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Is pre-attentive processing compromised by prolonged wakefulness? Effects of total sleep deprivation on the mismatch negativity

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Abstract

We investigated the potential influence of sustained wakefulness on pre-attentive capacities by recording the mismatch negativity (MMN), an electrophysiological manifestation associated with nonintentional detection of auditory oddball stimuli. The MMN was elicited by pitch deviants presented to both ears via earphones, at the beginning of a total sleep deprivation session (baseline), after 24 hr, and after 36 hr of continuous controlled wakefulness. A conspicuous MMN response was elicited at all three sessions. With time, however, a small yet significant gradual reduction in the MMN amplitude was evident. Whereas previous research suggested that controlled attention-demanding tasks are hampered by sleep deprivation, the balance of the present results suggests that passive (total) sleep deprivation may also bring about some degradation in the pre-attentive detection of environmental irregularities and as a consequence may disrupt the reflexive shift of attention induced by such events.

Descriptors: Mismatch negativity, Pre-attentive processing, Total sleep deprivation, Event-related potentials

The implications of sleepiness to society are substantial. Sleepiness is considered one of the most common causes of accidents (Mitler et al., 1988). In the United States alone sleepiness is blamed for around 200,000 traffic accidents every year and probably contributes at least partly to many other catastrophes or near catastrophes. Accidents are the fourth cause of mortality in the United States with motor-vehicle accidents representing 51% of total deaths caused by accidents (Coren, 1996; Leger, 1994; Transportation-related sleep research, 1985).

Sleep deprivation (SD) is a controlled way to elicit and scientifically monitor gradual sleepiness and fatigue. SD assays draw on data from animal models (e.g., Rechtschaffen & Bergmann, 1995; Rechtschaffen, Bergmann, Everson, Kushida, & Gilliland, 1989; Rechtschaffen, Gilliland, Bergmann, & Wnter, 1983), human experiments (e.g., Horne, 1978, 1988, 1991, 1993; Johnson, 1982; Naitoh, 1976; Wilkinson, 1965), and clinical sleep disorders findings (e.g., Parkes, 1985; Webb, 1975, 1982). These well-controlled SD laboratory studies, however, do not easily explain many of the effects seen ecologically (Carlson, 2000, p. 277). A plausible reason for such discrepant findings concerns the ability of sleep-deprived subjects to compensate for the potentially detrimental effects of weariness by recruiting conscious effort. Manifestly, when explicit performance is called for in a laboratory SD context, subjects are better placed to intentionally regulate and efficiently control their performance than in a real-life environment. Nevertheless, controlled total SD (TSD) studies did reveal some deficits in cognitive performance.

Early studies of extreme (120–264 hr) TSD showed that whereas physical performance was largely unhindered, transitory cognitive consequences ranged from simple irritability to bizarre behavior (e.g., Gulevich, Dement, & Johnson, 1966; Kollar, 1966; Morris, Williams, & Lubin, 1960; Pasnau, Naitoh, Stier, & Kollar, 1968; Ross, 1965). More recent studies, carried over shorter periods, suggested that TSD affected mood (Pilcher & Huffcutt, 1996), and induced some decrease in decision-making performance, vigilance, and some forms of memory and learning (e.g., Babkoff, Mikulincer, Caspy, Kempinski, & Sing, 1988; Dinges & Kribbs, 1991; Horne, 1978, 1988, 1993). Visual and auditory tasks showed a similar pattern of deficits, suggesting that the failure to maintain attention was the critical common factor underlying slumberous performance (Dinges & Powell, 1989).

Presently, it is not clear whether or not uncontrolled processes, which ostensibly do not entail endogenous attentional resources, escape the unfavorable effects of prolonged wakefulness. Although

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there is intuitive consensus that "pre-attentive" or automatic cognitive processes are more likely to remain intact during sustained wakefulness (cf. Doran, 1999), this premise remains to be empirically verified. With this in mind, the present study was designed to examine the potential variation of pre-attentional processing in sleep-deprived subjects within a controlled setting. The measure of pre-attentional processing was the mismatch negativity (MMN), an event-related brain potential elicited by different types of occasional changes in an otherwise recurrent stimulus sequence presented outside the focus of attention (Näätänen, Gaillard, & Mäntysalo, 1978). In addition to examining largely pre-attentive processing and the ability of unexpected stimuli to momentarily capture attention reflexively, the characteristics of the MMN paradigm circumvent the compensatory involvement of conscious intentional strategies that may veil pre-attentive processing decrements induced by TSD.

