Increased prefrontal event-related current density after sleep deprivation

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Abstract. To investigate how partial sleep loss affects temporal and spatial pattern of information flow, we analyzed sources of brain electrical activity during continuous attention test. Sixteen physicians recruited from the university hospitals participated in the study. Each participant served as his own control. All participants underwent two test sessions including the Stanford Sleepiness Scale (SSS), the Beck Depression Inventory (BDI), the Selective Reminding Test (SRT), and the Continuous Attention Test (CAT). The CAT items were used as stimuli in event-related potential (ERP) recordings. EEG was recorded from 21 electrodes, according to the international 10-20 system. The sources of bioelectrical activity were computed with low resolution electromagnetic tomography (LORETA). Estimated sleep time was significantly shorter on nights spent on duty than on nights of normal sleep at home. Sleep loss resulted in significant increase in SSS and BDI scoring, and impairment of immediate recall. Performance on the CAT remained relatively intact. Under the sleep loss condition compared to baseline, significant differences in brain activity occurred only for targets. Within the P1 time frame, sleep loss led to greater activation in the right Brodmann’s area 9/10. For the N1 component, significant differences were localized on the lateral surface of the right frontal lobe, in Brodmann’s areas 8 and 9. No significant effects of sleep deprivation on the P3 component were found. Our results are consistent with earlier data indicating that increased activation of the prefrontal cortex allows the maintainance of performance during periods of sleep loss.

Key words: brain functional imaging, LORETA, sleep deprivation
INTRODUCTION

Total sleep deprivation effects on human functioning have been well documented in laboratory studies. Many data indicate that there are behavioral domains particularly sensitive to sleep loss. Decrements in mood, lapses in attention, errors of omission, longer reaction time, and impairment of immediate recall have been consistently reported. Long, complex, sedentary and externally paced tasks are more vulnerable to sleep deprivation (for a review see Bonnet 2000). Moreover, sleep deprivation interferes with logical reasoning (Smith and Maben 1993), creative thinking (Horne 1988) and innovative or novel responses (Harrison and Horne 1998). Sleep deprived subjects select tasks of minimal difficulty (Engle-Friedman et al. 2003). A meta-analysis of 19 laboratory studies published between 1984 and 1993 revealed that sleep deprived individuals performed at a level 1.37 standard deviations lower than controls. Lower scores on cognitive testing have been documented after short term total sleep deprivation (less than 45 hours) and long term total sleep deprivation (more than 45 hours). The effects of partial sleep deprivation (sleep period of less than 5 hours in 24-hour period) appear to be qualitatively similar to those seen after total sleep deprivation (Pilcher and Huffcutt 1996). Decrements in cognitive performance may be also found after the curtailment of the total sleep time to 6 hours (Rosenthal et al. 1993) and even to 7 hours (Belenky et al. 2003). Repetitive sleep restriction results in cumulative deficits in cognitive performance. Some adaptation to repetitive moderate sleep restriction may occur. However, performance is then stabilized at a reduced level (Belenky et al. 2003, Dinges et al. 1997, Van Dongen et al. 2003).

Partial sleep loss is a common condition. According to Bonnet and Arand (1995), one third or more of normal adults may suffer from chronic sleep deprivation. Therefore, there is increasing concern about the potential deleterious effects of insufficient sleep on some groups in society. For instance, physicians work under conditions of repetitive sleep deprivation, although their work demands sustained attention and high quality of performance. A number of studies on the effects of sleep loss in residency training have utilized standardized psychomotor tests. Reaction time, alertness, sustained attention, creative thinking and mood were adversely impacted by sleep loss (for a review see Veasey et al. 2002). There are also investigations more directly related to real clinical performance. Smith-Coggins and coauthors (1994) demonstrated that when physicians slept during the night and worked during the day, they performed an intubation procedure significantly faster than when they were sleep deprived. Taffinder and coauthors (1998) found significantly more errors and observed that more time was required to perform simulated laparoscopic cholecystectomy on mornings after sleepless nights. In comparison to their performance when rested, interns deprived of sleep were significantly less able to recognize arrhythmic episodes on an electrocardiographic sustained-attention task (Friedman et al. 1971). These studies suggest that sleep loss contributes to adverse events and medical errors occurring in hospitals.

