depressed patients and normal subjects. They reported that HVA levels were highest in the morning and early afternoon and at nighttime. However, the rise in the morning and afternoon hours was not confirmed when the subjects were analyzed in a constant routine day protocol, suggesting that these increases were possibly due to a masking effect of diurnal activities. A number of confounding factors may account for these discrepancies in HVA data. Studies in rodents (Sternberg et al., 1983) and in humans (Swann et al., 1982) found that only 25–40% of total free levels of plasma HVA are derived from the central nervous system. Furthermore, plasma HVA levels appear strongly influenced by diet and motor activity (Kendler et al., 1983).

The spontaneous eye-blink rate (BR) provides a non-invasive peripheral measure of central dopamine activity (Karson et al., 1990). The eye-blink rate is reduced in Parkinson's disease (Karson, 1983), whereas it is increased in schizophrenia (Stevens, 1978; Karson et al., 1990). Because of this relationship with dopamine activity, eye-blink frequency has been used as a parameter to monitor the effects of neuroleptic treatment (Bartko et al., 1990; Mackert et al., 1991; Adamson, 1995). The eye-blink rate is reduced by neuroleptics, and a decreased variability in blink rate after neuroleptic treatment has been suggested as a possible marker of the development of neuroleptic tolerance (Mackert et al., 1991).

The eye-blink rate has also been used to test dopamine activity in patients with seasonal affective disorder (SAD). Depue et al. (1989, 1990) found an increased blink rate in SAD patients that was normalized by light therapy. Although Barbato et al. (1993) failed to replicate the finding of increased blink rate in SAD, they also found a decreased blink rate following light therapy in premenopausal SAD patients, suggesting that light therapy might stimulate the activity of structures which inhibit the blink rate.

Individual blink rate appears to be influenced by psychophysiological factors. In their seminal study, Ponder and Kennedy (1927) implicated higher nervous processes as the major determinant of blink enhancement and inhibition. Higher levels of activation or arousal are associated with elevated blink rate (Stern et al., 1984). Blinks occur more frequently when subjects perform tests involving higher levels of attention (Gille et al., 1977; Tanaka and Yamaoka, 1993). A higher level of electroencephalographic (EEG) activation has also been associated with an increased eye-blink rate (Gille et al., 1977).

Karson et al. (1990) have hypothesized a functional linkage between eye-blink rate and alpha EEG activity. In their view, the eye-blink rate is regulated through a blink alpha neurocircuit (BANC) which begins in rostral pons and involves subcortical structures (midbrain tectum, substantia nigra, lateral geniculate bodies) and the occipital cortex. An increased blink rate may be related to a reduced inhibitory activity of the occipital cortex.

Previous studies have found that blink rate changes as a function of time on task (Wilson and Fisher, 1991; McGregor and Stern, 1996; Brookings et al., 1996). Morris and Miller (1996) found that variation in blink rate was one of the best predictors of changes in error rates during simulated flight between 13.00 and 17.30 h (Morris and Miller, 1996). Increased blink rates parallel the decline in task performance, suggesting that blink rate could reflect an increased level of fatigue (Stern, 1994).

Although some studies have addressed blink rates across time intervals, to the best of our knowledge, no study has systematically investigated a spontaneous diurnal variation of blink rate. Thus, the aim of the present study was to assess blink rates at different times of the day. To

investigate the role of vigilance factors, possibly implicated in blink-rate regulation, subjective and objective measures of sleepiness were also assessed.

## 2. Methods

Twenty-four young subjects (16 females, 8 males), aged 18–23 years, were recruited for the experiment. All provided their informed consent. The 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 ophthalmological illness. To exclude subjects with sleep impairments or substance abuse, a questionnaire assessing life and sleep habits was administered to all subjects.

To accustom them to the instruments, protocol and environment, all 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 experiment, and neither coffee nor alcoholic beverages were allowed across the whole day session.

For the eye-blink recording, subjects were asked to sit silently in front of a blank, neutral wall; none of them fell asleep during the test. Vertical