In a typical MMN paradigm, a "deviant" auditory stimulus is sporadically distributed within a sequence of "standard" auditory stimuli. The MMN is evident in the difference waveform resulting from the subtraction of the ERP elicited by the standard stimulus from that elicited by the deviant stimulus. The difference waveform is characterized by a negative-going wave, normally peaking between 100 and 250 ms from the onset of the deviant event (depending on the dimension of deviance and its magnitude). MMN has been demonstrated by manipulating basic physical features of pure and harmonic tones (e.g., frequency, intensity, duration, interstimulus interval, and location), as well as by more intricate dimensions of deviation such as phonetic information, temporal order, or an abstract relation between pairs of tones (for reviews, see Näätänen, 1990, 1992, pp. 136–200; Näätänen & Alho, 1995). The MMN is presumably associated with a mechanism that compares the current auditory input to the memory traces formed by previous auditory inputs, and signals the occurrence of a mismatch (Cowan, Winkler, Teder, & Näätänen, 1993; Näätänen, 1990, 1992; Ritter, Deacon, Gomes, Javitt, & Vaughan, 1995; see Winkler, Karmos, & Näätänen, 1996 for a recent variation of this view).

The cognitive mechanisms associated with MMN are assumed to be pre-attentive, that is, they do not draw on limited attentional resources, although a momentary shift of attention towards the deviant stimulus is most probably induced reflexively (e.g., Schröeger, 1996; Schröeger & Wolff, 1998). In its purest form, MMN is elicited when a subject does not attend to the auditory stimuli. For example, a subject may be reading a book, watching a silent movie, or engaged in some demanding visual computer game. Although attention may augment MMN (Woldorff, Hackley, & Hillyard, 1991), it is clearly elicited even when attention is strongly focused elsewhere (Näätänen, 1991; Näätänen, Paavilainen, Tiitinen, Jiang, & Alho, 1993). Moreover, inasmuch as these responses reflect the same process, MMN-like responses have been elicited in awake (e.g., Ruusuvirta, Penttonen, & Korhonen, 1998) and anesthetized laboratory animals (e.g., Csépe, Karmos, & Molnar, 1987; Csépe, Molnar, Karmos, & Winkler, 1989), comatose human patients (e.g., Kane et al., 1996), and in sleeping human newborns (e.g., Cheour-Luhtanen et al., 1995; whether or not MMN appears in adult human sleep is still controversial, see Atienza, 2000; Atienza & Cantero, 2001; Atienza, Cantero & Gomez, 1997, 2000; Doran 1999; Harsh, Voss, Hull, Schrepfer, & Badia, 1994; Loewy, Campbell, & Bastien, 1996; Näätanen & Lyytinen, 1994; Nakagome et al., 1998; Nashida et al., 2000; Nielsen-Bohlman, Knight, Woods, & Woodward, 1991; Paavilainen et al., 1987; Sallinen, Kaartinen, & Lyytinen 1994, 1996, 1997; Sallinen & Lyytinen, 1997; Winter, Kok, Kenemans, & Elton, 1995). The bulk of these studies supports the automatic, bottom-up nature of MMN, and confirms that endogenous attention is not needed for MMN to be educed. Indeed, MMN is legitimately regarded as an index for a pre-attentive, and not just nonattentive, mechanism as the detection of the mismatch seems to trigger a stimulus-driven involuntary shift of attention (Alho, Escera, Diaz, Yago, & Serra, 1997; Escera, Alho, Winkler, & Näätänen, 1998; Näätänen, 1990, 1992; Novak, Ritter, & Vaughan, 1992; Schröger, 1996; Schröger & Wolff, 1998).

SD experiments are large-scale projects, which require meticulous planning and considerable resources. Therefore, previous relevant studies of MMN were mainly limited to the effect of sleep-time fatigue, induced by nighttime circadian rhythms, and did not address the effect of substantial SD (e.g., Sallinen & Lyytinen, 1997). These studies suggested some decline in MMN during drowsiness, before falling asleep and even during Stage I sleep (e.g., Doran, 1999; Nakagome et al., 1998; Sallinen & Lyytinen, 1997; Winter et al., 1995). However, none of these studies followed a rigorous TSD protocol, which controls the subjects' sleep and daytime behavior both before and strictly during the sleep deprivation period.