Much less is known about how the brain attempts to cope with the behavioral and cognitive effects of sleep deprivation. As Horne’s (1993) work first suggested, sleep loss may be associated with reversible prefrontal cortex dysfunction.


As far as we know, there are no published studies on sleep deprivation in which electrophysiological imaging has been used. To investigate how partial sleep loss affects temporal and spatial pattern of information flow, we analyzed sources of brain electrical activity during continuous attention test.

METHOD

Subjects

The study group consisted of 16 right-handed male volunteers, 7 psychiatrists, 3 interns and 6 surgeons,
recruited from the Warsaw Medical University hospitals. Their average age was 29.6 ± 4.7 years (range 25 to 41 years). All were medication free and in good physical health. No subject had current or past history of mental or sleep disorders. All of the subjects worked 2–7 nights per month (mean: 3.9 ± 1.4).

**Procedure**

Prior to entering the study, each subject kept a sleep diary for 7 days which allowed to confirm data on stability of sleep-wake behavior and assess sleep duration during night on duty and control night. The subjects served as their own controls and were tested twice, once after duty and once at a similar time after night spent at home. To control for practice effects, all were randomly assigned to two groups; half were first assessed when rested and half when deprived of sleep. At least 4 days elapsed between the two assessments. On experimental days, five tests were administered in the same order. The participants first completed three subjective ratings, including the Beck Depression Inventory (BDI) (Beck et al. 1961), the Visual Analogue Scale (VAS) and the Stanford Sleepiness Scale (SSS) (Hoddes et al. 1973). They then carried out the Continuous Attention Test (CAT) (Tiplady 1988) and the Selective Reminding Test (SRT) (Buschke and Fuld 1974). The VAS measured work stress experience during preceding 24 h, using a 100-mm line, scaled from 0 (negligible) to 100 mm (intense). The CAT visual stimuli consisted of 240 random presentations of abstract images built up from a variable pattern of 5 dark and 4 light squares. The stimuli were presented on a computer screen for 0.1 second. The interstimulus interval varied randomly from 1.0 to 2.5 s. The subjects had to press a button at the moment of detection of a direct repetition of the same pattern. Reaction time (RT) and error rates were recorded.

The CAT items were also used as stimuli in event-related potentials (ERP) recording. The direct repetitions of the same pattern were target stimuli. The probability of target appearance was 16%. Each CAT session lasted about 8 min. The task was repeated three times in order to obtain sufficient number of ERP sweeps. The three tasks were performed at one go, with a 5 min break between each task. The SRT was used to assess short-term and long-term components of memory. The given version of the SRT required approximately 8 min. All the tests were given in the morning, between 10:00 A.M. and 12:00 A.M., with a 5 min break between each test. The entire battery took 45 min to one hour. Each subject provided written informed consent. The study was approved by the University Ethics Committee.

**ERP recording and spatial analysis**

EEG was recorded from 21 electrodes, according to the international 10-20 system, with the reference electrode placed between Fz and Cz. Eye movements were monitored with a vertical electrooculogram. The sampling rate was 500 Hz, filters were set between 0.15 and 35.0 Hz. The impedance at each electrode was below 5 000 ohms. After visual screening, trials free of artifacts were stored for further analysis. The analyzed epoch was 1 000 ms, including 100 ms before each stimulus. Responses to correctly detected target and nontarget stimuli were averaged off-line and recalculated to the average reference. All further computations were performed with the aid of low resolution electromagnetic tomography (LORETA – version dated June, 2003) (Pascual-Marqui et al. 1994, 1999). Limits of successive components were assessed using Global Field Power (GFP) (Lehmann 1987, Lehmann and Skrandies 1980) of the grand average ERP, and the scalp map configurations, for all subjects and all conditions. P1 latency was defined as the maximal GFP value between 92 and 128 ms, N1 between 160 and 190 ms, and P3 between 338 and 546 ms. The sources of bioelectrical activity were computed with the June, 2003 version of LORETA-KEY. This version uses the three-shell spherical head model registered to the Talairach and Tournoux human brain atlas (Talairach and Tournoux 1988). Computations are restricted to cortical gray matter, and images represent bioelectrical power in each of the total 2 394 voxels.

