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Is the failure to detect stimulus deviance during sleep due to a rapid fading of sensory memory or a degradation of stimulus encoding?

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SUMMARY The mismatch negativity (MMN) is thought to reflect the outcome of a system responsible for the detection of change in an otherwise repetitive, homogenous acoustic environment. This process depends on the storage and maintenance of a sensory representation of the frequently presented stimulus to which the deviant stimulus is compared. Few studies have been able to record the MMN in non-rapid eye movement (NREM) sleep. This pattern of results might be explained by either a rapid fading of sensory memory or an inhibition of stimulus input prior to entry into the cortical MMN generator site. The present study used a very rapid rate of presentation in an attempt to capture mismatch-related negativity prior to the fading of sensory memory. Auditory event-related potentials were recorded from 12 subjects during a single sleep period. A 1000 Hz standard stimulus was presented every 150 ms. At random, on 6.6% of the trials, the standard was changed to either a large 2000 Hz or a small 1100 Hz deviant. In wakefulness, the large deviant elicited an extended negativity that was reduced in amplitude following the presentation of the small deviant. This negativity was also apparent during REM sleep following the presentation of the large deviant. These deviant-related negativities (DRNs) were probably a composite of N1 and MMN activity. During NREM sleep (stage 2 and slow-wave sleep), only the large deviant continued to elicit a DRN. However this DRN might be overlapped by the initial activity of a component that is unique to sleep, the N350. There was little evidence of the DRN or the MMN during sleep following the presentation of the small deviant. A rapid rate of presentation, therefore, does not preserve the MMN following small deviance within sleep. It is possible that inhibition of sensory input occurs before entry into the MMN generating system in the temporal cortex.

KEYWORDS auditory event-related potentials, deviant-related negativity, mismatch negativity, NREM sleep, REM sleep, sensory memory

INTRODUCTION

In order for sleep to occur, it would appear that processing of all but the most relevant of external stimulus input needs to be gated or inhibited. There is good evidence that a thalamocortical loop is involved in the inhibition of information during sleep (Steriade *et al.*, 1993). Single-unit studies in animals have confirmed a large decrease in responsiveness to auditory stimuli during non-rapid eye movement (NREM) sleep for a high percentage of cells in different subthalamic and thalamic nuclei (Coenen, 1998; Coenen and Drinkenburg, 2002; Steriade *et al.*, 1993). Positron emission tomographic studies in humans have consistently reported thalamic deactivation in stage 2 and slow-wave sleep (SWS) (Braun *et al.*, 1997;

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Kajimura *et al*., 1999; see Maquet, 2000 for a review). Nevertheless, the inhibition of processing is not total.

The present article examines the extent to which a physical change to a frequently occurring auditory stimulus can be detected during sleep. A major difference between natural sleep and other unconscious states is that the former is rapidly reversible. The sleeper must become aware of highly relevant biological or personal information in order to switch from a state of unconsciousness (sleep) to one of consciousness (wakefulness) and take appropriate action. There is some debate about the extent to which cortical regions remain active during sleep. During NREM sleep, functional neuroimaging studies suggest that the auditory cortex is much less active than in the waking state (Braun *et al*., 1997; Czisch *et al*., 2002; Kajimura *et al*., 1999). Nevertheless, a number of cells in the auditory cortex do show similar response activation in waking and NREM sleeping states in both humans (Braun *et al*., 1997; Edeline *et al*., 2001) and animals (Coenen and Drinkenburg, 2002). By comparison, during REM sleep, the auditory cortex appears to be more responsive to external stimuli (Czisch *et al*., 2002), particularly if the stimulus is either biologically or psychologically salient (Portas *et al*., 2000). Thus, an infrequently presented very loud tone (Cote *et al*., 2001) or the subject's own name (Perrin *et al*., 1999; Pratt *et al*., 1999) may elicit a large positive peak event-related potential (ERP) (P300) that is generally associated with overt signal detection in the waking state.