Other studies reported effects of exhaustion (rather than SD) on MMN. Some of these studies deduced such effect only indirectly by assessing, for example, the influence of extended wakefulness on automatic and nonautomatic processing (Humphrey, Kramer, & Stanny, 1994). Other data emerged from investigation of the effects of anesthetic gas or triazolam administration on MMN (Pang & Fowler, 1999; Nakagome et al., 1998), from anecdotal or intuitive data (e.g., unpublished data by Mikola, Lang, & Eerola cited in Näätänen, 1992, p. 157), or from experiments employing unusual recording posture (e.g., Doran, 1999). By and large, these studies indicated that MMN might be adversely affected by reduced arousal or fatigue. However, it remains difficult to decisively conclude whether sleep deprivation or some other factors affected the MMN response. In this study, we were interested in what influence a substantial, strictly controlled, lack of sleep might have on the pre-attentive processes as reflected in MMN. In order to focus on the effects of drained resources, on the one hand, and reduce the likelihood of enhanced psychological stress and severe physiological reactions on the other hand, we have opted for a TSD period of 36 hr. Such a vigil is not long enough to invoke any exceptional symptoms, but is indeed sufficient to instigate marked yet well-controlled exhaustion.

Methods

Participants

The participants were fourteen 18 to 28 ($M = 23.8 \pm 2.8$) year-old male students from the Hebrew University of Jerusalem. All participants were right handed, Hebrew-speakers, with normal hearing and normal (or corrected to normal) vision.

Participants were initially screened through an open-response questionnaire administered as part of a multiquestionnaire screening session offered to about 120 interested students. The screening was aimed at categorizing candidate participants into subgroups of comparable sleepiness profiles, along the "morningness-eveningness" and "sleepy-alert" scales (Lavie & Segal, 1989; Lavie & Zvuloni, 1992). Morningness-eveningness relates to those retiring to bed early ("larks") as opposed to those retiring late ("owls"). Sleepy-alert relates to those who easily fall asleep, night and day, as opposed to those who have difficulty falling asleep.

Participants were excluded if they were either smokers, using any kind of medication, regular caffeine consumers,[1] or if they had any history of neurological disease, substance abuse, head injury, or any medical condition that could jeopardize safety or ability to stay awake. Because very rarely, and indeed probably only in predisposed individuals, extreme TSD may provoke a psychotic episode (e.g., Bliss, Clark, & West, 1959; Brauchi & West, 1959; Johnson, 1969; Katz & Landis, 1935; Kornyi & Lehmann, 1960; Tyler, 1955), potential participants who passed the initial screening were accordingly informed and administered a variation of the Structured Interview for DSM III-R Non-Patient edition (Spitzer, Williams, & Gibbons, 1987) for psychiatric conditions. Any past or present DSM III-R Axis I disorder excluded participants from further participation. Two candidates were excluded on these grounds. Sleep-related exclusion criteria included any possible intrinsic sleep disorder, poor sleep "hygiene" (i.e., highly variable sleep schedules, sleep restriction, etc.), circadian rhythm sleep disorders, or any history of sleep abnormality.

Participants were paid the equivalent of US$200 to partake in this experiment, and were exhorted to put as much effort as possible throughout the entire vigil (see Horne & Pettitt, 1985, for the importance of motivation in TSD experiments). Any pair of participants was given a "fault" if any one of them dozed. A cumulative count of three faults per pair resulted in a considerable money penalty to both subjects, to be deducted from the experimental reward. This technique was used in order to motivate the participants to assist each other in the battle against sleepiness, and proved very successful. No penalties were ever required. Any subject wishing to terminate the study was allowed to do so at any time, although this did not occur.

Stimuli

The stimuli consisted of 75-ms long harmonic tones with 5-ms rise and fall time, that were composed of a fundamental and two harmonics. The intensity of the first and second harmonics was reduced by a factor of 2 and 4, respectively, relative to the intensity of the fundamental frequency. The stimuli were presented simultaneously to both ears via headphones (Senheiser HD 480) with an intensity of 70 dB (SPL). The stimulus onset asynchrony was random, ranging between 385 and 415 ms. Eighty percent of the stimuli ("standards") had a fundamental frequency of 600 Hz (with harmonics of 1200 Hz and 1800 Hz). The rest were four types of "deviant" stimuli that deviated in frequency upwards or downwards from the standard by 5% (down: 570 Hz; up: 630 Hz) or 10% (down: 540 Hz; up: 660 Hz).

Experimental Procedure

The study received prior approval by the appropriate institutional review committee and took place on the Mount Scopus campus of the Hebrew University of Jerusalem, Israel.