**Statistical analysis**

Behavioral results and subjective rating data are given as mean and standard deviation. SPSS software was used to perform Wilcoxon’s Non-Parametric Test and Spearman Rank Order Correlation Test. Statistical significance of differences in the current source density under baseline and sleep loss conditions was assessed with statistical nonparametric mapping tests for paired samples, implemented in the version of LORETA used (Nichols and Holmes 2002).
RESULTS

Behavioral effects and subjective rating data

As can be seen in Table I, estimated sleep time was significantly shorter during night shifts than during day shifts. Mood state assessed by the BDI deteriorated significantly after duty as compared to baseline measures. Higher scoring on VAS was associated with significantly more negative mood ratings after night duty ($\rho = 0.735$, $P < 0.001$). Significantly higher ratings on the SSS were found after sleep restriction.

No significant differences were found for the number of omissions or commissions. Reaction time in the CAT session 1 was significantly slower for sleep loss conditions than for control conditions.

Following sleep loss, the participants performed more poorly on immediate recall, but differences in learning failed to yield significant results.

Event-related activity

Figures 1 and 2 present superimposed grand average ERPs for the nontarget and target trials. For the P1 time range, nontarget stimuli elicited bilateral activation in the primary visual cortex and extrastriate areas (Fig. 3). These activations were observed under both baseline and sleep loss conditions. Maxima of activation were found in Brodmann’s area 17 (Talairach coordinates: $x = 4$, $y = -81$, $z = 8$). For targets, LORETA revealed the same pattern, with the strongest source of P1 in Brodmann’s area 17, but only under baseline conditions. Following sleep loss, activations in visual cortices were also visible. However, the strongest source of current density was found on the left medial side of the frontal lobe, in Brodmann’s area 10 (Talairach coordinates: $x = -3$, $y = 52$, $z = 1$). Sustained activity in visual sensory areas continued over N1 time, for targets and nontargets, under baseline and sleep loss conditions.

Table I

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline condition</th>
<th>Sleep loss condition</th>
<th>Wilcoxon z</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated sleep time (h)</td>
<td>6–9.5; 7.5 ± 1.1</td>
<td>1–6; 3.9 ± 1.6</td>
<td>-3.3</td>
<td>0.001</td>
</tr>
<tr>
<td>BDI</td>
<td>0–4; 1.7 ± 1.4</td>
<td>0–9; 3.1 ± 2.7</td>
<td>-2.0</td>
<td>0.039</td>
</tr>
<tr>
<td>VAS</td>
<td>-</td>
<td>17–92; 56.2 ± 21.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SSS</td>
<td>1–4; 1.9 ± 0.9</td>
<td>2–6; 3.7 ± 1.3</td>
<td>-3.0</td>
<td>0.003</td>
</tr>
<tr>
<td>CAT 1st session</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omissions</td>
<td>1–8; 4.3 ± 2.5</td>
<td>1–17; 6.0 ± 4.8</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Commissions</td>
<td>1–6; 2.2 ± 1.5</td>
<td>0–6; 2.6 ± 2.0</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>RT (ms)</td>
<td>398.8–648.7; 543.1 ± 65.1</td>
<td>398.0–759.0; 575.0 ± 82.5</td>
<td>-2.0</td>
<td>0.05</td>
</tr>
<tr>
<td>CAT 2nd session</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omissions</td>
<td>1–11; 4.8 ± 3.5</td>
<td>1–14; 6.5 ± 4.9</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Commissions</td>
<td>1–4; 2.2 ± 1.3</td>
<td>1–6; 1.9 ± 1.5</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>RT (ms)</td>
<td>424.9–692.0; 544.5 ± 73.7</td>
<td>364.8–745.2; 570.3 ± 89.8</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>CAT 3rd session</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omissions</td>
<td>1–18; 5.7 ± 5.1</td>
<td>1–15; 6.6 ± 4.9</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Commissions</td>
<td>1–5; 1.9 ± 1.5</td>
<td>1–4; 1.8 ± 1.0</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>RT (ms)</td>
<td>359.0–640.7; 537.6 ± 70.1</td>
<td>373.9–750.1; 556.6 ± 89.1</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>CAT overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omissions</td>
<td>2–34; 13.3 ± 9.7</td>
<td>2–45; 17.1 ± 13.6</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Commissions</td>
<td>1–12; 3.6 ± 3.1</td>
<td>1–15; 4.5 ± 4.0</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>RT (ms)</td>
<td>394.2–656.9; 541.6 ± 66.2</td>
<td>378.9–751.2; 567.7 ± 84.9</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>SRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall (number of items)</td>
<td>4–9; 6.4 ± 1.2</td>
<td>6–10; 7.9 ± 1.1</td>
<td>-3.0</td>
<td>0.003</td>
</tr>
<tr>
<td>Learning (number of presentations)</td>
<td>2–7; 3.3 ± 1.5</td>
<td>1–4; 2.3 ± 0.8</td>
<td>ns</td>
<td></td>
</tr>
</tbody>
</table>