A variation in an otherwise homogenous acoustic environment is highly relevant for both humans and animals (Näätänen, 1992). Detection of change is thought to occur preattentively prior to conscious awareness of the actual acoustic change. The detection process requires that the encoding of a new incoming stimulus be compared to an existing stored memory (or neural representation) of the immediate acoustic past. If this encoding matches the neural representation, further processing ceases. If, on the other hand, the encoded stimulus fails to match the neural representation, environmental 'change' will be detected, and as a consequence further processing will be warranted. Both animal and human studies indicate that this detection of change occurs in the supratemporal plane of the auditory cortex (Alho *et al*., 1998; Csépe, 1995; Opitz *et al*., 1999, 2002; Sabri *et al*., 2004).

Automatic change-detection processes have been studied extensively during wakefulness by using an electrophysiological measure, the mismatch negativity (MMN) or its electromagnetic equivalent, the MMNm (Näätänen, 1992). The MMN is typically a small amplitude (1–3 μV), fronto-central, negative auditory ERP deflection that is elicited in response to an acoustic change or irregularity. It is often recorded in the so-called 'oddball' paradigm: the subject is presented with a series or a train of repetitive sounds (the 'standards') while at rare and random times, the sound is changed to a 'deviant' or an 'oddball' by varying some physical feature of the standard (e.g. frequency, intensity, duration, location). The MMN can also be elicited by more complex changes in stimulus parameters, or in the pattern or timing of the acoustic stimuli. The MMN is considered by many authors to reflect the outcome of a comparison process taking place in sensory memory (Näätänen and Winkler, 1999; Winkler and Näätänen, 1995). Memory representation is well established for the standard stimulus because its frequent presentation strengthens the neuronal trace. The encoded acoustic features of the incoming deviant stimulus fail to match the neural representation of the standard, and as a result the MMN is elicited. Importantly, if the physical mismatch between the incoming deviant stimulus and the existing neural representation is sufficiently large, its detection may also trigger an involuntary attentional switch that allows the participant to become aware of biologically relevant changes in an otherwise unattended acoustic environment. A centro-frontal positive wave, labeled the P3a (to distinguish it from the later and more parietal P3b or P300), has been claimed to reflect the actual attentional switch (Escera *et al*., 1998, see Friedman *et al*., 2001 for a review).

A number of studies have now attempted to record the MMN during the sleep onset period and within definitive sleep itself (for reviews, see Atienza *et al*., 2002; Campbell and Colrain, 2002). An attenuated MMN can be reliably recorded during REM sleep following presentation of large changes in tonal frequency (Atienza *et al*., 1997, 2000; Loewy *et al*., 1996; Nashida *et al*., 2000). Nevertheless, the duration of the sensory memory as reflected by the MMN appears to be shorter in REM sleep than in the waking state (Atienza *et al*., 2000). Studies that have reported an MMN during REM sleep have presented stimuli relatively rapidly (every 450–600 ms). When stimuli are presented at slower rates (every 1.5–2 s), the MMN cannot be elicited by similar frequency changes (Niiyama *et al*., 1994; Nordby *et al*., 1996), although it has been observed in the waking state. The duration of sensory memory during REM sleep might be extended up to 3 s provided that stimuli are presented rapidly within blocks (Atienza *et al*., 2000), but this is still much reduced compared to the 4–9 s duration of sensory memory observed in the waking state using a similar stimulus train paradigm (Böttcher-Gandor and Ullsperger, 1992; cf. Sabri and Campbell, 2001). Nonetheless, when stimuli are presented as often as every 600 ms, small changes to tonal frequency or even large changes to stimulus intensity will not elicit the MMN during REM sleep (Loewy *et al*., 1996, 2000).