During the pre-experiment week, participants were required to complete sleep diaries and instructed to conform to a conservative sleep-hygiene regime as follows: immediately preceding the experiment, participants were required to complete at least four consecutive nights of uninterrupted normal sleep, going to bed between 10:00 and 11:00 p.m. and rising between 6:00 and 8:00 a.m., and to refrain from aberrantly strenuous physical activity. Also, participants were required to abstain from all caffeine-containing products, tobacco, and other drugs that might affect sleep. Detailed questionnaires and personal interviews were used to ascertain adherence to these guidelines. In four participants, actigraph recordings were used (Minilogger AM32) to monitor activity and rest, starting three days before TSD onset and ending at the end of the experimental period.

The sleep deprivation period started at 8:00 a.m. on a Friday and ran all through Saturday to terminate at 8:00 a.m. on the following Sunday, altogether spanning 48 consecutive hours. On the day of the experiment, participants awoke from sleep no earlier than 6:15 a.m. and arrived at the laboratory by 7:30 a.m. in order to settle in, sign a previously provided consent form for TSD, and go through data verification and a final debriefing. Two participants participated in each TSD session, and each pair was tested on a different weekend.

The participants were kept in an isolated, self-contained and air-conditioned suite of interconnected rooms where humidity (25%), temperature (22 °C) and light (150 Lux) were uniform throughout the entire 48-hr vigil. The suite, located at the underground level of the Hebrew University's Psychology Department, provided an acoustically attenuated environment and muffled ambient external noise. Owing to the lack of activity at the university quarters over weekends, the suite was all the more buffered throughout the experimental sessions.

No external time-cues (*zeitgebers*) were available to the participants throughout the experiment and they were completely isolated from the outside world. Arriving at the experiment they surrendered their wristwatches (and all other such time-telling devices, cellular phones, etc.) only to collect them at the end of the vigil. To avoid formal meal times, nonstimulating vegetarian food and beverage were continually available in an open buffet style. The food provided contained no substances known to affect sleep parameters (i.e., chocolate, certain hard cheeses, etc.). Because physical activity influences the biological rhythm (e.g., Youngstedt, O'Connor, & Dishman, 1997), all nontrivial volitional physical exercise was banned throughout the experiment and the vigil was conducted leading a strict sedentary protocol. Throughout the sleepless period, blood pressure and heart rate were periodically registered, primarily as a medical indication of the participants' well-being. Oral temperature was measured hourly as an indication of circadian rhythmicity.

To minimize the possibility of microsleeps, vigilant research assistants (RAs), rotating in predetermined and irregular shifts, personally and constantly scrutinized the participants for wakefulness throughout the experiment. Thus, RAs were physically present around the participants at all times,[2] providing steady interaction and preventing them from slumbering however briefly. During body-temperature nadirs, when participants often appeared very torpid, RAs were particularly alert to display a stern and uncompromising attitude towards wakefulness, and engaged in occasional "encouragement talks," to further motivate the participants at critical moments.

In between electrophysiological measurements, participants periodically engaged in a battery of behavioral tests (reported in Raz,

[1] In order to avoid caffeine withdrawal syndromes (e.g., Hughes, Gust, Skog, & Fenwick, 1991; Silverman, Evans, Strain, & Griffiths 1992; Strain, Mumford, Silverman, & Griffiths, 1994) a caffeine dosage of 35 mg/day (about one medium cup of regular coffee or a can of caffeinated soft drink) served as the upper limit for participation (cf. Griffiths et al., 1990a, 1990b).

[2] RAs escorted all toilet visits although subjects' privacy was obviously maintained. On such occasions participants were required to sing or whistle throughout.

1999) and were otherwise free to engage in a variety of quiescent (fully supervised) activities: talk, read, watch video tapes, study, play chess, and so forth.

MMN Recording

Three separate MMN recording sessions were carried out at 0 (baseline), 24 and 36 hr into the vigil.[3] Every MMN session lasted a little over an hour per participant. One RA always accompanied a participant into the recording booth and was present all throughout the MMN session, ascertaining subject wakefulness.

When tested, participants were seated in a comfortable reclining armchair in a dimly lit, sound attenuated and electrically shielded chamber. The participants were presented with five blocks of 500 stimuli, divided between standards (80%), and four types of deviants (5% each). The standards and the deviants were randomly ordered with the constraint that at least three standard stimuli preceded each deviant.

The participants were instructed to disregard the auditory stimuli, and to score as high as they possibly could on a visual (silent) computer game displayed on a computer screen directly in front and at a distance of 65 cm. The game was an engaging three-dimensional version of "Tetris" operated by four keyboard keys. A parallel screen outside the recording chamber allowed the experimenter to continuously monitor the subjects' performance on the game. The game's level of difficulty was adjusted so that performance would remain relatively constant across all sessions and subjects. The game was restarted when subjects occasionally failed the task. This procedure precluded accurate recording of behavioral performance over prolonged time periods (see Discussion).