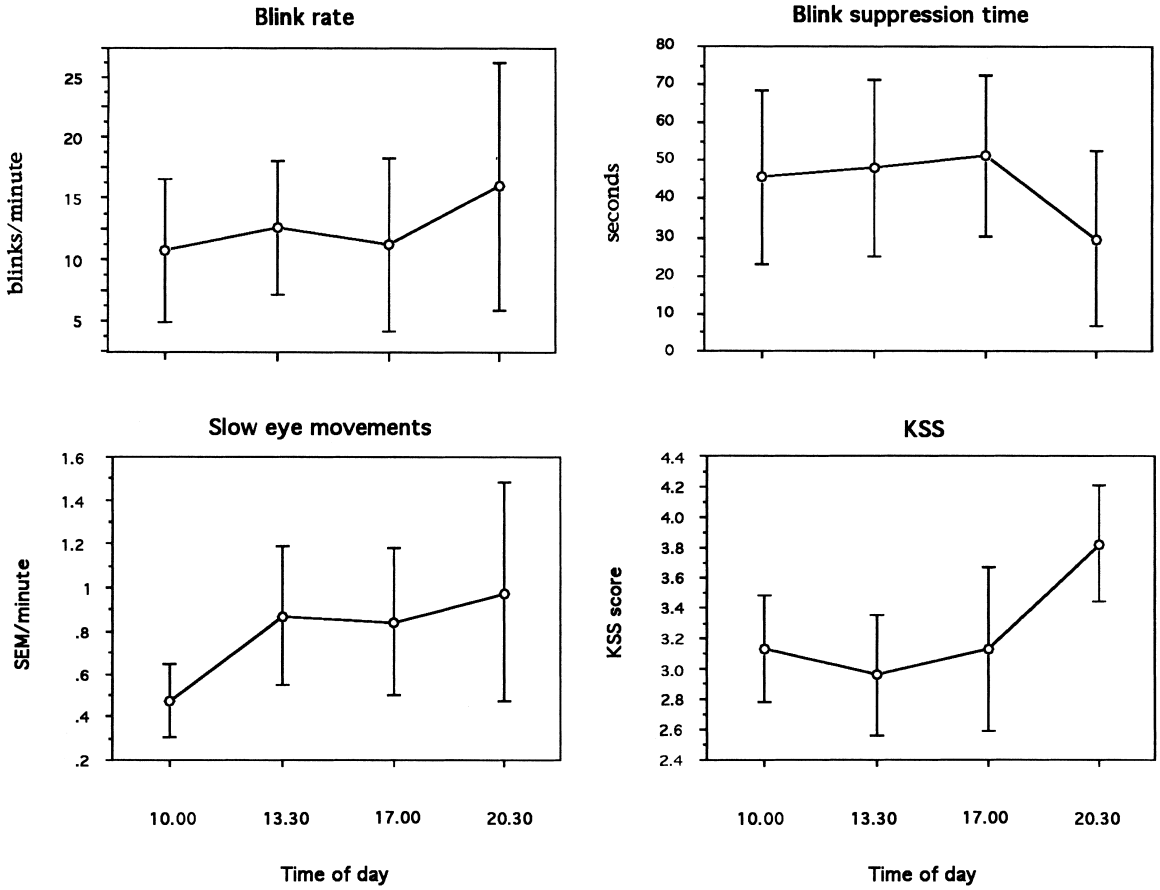


Fig. 1. Diurnal average profiles of blink rate, blink suppression time, slow eye movements and Karolinska Sleepiness Scale.

and horizontal electro-oculograms (EOGs) were recorded on an Oxford CEEGRAPH polygraph. Gold skin electrodes were placed above and below the left eye, and at the outer canthi. An eye blink was defined as a sharp high amplitude wave $\geq 100$ μV and $< 400$ ms in duration. The eye-blink rate was defined as the mean number of blinks that occurred during the first two consecutive minutes after a 3-min accommodation period; subjects were unaware of the accommodation period. The number of slow eye movements for each 2-min recording session was visually scored throughout horizontal EOGs.

Subjects also performed a blink-suppression test (BST) in which they tried to avoid blinking for the longest time possible. This time interval was defined by the number of seconds from the end of an eye blink to the first eye movement occurring during the suppression task.

The blink rate (BR), number of slow eye movements, and blink suppression time were measured at four points throughout the same day: 10.00; 13.30; 17.00; and 20.30 h. Before each recording session, subjects were administered the Karolinska Sleepiness Scale (KSS) (Akerstedt and Gillberg, 1990).

Changes across time of blink parameters and sleepiness were assessed with a one-way analysis of variance (ANOVA) for repeated measures with time of day as factor. A Greenhouse–Geisser correction for sphericity was applied to meet requirements of compound symmetry. In case of significant results, post-hoc contrasts were performed to check the exact measures generating the difference. Absent values have been excluded listwise. Spearman analysis was performed to assess correlations between eye-blink rate and eye-blink suppression time.

## 3. Results

All but one subject, who was not available for the 13.30 h session, completed the four experimental sessions. For another subject, blink suppression time was not recorded at the 17.00 h session.

Blink rate increased significantly across the day (Fig. 1) ($n = 23$; $F_{3,66} = 5.8$, $P = 0.005$); as shown by post-hoc contrasts, the point that contributed most to the overall result was that at 20.30 h, where blink rate was significantly higher than at the other three points (20.30 vs. 10.00, $F_1 = 12.3$, Greenhouse–Geisser = 0.002; 20.30 vs. 13.30 h, $F_1 = 5.2$, Greenhouse–Geisser = 0.04; 20.30 vs. 17:00 h, $F_1 = 10.2$, Greenhouse–Geisser = 0.005).

A similar pattern was shown for the KSS sleepiness scores (Fig. 1) ($n = 23$; $F_{3,66} = 3.7$, $P = 0.022$), with a significantly higher value at 20.30 h (20.30 vs. 10.00 h, $F_3 = 6.1$, Greenhouse–Geisser = 0.02; 20.30 vs. 13:30 h, $F_3 = 9.5$, Greenhouse–Geisser = 0.005; 20.30 vs. 17:00 h, $F_3 = 6.1$, Greenhouse–Geisser = 0.02).