During NREM sleep, the MMN has been consistently reported to be difficult to elicit in either stage 2 or SWS (Loewy *et al*., 1996, 2000; Nashida *et al*., 2000; Nielsen-Bohlman *et al*., 1991; Nittono *et al*., 2001; Nordby *et al*., 1996; Paavilainen *et al*., 1987; Sallinen *et al*., 1994; Winter *et al*., 1995), even when the extent of deviance is very large or stimuli are presented as often as every 450–600 ms. Sallinen *et al*. (1994) did report an MMN-like wave following frequency deviants in stage 2 sleep, but only when the deviant stimulus also elicited a very large amplitude (about 100 μV) K-Complex. Unfortunately, the same laboratory was unable to replicate this finding in a later study using similar experimental conditions (Sallinen *et al*., 1996). During the brief transition from a waking to a

NREM sleeping state, Sabri *et al*. (2000) did observe a small MMN during stage 2 sleep, but only for a large, 1000 Hz frequency difference between the standard (1000 Hz) and deviant (2000 Hz). The MMN could not be observed in stage 2 sleep following the presentation of a smaller 1100 Hz deviant. Nittono *et al*. (2001) also studied the effects of sleep onset on the MMN. Like Sabri *et al*. they were unable to observe an MMN at the beginning of stage 2 when the difference between the standard and the deviant was small (either 100 or 200 Hz).

In the waking state, most MMN researchers tend to use a deviant that is physically similar to the standard because it is assumed that similar standard and deviant stimuli activate essentially identical neuronal populations in the auditory cortex. The exogenous N1 component, elicited by sensory input of the standard and deviant, should therefore also be identical. The subtraction process (deviant minus standard waveform) will cancel common processing (the N1) leaving only ERPs that are associated with change detection (the MMN). However, when a deviant is physically quite distinct from the standard, a 'fresh' and different neural population will be activated. The N1 following the standard and the large deviant, therefore, will not be identical. The time between standards is very short resulting in smaller N1 amplitude due to neural refractory period. By contrast, the time between deviants is much longer, resulting in a larger N1 amplitude. Deviants that are physically quite distinct from the standard will also elicit a large amplitude, short latency MMN, peaking at about the time of N1. The difference wave formed by subtracting the deviant and standard ERPs thus will represent a composite of N1 and MMN activity, which overlap and summate both in temporal and spatial manner. This composite deviant-related negativity (DRN)[1] may therefore not be a 'pure' MMN (Alho *et al*., 1992; Woldorff *et al*., 1998). During NREM sleep the amplitude of N1 is greatly attenuated (see Campbell and Colrain, 2002 for a review), even for stimuli that are presented very slowly, circumventing the overlap problem of the N1 and MMN. Unfortunately, other problems arise; specifically, a physically distinct deviant may also elicit a large amplitude negative wave peaking from 300 to 350 ms, perhaps related to the vertex sharp wave (Bastien *et al*., 2002). The initial portion of the large amplitude N350 may also overlap and summate with the much smaller and earlier MMN, again making the interpretation of the DRN ambiguous. Nevertheless, very few studies have been able to record even a DRN in NREM sleep. Finally, during REM sleep, N1 returns to 25–50% of its waking amplitude, revisiting the problem of overlap of the N1 and MMN sources, particularly when large deviants are employed. Unfortunately, it would appear that only very large deviants can elicit a DRN during REM sleep.

Two different explanations for the failure to observe an MMN (or DRN) during NREM sleep have been proposed (Atienza *et al*., 2001, 2002; Campbell and Colrain, 2002). For the MMN to be elicited in response to a stimulus change, the standard stimulus must be adequately encoded, subsequently stored, and then remain active in sensory memory (Cowan *et al*., 1993; Näätänen and Winkler, 1999). The inability to observe an MMN during NREM sleep might be explained by a failure of the initial encoding of the standard stimulus because of prior thalamic inhibition or degradation. On the other hand, it is possible that initial encoding and even the formation of the sensory representation are unaffected by sleep. There is, however, evidence that sensory representation of the standard may fade very rapidly during REM (Atienza *et al*., 2000) and will probably fade even more rapidly in NREM sleep. The inability to observe an MMN during NREM sleep might therefore also be explained by a rapidly fading sensory memory.