The EEG was recorded from 48 tin electrodes mounted on a custom-made cap (ECI) and referenced to the tip of the nose. Two electrodes recorded the EOG: one located at the outer canthus of the right eye and the other at the infraorbital region of the same eye.

The EEG was continuously sampled at 250 Hz, amplified by a factor of 20K with an analog band-pass filter of 0.1 Hz to 30 Hz, and stored for off-line analysis. For ERP averaging, the EEG was parsed into 460-ms epochs starting 60 ms before the stimulus. Epochs with EEG or EOG exceeding ± 100 μV were excluded from the averaging process. The epochs were averaged separately for each stimulus type. The baseline was adjusted by subtracting the mean amplitude of the prestimulus period of each ERP from all the data points in the epoch. For MMN analysis, frequencies lower than 1 Hz and higher than 12 Hz (-3 dB points) were digitally filtered out from the ERPs after averaging (cf. Sinkkonen, 1998).

Data Analysis

MMN properties were measured on difference waveforms computed by subtracting the ERPs elicited by standards from those elicited by deviants in the same block. For each subject and condition, the peak amplitude was detected within a predetermined latency window of 100–250 ms, following digital rereferencing to the averaged mastoids (Schröger, 1998). Differences between conditions were validated by repeated-measures ANOVA in which the dependent variables were calculated by averaging peak amplitudes recorded over frontal sites (Fz, FCz, F3/4, F5/6, F7/8, FT7/8, Fc5/6, and FC1/2).

[3]In a pilot study, we attempted ERP measurements following 0, 24, and 48 hr, but because on the last session, participants were overly weary and recordings too noisy, we have opted for 36 hr instead.

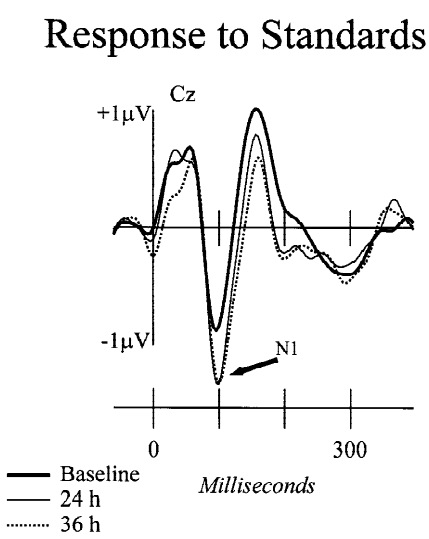

Figure 1. Response to standards recorded at electrode Cz for the baseline session and after 24 and 36 hr into the vigil.

Results

Standard Stimuli

A complete data set from 9 participants was available for the repeated measures analysis of N1. Data from 5 more participants were missing due to technical difficulties or discarded due to excessive artifacts. N1 was enhanced at the 24-hr and 36-hr sessions relative to the baseline measurement (Figure 1). A one-way ANOVA revealed that the difference was significant, $F(2,16) = 4.092$, $p < .05$. Post hoc comparisons revealed a significant enhancement of N1 from baseline to 24 hr, $F(1,8) = 10.382$, $p = .012$, with no significant difference between the two later sessions (24 and 36 hr into the vigil). In fact, as Figure 1 reveals, the enhanced negativity at 24 and 36 hr was not limited to the N1 latency alone, as a negative shift in the waveforms elicited at those sessions started at 80 ms and continued until 250 ms poststimulus.

Deviant Stimuli

Because the direction of pitch-deviance did not influence the MMN, $F(1,9) < 1$, the up- and down-deviating conditions were collapsed into one average. Thus, for each subject, the averages of small (5%) and large (10%) deviations included 250 trials in each condition, with the exception of artifact-contaminated trials. Visual inspection of the difference waves revealed a conspicuous MMN in all three sessions and for both large and small deviations (Figures 2 and 3). As expected, larger (10%) deviations elicited bigger MMN than smaller (5%) deviations. For both magnitudes of deviance, there was an apparent decrease of MMN amplitude as the vigil progressed. A complete data set was available for 10 subjects.[4] Data from 4 more participants were missing due to technical difficulties or discarded due to excessive artifacts. A two-way ANOVA of Deviance-size (5%, 10%) $\times$ Session (baseline, 24 hr,

[4]The reason for a 9-subject data set for the N1 analysis versus a 10-subject data set for the MMN analysis is that for 1 subject the automatic peak-detection procedure identified no clear crest at the latency designated for N1 in one of the sessions. On the other hand, a clear peak in the difference waves at the MMN latency window was available for the same subject.