No significant changes in eye-blink suppression time (Fig. 1) ($n = 22$; $F_{3,63} = 1.37$, $P = 0.26$) and slow eye movements (Fig. 1) ($n = 23$; $F_{3,66} = 2.0$, $P = 0.12$) were found. For eye-blink suppression time, a decreasing trend at the evening recording time point was recognizable. Significant negative correlations between eye-blink rates and ability to suppress eye blinks were found only at two (13.30 and 20.30 h) of the four time points examined (Table 1).

## 4. Discussion

In the present study, the spontaneous eye-blink rate showed a stable pattern in morning, midday

Table 1
Relationship between eye-blink rate (BR) and blink-suppression time (BST)[a]

| Time | BR | BST | rho | *P* |
|---|---|---|---|---|
| 10.00 | 11 ± 6 | 45.7 ± 52.5[b] | −0.285 | 0.1808 |
| 13.30 | 13 ± 5 | 48.1 ± 53.1[b] | −0.731 | 0.0006 |
| 17.00 | 11 ± 7 | 51.3 ± 48.3 | −0.329 | 0.114 |
| 20.30 | 16 ± 10 | 29.6 ± 53.1 | −0.543 | 0.009 |

[a] Eye blink rate (BR): mean number of blinks during two 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.

[b] Blink suppression time was not available in the record of one of the subjects.

and afternoon sessions, whereas a significant increase was present in the evening session. Using a constant routine protocol, Cajochen et al. (1998) also recently demonstrated that the blink rate reached peak levels after 16 h of sustained wakefulness and declined thereafter.

The findings are compatible with an evening increase in central dopamine activity and suggest an increased level of arousal throughout the course of the day. However, during the evening session, we found an increased level of subjective sleepiness, at the time point corresponding to the 'evening wake maintenance zone' (Strogatz and Kronauer, 1985) or the 'forbidden zone for sleep' (Lavie, 1986).

Previous studies have suggested that physiological arousal and sleep drive are relatively independent processes (Jones, 1994; Sangal et al., 1992). Bonnet and Arand (1998) have recently reported that sleepiness as measured by the Multiple Sleep Latency Test (MSLT) varies as a function of preceding activity. Compared with watching television for 15 min, a 5-min walk, by inducing an increase in physiological arousal, increases sleep latency.

Objectively measurable sleepiness appears to be the result of the combination of sleep drive and arousal (Bonnet and Arand, 1998). Physiological arousal may mask sleepiness by overriding an accumulated sleep drive.

Folkard and Akerstedt (1991) have proposed a three-process model for the regulation of sleepiness/alertness. Changes in daytime alertness are suggested to result from 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 not expressed because it is opposed by an alerting process generated in the suprachiasmatic nucleus.

The evening increase in 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). This hypothesis is consistent with the increase of eye-blink rate that follows a moderate amount of sleep deprivation. In a previous study (Barbato et al., 1995), we found that the blink rate increased significantly after 1 night of sleep deprivation. We 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 the beta (12.25–16 Hz) band following sleep deprivation. Dumont et al. (1999) have recently reported that the waking EEG between 18.00 and 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 is also in accord with the changes in blink rate that have been observed as a function of time on task (Brookings et al., 1996; McGregor and Stern, 1996; Morris and Miller, 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 observed (unpublished report cited in Karson et al., 1990) that voluntary eye-blink suppression in schizophrenic patients was shorter than in normal subjects. This variable appears inversely correlated to blink rate, being shorter when blink rate is higher. In agreement with this view, the duration of blink suppression showed a decreasing trend across time, in contrast to the increasing profile of blink rate. However, the two eye-movement measures did not show consistent negative correlations, suggesting that different factors could contribute to the control of these parameters. Subjective levels of cooperativeness and motivation may specifically interfere with the task of suppressing blink rate. Furthermore, the ability to suppress eye blinks 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. Analysis of blink rate and blink suppression time during the maintenance of wakefulness test (MWT; Mitler et al., 1982) may provide

a useful condition to assess the respective significance of the two eye-blink measures reported in this study.

The present findings confirm the diurnal variation in dopamine function suggested by previous clinical and biochemical studies. Although this variation needs to be confirmed in patient populations, it should be considered both at a clinical and a pharmacological level. A diurnal rhythm of depressive symptoms is well recognized in patients with major depression, whereas there are no specific data on the presence of a diurnal variation of psychotic symptoms in schizophrenic patients, and few studies have addressed possible alterations of circadian rhythms in these patients (Mills et al., 1977; Rao et al., 1993, 1994, 1995; Van Cauter et al., 1991; Wirz-Justice et al., 1997). Further studies should address the issue of diurnal variation in dopamine activity in view of its heuristic value both in the choice of treatment regimen, and in the evaluation of biological and neuropsychological modifications in schizophrenic patients.

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