Recently, Sabri *et al*. (2003) examined the MMN during a brief 10-min sleep onset periods. A stimulus was presented very rapidly, every 150 ms. The authors reasoned that if inhibition or degradation of stimulus input prior to entry into the MMN generating system caused the failures of the MMN elicitation in previous sleep studies, then rapid stimulus presentation should not have an effect. Instead, the MMN would gradually be reduced in amplitude during the sleep onset process, and would not be apparent during definitive sleep. On the other hand, if sleep shortens the duration of sensory memory, then a very rapid rate of stimulus presentation can assure that a deviant will be presented within the still active standard representation, and potentially MMN will be elicited throughout the entire sleep onset period. Subjects heard either a large (2000 Hz) or a small (1100 Hz) deviant embedded in a train of frequently occurring standards (1000 Hz). The large deviant elicited an extended negativity that might have included the MMN in both stages 1 and 2 of sleep. The small deviant failed to elicit any MMN-like activity early in the NREM sleep onset process.

In the Sabri *et al*. (2003) study, subjects were repeatedly awakened after a short 10-min sleep onset period. Only a brief period of definitive sleep (stage 2) was therefore captured. A sufficient amount of SWS (stages 3 and 4) was unavailable to permit an analysis of the MMN. During the brief sleep onset period, none of the subjects entered REM sleep. The present study will examine whether an all-night sleep including long duration NREM (stage 2 and SWS) and REM sleep will alter the MMN recorded in the waking state when stimuli are presented rapidly, for both small and large deviance. The occurrence of the MMN or DRN in sleep would support the hypothesis that the sensory memory trace for the standard stimulus remains active at least for a very brief period of time. Failure to observe the MMN or DRN within sleep would be consistent with the hypothesis that sensory encoding has already been degraded prior to entry into the cortical MMN comparison system.

[1]The use of the label 'deviance-related negativity (DRN)' was introduced by Woldorff *et al*. (1998): 'The term deviance-related negativity (DRN) is used to refer to the observed additional negativity in the deviant-stimulus ERP relative to the standard-stimulus ERP in the same channel over the interval 130–280 ms. We use DRN as a neutral term to avoid prejudging the controversial question about which functional components may be included in the overall negativity' (p. 283).

METHODS

Subjects

Twelve (seven men) healthy, right-handed undergraduate university students volunteered to participate in this study. Subjects were between the ages of 18 and 27 years (mean = 23.2 years). All were self-reported good sleepers with no history of hearing or neurological disorders. Subjects were instructed to refrain from alcohol and caffeine use within 24 h of testing. Prior to testing, informed consent was obtained from each subject. All subjects received an honorarium for their participation in the study. This study was conducted following the Canadian Tri-Council (Natural, Health, and Social Science) Ethical Guidelines.

Physiological recording

The electroencephalogram (EEG) and electrooculogram (EOG) were recorded using Grass gold-cup electrodes. They were filled with electrolytic paste, and affixed to the skin by surgical tape and to the scalp by gauze. The EEG was recorded from five scalp locations placed at midline frontal (Fz), central (Cz), parietal (Pz), and occipital (Oz) sites, and from the right mastoid (M2). The reference was the tip of the nose. A vertical EOG was recorded from electrodes placed at the supra- and infra-orbital ridges of the right eye. A horizontal EOG was recorded from electrodes placed at the outer canthus of each eye. A ground electrode was placed on the forehead. Inter-electrode impedances were kept below 5 kΩ. The filter band-pass of the analogue amplifiers was from 0.16 to 35 Hz.