(ns) nonsignificant
Under sleep loss condition compared to baseline, significant differences in brain areas occurred only for targets (Fig. 4). Within the P1 time frame, sleep loss resulted in greater activation in the right frontopolar area (Brodmann’s area 9/10, Talairach coordinates indicating the voxel of maximal significance: $x = 11, y = 59, z = 36, t = 3.41$). For the N1 component, significant differences were localized on the lateral surface of the right frontal lobe, in Brodmann’s area 8 (Talairach coordinates: $x = 18, y = 31, z = 50, t = 2.05$; $x = 25, y = 24, z = 43, t = 2.05$) and 9 (Talairach coordinates: $x = 39, y = 38, z = 36, t = 2.17$). No significant effects of sleep deprivation on the P3 component were found.

**DISCUSSION**

The participants reported sleeping at home a mean of $7.5 \pm 1.1$ hours per night. On duty, they slept an average of $3.9 \pm 1.6$ hours, less than minimum amount needed to maintain performance at a stable level (Belenky et al. 2003). As expected, the subjects did poorly on test involving immediate memory, and they also scored higher on SSS and BDI. Impairment of short-term memory is a classical finding in sleep deprived subjects (for a review see Bonnet 2000). It is also consistently reported that mood state deteriorates substantially due to sleep loss (Orton and Gruzelier 1989, Pilcher and Huffcutt 1996). As indicated above, accuracy and latency of response are two prominent variables affected by sleep deprivation. However, the subjects achieved nearly a perfect performance on the CAT. Number of hits and false alarms was not different under the sleep loss condition, and significant slowing of reaction time was found only in the CAT session 1. An extensive review of clinical trials published between years 1977 and 2001 (Veasey et al. 2002) showed that out of 32 studies evaluating effects of sleep loss on medical residents, 8 reported no differences on cognitive measures. Many variables can be invoked to explain these discrepancies. Individuals have different needs for sleep (Aeschbach et al. 2003) and different personal demands outside of work hours (Baldwin and Daugherty 2004). Substantial inter-individual differences in neurobehavioral deficits are observed (Deary and Tait 1987, Leproult et al. 2003, Van Dongen et al. 2004). Participants may more willingly take part in sleep deprivation experiments if they are able to cope well with the demands placed on them under sleep loss conditions (Deary and Tait 1987).

Although their scores on the CAT were only marginally affected, the subjects used different cognitive strategies. To evaluate influence of partial sleep loss on
information processing, this study utilized LORETA (Pascual-Marqui et al. 1994, 1999), a noninvasive method for localizing electrical activity (i.e., current density) in the brain. Based on multichannel surface EEG recordings, LORETA images reflect synchronized neuronal mass activity, showing significant correspondence with results provided by functional magnetic resonance (fMRI) (Vitacco et al. 2002). The method has proven to be useful in testing hypotheses about the neural substrates of cognition and emotions (Esslen et al. 2004, Frei et al. 2001, Herrmann et al. 2004, Lavric et al. 2001, Mulert et al. 2004, Pizzagalli et al. 2000, Vitacco...
et al. 2002), and sleep mechanisms (Anderer et al. 2001). It has been also successful in exploring brain dysfunction in major depression (Pizzagalli et al. 2001, 2002, 2004) and schizophrenia (Fallgatter et al. 2003, Gallinat et al. 2002, Pascual-Marqui et al. 1999, Winterer et al. 2001).