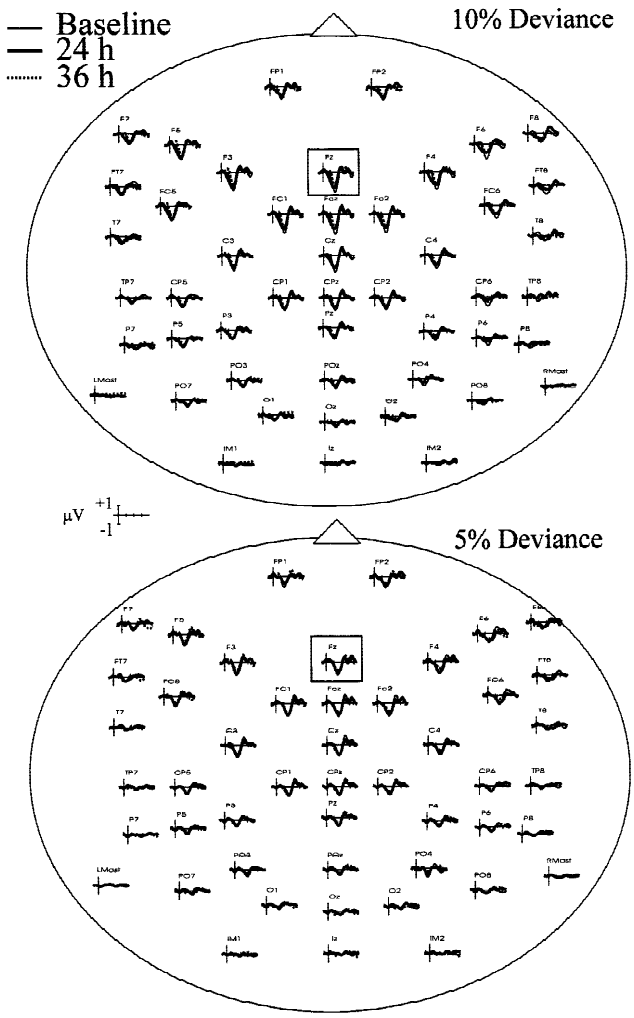

Figure 2. Difference waves (deviant − standard) displaying MMN elicited at baseline and after 24 and 36 hr of continuous wakefulness, by small (5%) and large (10%) frequency deviances. The vertical bars cross the horizontal axis at stimulus onset time. Each tick mark on the horizontal axis represents 100 ms. Activity at the boxed electrode (Fz) is enlarged in Figure 3. Data were referenced to averaged mastoids.

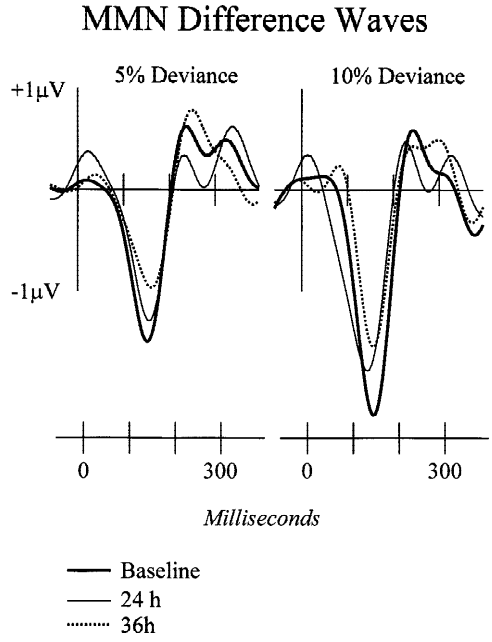

Figure 3. MMNs (difference waves) elicited at electrode Fz by small (5%) and large (10%) deviance, in the three recording sessions.

36 hr) revealed a significant Deviance-size effect, $F(1,9) = 6.35$, $p < .05$, whereas the Session effect was not significant. The interaction between the two effects, however, approached significance, $F(2,18) = 3.03$, $p = .073$. Testing separately for the two deviance sizes revealed a marginally significant difference between the three sessions in response to the larger (10%) deviance, $F(2,18) = 3.906$, $p = .068$, whereas no significant session effect was found for the smaller (5%) deviance. Post hoc analysis of the session differences in response to the larger deviance size revealed that the baseline (-2.37 μV) to 24-hr session (-1.96 μV) difference was significant, $F(1,9) = 9.939$, $p < .02$, as was the baseline to 36-hr session (-1.71 μV) difference, $F(1,9) = 5.242$, $p < .05$. The 24-hr to 36-hr difference was not significant, $F(1,9) = 1.380$, $p = .27$.