The EEG and EOG data were digitized at a 256 Hz sampling rate, using a 12-bit analogue-to-digital (A/D) converter and stored continuously to hard disk. Off-line, the continuous data were reconstructed into discrete trials or 'sweeps'. A sweep began 50 ms prior to stimulus onset and continued for another 450 ms following it (i.e. the total sweep time was 500 ms). Guidelines for measurement of the MMN in the waking state recommend a low filter setting of 2 Hz (Schröger, 1998). Sabri and Campbell (2002) have noted that the low filter setting may need to be increased to 3 Hz during sleep in order to attenuate low frequency activity in the background EEG. The 3 Hz low filter has minimal effect on the waking MMN. The averaged waveforms for each condition were therefore subsequently digitally filtered using an inverse FFT algorithm with a bandwidth of 3–20 Hz (3 dB cut-off).

Stimuli

To ensure comparison with previous studies, stimuli identical to those used by Sabri *et al.* (2003) were employed. Evoked potentials were elicited using 'standard' 1000 Hz tone pips (80 dB SPL; 55 ms total duration; 5 ms rise/fall time). Two different infrequently occurring deviant stimuli were employed. The frequency of the large deviant was 2000 Hz while that of the small deviant was 1100 Hz. The auditory stimuli were synthesized using a 16-bit waveform generator card. Stimulus probability was 0.934 for the standard stimuli and 0.033 for each of the two deviant stimuli. Standard and deviant stimuli occurred pseudo-randomly with the restriction that two deviants could not be presented consecutively. Stimuli were presented at a constant rapid stimulus-onset asynchrony (SOA) of 150 ms. A deviant was therefore presented, on average, every 4.5 s. A total of 5000 trials was presented per block. All auditory stimuli were presented monaurally to the left ear via Eartone 3A insert earphones (Etymotil Research, Elkgrove Village, IL, USA). A Bruel and Kjaer 2209 (Naerum, Denmark) sound level meter equipped with a 2 cm^3 coupler was used to calibrate the auditory signals.

Procedure

Testing began in wakefulness during which subjects were instructed to read a self-chosen book while ignoring the tones. This condition was repeated four times (i.e. a total of 20 000 trials). The EOG was monitored to ensure that subjects continued reading. During sleep, each condition was repeated at least 10 times for each participant. Stimulus presentation did not begin until at least 10 min of definitive sleep (marked by delta activity, spindles and K-Complexes) had accumulated. A minimum of 50 000 trials was presented per participant (i.e. 46 700 standards, 1650 large and 1650 small deviants across the various stages of sleep). If the subject awoke during the testing period, stimulus presentation was halted and the data rejected from further analysis.

Data scoring and analysis

The different stages of sleep were classified by an experienced scorer according to the standard criteria of Rechtschaffen and Kales (1968). An epoch of 10 s was used for sleep staging rather than the usual 30 s in order to increase the precision of the scoring. In cases of stage ambiguity, the epoch was excluded from further analysis. ERPs were sorted into three different sleep stages: stage 2, REM, and SWS (combined stages 3 and 4 sleep). In the waking state, trials in which the EEG or EOG exceeded ± 100 μV were rejected from averaging. This was typically because of unusually large amplitude saccadic (horizontal) eye movements while reading or because of eye blinks. Single trial data in stage 2, SWS or REM were rejected if either the EEG or EOG amplitude exceeded ± 150 μV (to permit inclusion of high amplitude delta waves).