The CAT elicited activation in visual sensory areas, for targets and nontargets, under baseline and sleep loss conditions, over the P1 as well as the N1 time. This is consistent with earlier data. Neuroanatomical locations of the visual ERP sources are still debated but both the P1 and N1 components are supposed to derive primarily from activity in the striate and extrastriate visual cortical areas (Foxe and Simpson 2002, Gomez-Gonzalez et al. 1994, Simpson et al. 1995, Vanni et al. 2001). Sustained activation of primary visual cortex may be seen for 100–400 ms prior to a motor response (Foxe and Simpson 2002, Simpson et al. 1995).

When compared with baseline values, sleep loss resulted in greater current density in the right frontopolar area and on the lateral surface of the right frontal lobe. Data from neuroimaging studies indicate that the lateral prefrontal cortex is the neural substrate of cognitive functions supporting temporal organization of behavior (Fuster 2001). During sustained attention, an ascending basal forebrain system, activated by direct connections from the prefrontal cortex, has been proposed to contribute to the enhancement of cortical information processing (Sarter et al. 2001). There is also evidence that right prefrontal areas (Brodmann’s areas 9, 10 and 32) are engaged in a fronto-parietal-thalamic-brainstem cerebral network subserving alertness (Sturm et al. 1999).

In the 1990s, neuroimaging studies started mapping brain changes occurring due to total sleep deprivation (Drummond et al. 1999, 2000, 2001, 2004, Portas et al. 1998, Thomas et al. 2000, 2003, Wu et al. 1991). Collectively, the aforementioned studies found either decreases in cerebral metabolic rate for glucose in the prefrontal-thalamic network (Thomas et al. 2000, 2003) or reduced blood oxygen level-dependent (BOLD) fMRI activation in prefrontal and parietal areas (Drummond et al. 1999). This reduced function was observed when task load exceeded the behavioral capacity of the sleep deprived subjects. On the other hand, increased BOLD fMRI activation in thalamus (Portas et al. 1998), prefrontal and parietal areas (Drummond et al. 2000, 2001, 2004) was reported, coincident with relatively intact performance. It has been proposed that recruitment of new brain regions or spatially larger response to cognitive tasks may overcome the effects of sleep loss (Drummond and Brown 2001, Drummond et al. 2000, 2001, 2004, Portas et al. 1998). In turn, Starbuck and coauthors (2000) demonstrated that sleepiness, spontaneous or induced by medication, results in an increase in frontal brain activation during performance of a familiar task. A further support of this increase comes from an event-related potentials study by Ferrara and coauthors (2002) in which they found a frontal increase in N1-P2 amplitude related to the greater effort under periods of increased homeostatic drive for sleep. Thus electrophysiological and hemodynamic/metabolic imaging studies converge in indicating that increased activation of the prefrontal cortex is needed to maintain performance despite sleep loss.

It would also be of interest to explore changes occurring over time and identify the stage at which sleep loss begins to affect information processing. Towards this end, electrophysiological imaging is particularly useful because of its high time resolution. A large number of prior studies showed that both the P1 and N1 compo-
ments are sensitive to attentional demands (for a review see Luck et al. 2000, Taylor 2002). In the current study, the continuous attention test after partial sleep deprivation led to increased activation of the prefrontal cortex as early as the P1 and N1 time frame. This early activation of the prefrontal cortex is consistent with the idea that the shortest latencies of visual responses may not correspond to the lowest stages of the signal transmission hierarchy. It is also in accordance with models of visual processing that assume rapid spread of activity through the visual sensory pathways and frontal cortex (Bullier 2001, Foxe and Simpson 2002). Cingulate, medial and dorsolateral prefrontal area involvement at early latencies have been previously reported (Simpson et al. 1995). Dorsolateral prefrontal cortex may be active already by 80 ms (Foxe and Simpson 2002). This rapid input to prefrontal areas, distinct from prefrontal executive functions, allows for top-down influences on sensory areas, and it may have an alerting role (Bullier 2001, Foxe and Simpson 2002).

CONCLUSION

Our findings are consistent with the previous data indicating that increased activation of the prefrontal cortex is needed to maintain performance under sleep loss conditions. This increased activation was found as early as the P1 and N1 time frame.

REFERENCES


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