Discussion

In the present study, we assessed the effect of experimentally induced sleep deprivation on pre-attentive auditory discrimination by recording ERPs to standard and deviant tones in an MMN paradigm, and observing possible changes in the MMN amplitude along the vigil.

Although MMN elicited by pitch deviants was still clearly evident following 36 hr of controlled passive TSD, its amplitude was moderately reduced. This effect was observed for both small (5%) and large (10%) deviances, but was significant only for the latter condition. It is possible that the absence of significance in the smaller deviance condition reflects a reduced signal-to-noise ratio relating to the slighter MMN elicited by the small deviance.

Whereas the effects of longer TSDs on subjective feeling are dramatic, the only objective result of relatively short-term (36–48 hr) TSDs seemed to be marked weariness and a decrease in the ability to sustain attention (Dinges & Kribbs, 1991). In most but not all studies, effects on cognitive performance tests do not become consistently apparent until about 36 hr of TSD, and sometimes these effects are small or even absent (cf. Binks, Waters, & Hurry, 1999). For example, the early Walter Reed Army Institute of Research studies (e.g., Morris et al., 1960; Williams, Lubin, & Goodnow, 1959) showed that the primary impairment during acute sleep loss takes the form of lapses and reduced vigilance: The subject is unable to maintain efficient behavior and increasingly shows short periods when performance falters or stops. Several studies have shown that the most crucial factor producing the performance deficits appears to be impaired attention (e.g., Bonnet, 1994; Johnson, 1969). In contrast, performance based on processes that do not rely on allocation of attentional resources, such as implicit memory and "pop-out" effects in visual search tasks, do not seem to be noticeably affected by short-term extended wakefulness (e.g., Humphrey et al., 1994). However, if this were the case, then the MMN, which is considered to be associated with an involuntary automatic mechanism that does not draw on intentional allocation of attentional resources, should not have been particularly influenced, if at all, by a 36-hr TSD. Nevertheless, the reduction of the MMN with sleep deprivation in the

present study showed that at the neural level, pre-attentive, uncontrolled processes triggered by changes in the auditory environment were slightly but significantly affected by sleep deprivation, albeit voluntary allocation of attentional resources was not required or applied.

The absence of an attenuation of N1 amplitude across sessions suggests that TSD did not effect the early encoding of auditory stimuli in the primary auditory cortex, but the later processes associated with the MMN. These probably include processing of the deviance as well as adaptations of an ongoing echoic representation (model) to include the variance in the deviant dimension (Winkler et al., 1996). In addition, the deviant auditory stimuli may capture attention reflexively as part of the orienting reflex (Näätänen, 1990; Schröger, 1996; Sokolov, 1963). Indeed, it is possible that the momentary switch of attention also facilitates (or is required for) the effective completion of the deviance-related processes. The present design could not elucidate which of these processes (if not all of them) were affected by TSD. Nevertheless, contrary to previous opinions, which were based on performance (Dinges & Kribbs, 1991; Dinges & Powell, 1989; Horne, 1978), the detrimental effect of a prolonged vigil on the MMN suggests that TSD does affect pre-attentive processes. The nature of "pre-attentiveness," however, needs further refinement.

The term "pre-attentive" has been used to reflect two different notions: one relating to its being an early, data-driven, and unintentional process; the second implying a resource-free mechanism, capable of generating expedient responses in parallel (e.g., Broadbent 1958, 1982; Bundesen, 1990; Hasher & Zacks, 1979; Kahneman, 1973; Neisser, 1967; Shiffrin & Schneider, 1977; Sperling, 1963; Treisman, 1964, 1988). Although these two features are often assumed to coexist (e.g., as features characterizing automaticity; Norman & Shallice, 1986; Posner & Snyder, 1975), there is no a priori reason why they should necessarily be yoked. A few studies have, in fact, demonstrated that whereas MMN was never abolished even when highly attention-demanding tasks were used (stressing its automatic nature; Näätänen et al., 1993), it was nonetheless affected (Woldorff, Hillyard, Gallen, Hampson, & Bloom, 1998; Woldorff et al., 1991). This may suggest that the processes involved with the mismatch detection, although automatic in the sense of being involuntary and data-driven, may not be entirely immune to attentional manipulations. Along this line of reasoning, it could have been argued that the MMN was reduced in the present study because TSD diminished cognitive/attentional resources (Dinges & Kribbs, 1991; Dinges & Powell, 1989; Horne, 1978). A caveat for such interpretation, however, is the finding that the amplitude of N1 was not only maintained along the vigil, but indeed increased in the two later sessions (24 and 36 hr), as compared to baseline. This would not be expected had attentional resources allocated to the auditory input been reduced, because attention has a facilitatory effect on N1 (cf. Näätänen & Picton, 1987; for a more recent review see Luck, 1988).