Single-trial ERPs were sorted and averaged within each sleep stage. The amplitude of the sleep EEG is very high relative to the waking state. Signal averaging techniques can be used to reduce the amplitude of this background noise, provided that a sufficient number of trials are available for averaging. Data in different blocks were therefore collapsed and averaged. Previous studies have not shown either time-of-night or repetition effects. Separate averages were computed for the standard and deviant stimuli. The MMN is best observed in a subtraction waveform. Because a large deviant was employed in this study, the resulting negative difference

wave will be labeled, the DRN. The difference waveforms were computed by subtracting, point-by-point, the standard from the deviant waveforms at each electrode site within each sleep/wake stage. The amplitude of N1 was expected to be very small in the waking state because of the very rapid rate of stimulus presentation. During NREM sleep, its amplitude was expected to be reduced further to near-baseline level. The scoring in the absence of a peak is problematic. In addition, the MMN often appears as a slow-wave rather than as a distinctive peak. Alho *et al*. (1989) have, thus, employed a mean interval averaging procedure to overcome these difficulties. This procedure was employed here for the scoring of the ERP data: The 400 ms poststimulus sweep period was subdivided into eight 50 ms latency intervals starting at stimulus onset. Within each of these intervals, the average of all data points was computed, yielding an average amplitude measure. The average of all data points in the 50 ms prestimulus period served as a zero amplitude baseline from which all amplitudes were measured.

One-tailed *t*-tests (negative directionality was predicted as the polarity of the MMN should be negative) were then computed for each of the eight latency intervals in order to evaluate whether the Fz (where the MMN is largest) mean amplitudes for each interval significantly differed from zero baseline. All differences were considered significant at $P < 0.05$. To restrict the likelihood of a chance finding, the time window of occurrence of the DRN and its scalp topography were constrained to conform to that observed in literature. The DRN had to occur only within a 100–250 ms time window after stimulus onset and be larger frontally/centrally than parietally. In addition, a polarity inversion had to be observed at the mastoid (M2). Once the existence of a DRN was determined within the different stages of sleep and wakefulness, a two-way repeated measures ANOVA was used to assess the effects of stage (wake, stage 2, REM, SWS) and deviant type (small, large) on the DRN. Greenhouse–Geisser corrections were used when appropriate. When a significant main effect was found, Newman–Keuls *post-hoc* comparisons (0.05 criterion level) were used to determine significant differences among the different conditions.

RESULTS

The total mean number of averaged trials per subject was 19 051, 30 517, 14 181, and 9243 during wakefulness, stage 2, REM, and SWS, respectively.

Large deviance

The grand-averaged waveforms to the standard and large deviant stimuli in the different waking and sleeping states are superimposed in Fig. 1. During wakefulness, only very small amplitude N1–P2 was observed following the standard because of the rapid rate of stimulus presentation (Näätänen and Picton, 1987). A large amplitude negative–positive complex was observed following presentation of the deviant. The negative deflection (the DRN), peaking at 129 ms, is probably

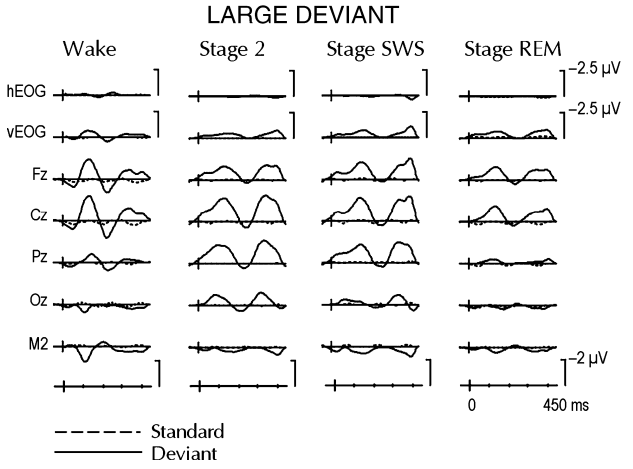

Figure 1. Deviant (2000 Hz) and standard (1000 Hz) grand-averaged waveforms for wakefulness, stage 2, SWS, and REM sleep.

a combination of N1 and MMN source activity. The grand-averaged difference waveforms for the large deviant appear in Fig. 2. The mean frontal amplitudes of the difference waveforms for each of the 50 ms intervals in all stages are depicted in Table 1. When subjects were awake, a long-lasting DRN was visible. The frontal DRN was significant in both the 100–150 and 150–200 ms intervals ($P < 0.05$). The mastoid (M2) showed a polarity inversion across both intervals. During stage 2, the long-lasting DRN began earlier being significant from 50 to 200 ms ($P < 0.05$). Within REM and SWS, the DRN was significant in the 100–200 and 100–250 ms periods, respectively ($P < 0.05$). The mastoid showed a small polarity inversion in each of these three stages.

A positive wave, probably a P3a, was also apparent during wakefulness ($P < 0.05$), peaking at about 250 ms. It had a centro-frontal maximum scalp distribution. A smaller and non-significant late positivity having a similar centro-frontal maximum was also seen during REM sleep. A non-significant positive peak was also visible during NREM (stages 2 and

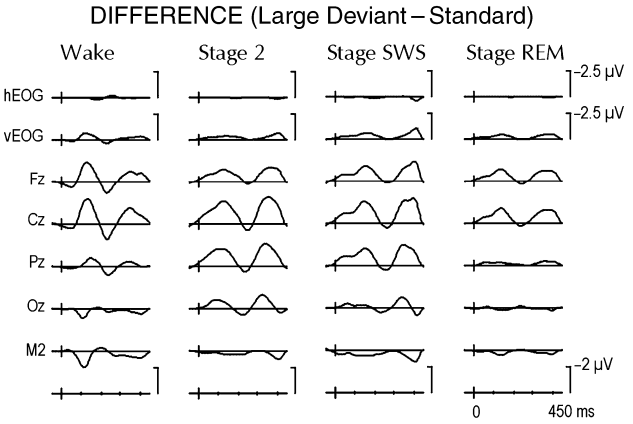

Figure 2. Grand-averaged large deviant difference waves. The differences waves were computed by subtracting the deviant from the standard waveforms observed in Fig. 1.

Table 1 Large deviance: mean amplitudes (μV) and standard deviations (parenthesis) of the difference waveforms at Fz for each 50 ms interval of the total 400 ms sweep

	1–50	*51–100*	*101–150*	*151–200*	*201–250*	*251–300*	*301–350*	*351–400*
Wake	0.56 (0.62)	−0.10 (1.01)	−2.72* (1.43)	−1.06* (0.74)	1.37† (0.72)	0.22 (0.63)	−1.28* (1.04)	−1.40* (1.14)
Stage 2	−0.44 (0.65)	−0.73* (1.16)	−1.18* (1.45)	−0.84* (0.90)	−0.04 (0.47)	0.01 (0.50)	−0.99* (1.29)	−1.36* (1.71)
SWS	−0.86 (1.93)	−0.89 (2.40)	−1.57* (2.32)	−1.53* (1.44)	−0.54* (0.87)	−0.09 (1.16)	−1.05 (2.43)	−2.02* (3.00)
REM	−0.23 (0.67)	−0.61 (1.14)	−1.30* (1.40)	−0.66* (0.96)	0.32 (0.53)	−0.11 (0.53)	−1.04* (1.20)	−1.05* (1.64)

For all conditions $n = 12$.
*Negative amplitude values significantly different from the baseline ($P < 0.05$).
†Positive amplitude values significantly different from the baseline ($P < 0.05$).

SWS), but it was more centro-parietally distributed over the scalp. The positive wave was followed by a late negativity, peaking on average at 350 ms. It was significantly different from baseline level in both waking and sleeping states ($P < 0.05$). However, the scalp topography of this late negative wave was different in the two states: during the waking and REM it was near baseline level at parietal and occipital sites while during NREM its amplitude remained large at these sites.