The N1 intensification could have resulted theoretically from a shortening of the auditory neurons' refractory period (cf. Näätänen & Picton, 1987 for the case of lengthened ISI). However, no corroborative data are available to substantiate this claim and intuition suggests that the refractory period is more likely to increase, not decrease, as a result of TSD. A more plausible interpretation of the augmentation of N1 is that, as fatigue developed, participants could not efficiently filter out the auditory stimuli and sustain their attention on the visual diversion, as requested by the task. This form of attentional "leakage" from the visual onto the auditory modality could have increased the "gain" (cf. Mangun and Hillyard, 1988) of neuronal populations contributing to the N1. Unfortunately, this possibility remains conjectural, because the nature of the diversionary visual game (see Method section) did not allow quantitative monitoring of the subjects' performance on the visual task. Nevertheless, behavioral data collected from a battery of attentional and pre-attentional visual tasks, which was periodically administered in between electrophysiological sessions, did reveal a gradual increase in both reaction time and error rate as the vigil unfolded, suggesting suboptimal performance in sustaining visual attention (Raz, 1999).

A consequence of the attentional leakage interpretation is that any underlying attenuation of the MMN response in the 24- and 36-hr sessions might have been actually mitigated by the facilitatory effect of attention on MMN (Woldorff et al., 1991, 1998). In turn, this line of reasoning would imply that the deficit induced by TSD might even be larger than what is evident in the present results. In the same fashion, the somewhat loud stimuli (70 db) could have awakened the subjects and served to oppose the effect of TSD on MMN. That the effects of TSD on the MMN might indeed be larger than those suggested by the present data can be also construed by the timing of the three recording sessions and the circadian factors connected with them, respectively. Diurnal changes in performance normally follow the circadian rhythm and are typified by reduced performance around dawn and the early morning hours, when body temperature is at a nadir, and enhanced performance in the evening, when body temperature peaks (e.g., Carskadon, Littel, & Dement, 1985; Dinges & Kribbs, 1991; Gillberg & Akerstedt, 1981; Johnson, 1969). The ERP measurements on the first two sessions in our study were administered in the morning (8:00–9:00 a.m.), exactly one day apart and are thus clearly comparable. The third session, however, was conducted around a time when a daily performance peak was normally evident (8:00–9:00 p.m.). At that time of the day, the interaction between TSD and circadian rhythm may have transiently ameliorated the detrimental effect of TSD (cf. Daan, Beersma, & Borbely, 1984; Dijk & Czeisler, 1995). This pattern is congruent with the larger difference between baseline and second session than between the two later sessions. The fact that in spite of all these ameliorating factors a significant effect was obtained reinforces the influence of TSD on the mechanisms reflected by the MMN.

The diminution of MMN in a state of TSD may reflect a progressive transition from an "awake" mechanism onto a "sleep" mechanism. Winter et al. (1995) suggested that changes in the environment were detected during sleep by a system different from the one reflected by MMN when awake. Their position was based on finding novel deviance-related ERP components during drowsiness (namely, finding a broad frontocentral early negative deflection in response to a 2000 Hz tone, as well as deviance-magnitude sensitive P210, N330, and P430, but no clear MMN) and stage 2 sleep (where P210, N330, and P430 amplitudes further increased). More research is needed to verify this hypothesis.

In conclusion, MMN was not abolished following a 36-hr vigil. The small diminution of amplitude observed as wakefulness prolonged suggests that pre-attentive mechanisms are not entirely immune to sleep deprivation, even after missing only one night of sleep. Recent data showing that the anesthetic gas nitrous oxide decreases MMN (Pang & Fowler, 1999) complement the results reported in the present study suggesting that arousal influences pre-attentional mechanisms. At the very least, short-term TSD seems to make pre-attentional processing more tenuous. Although the present study was not designed to directly test the correlation of MMN with behavior, previous studies established that the am-

plitude of MMN correlates well with the subjective sensitivity of subjects to minute changes in their environment (Lang et al., 1990; Tervaniemi, Ilvonen, Karma, Alho, & Näätänen, 1997; Näätänen et al., 1993). Based on these correlations, we speculate that the diminution of MMN may be reflected behaviorally by suboptimal detection of auditory changes in the environment. The subsequent deficiency in shifting involuntary attention to potentially important stimuli could entail hazards to the sleep deprived.

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