Small deviance

The grand-averaged waveforms to the standard and small deviant stimuli in the different waking and sleeping states are superimposed in Fig. 3. During wakefulness, a distinctive N1–P2 was again difficult to observe following the presentation of the standard. The difference waveform revealed a small amplitude DRN, peaking at 150 ms and followed by small amplitude positive wave, peaking at about 270 ms. The grand-averaged difference waveforms appear in Fig. 4. The mean frontal amplitudes of the difference waveforms for each of the 50-ms intervals in all stages are depicted in Table 2.

Within wakefulness, a small but significant frontal DRN was evident in the 150–200 ms interval ($P < 0.05$). The mastoid (M2) showed a polarity inversion. The frontal DRN elicited by the small deviant was significantly reduced in amplitude compared to that elicited by the large deviant ($P < 0.05$). Within REM and NREM sleep, very small negativities were observed in the 150–200 ms period. Their amplitudes did not significantly deviate from the zero baseline ($P > 0.05$). The DRN in wakefulness was followed by a significant positivity (probably the P3a) in the 250–300 ms interval and a late negativity in the 350–400 ms period ($P < 0.05$). This positivity was not apparent during stage 2 sleep or SWS. A small amplitude P3a was elicited during REM sleep, but it failed to attain significance. A significant late negativity in the 350–400 ms period was observed in the waking state ($P < 0.05$). This late negativity was not observed in either NREM or REM sleep.

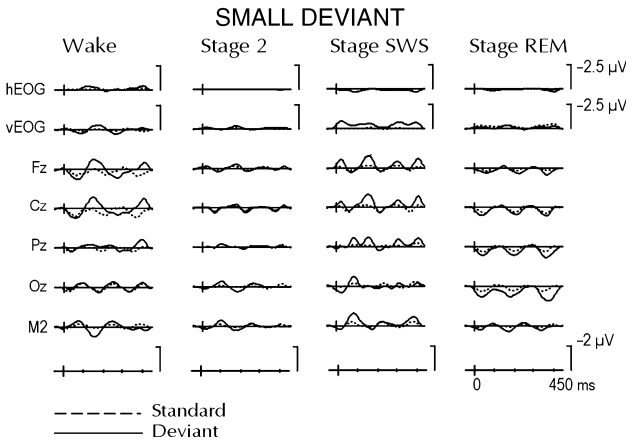

Figure 3. Deviant (1100 Hz) and standard (1000 Hz) grand-averaged waveforms for wakefulness, stage 2, SWS, and REM sleep.

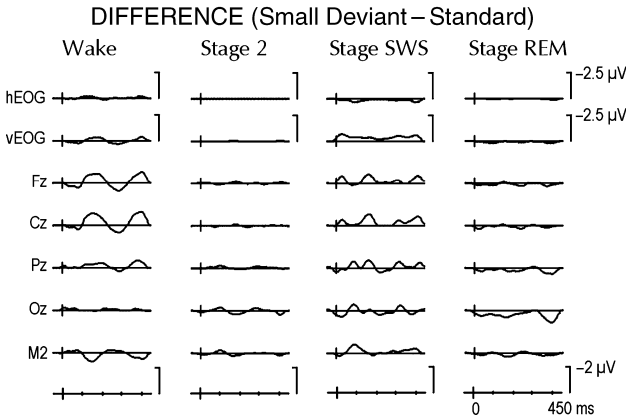

Figure 4. Grand-averaged small deviant difference waves. The difference waves were computed by subtracting the deviant from the standard waveforms observed in Fig. 3.

A two-way repeated measures ANOVA on the difference scores revealed a significant main effect of Deviant and Stage ($P < 0.005$). *Post-hoc* testing indicated that the deviant-related activity following the small deviant was significantly attenuated compared with that for the large deviant. In addition, the DRN in wakefulness was significantly larger than that observed in either stage 2, REM, or SWS ($P < 0.05$). No other effects were significant ($P > 0.05$).

DISCUSSION

The MMN is thought to represent the outcome of a system involved in the detection of stimulus change. In Näätänen's

Table 2 Small deviance: mean amplitudes (μV) and standard deviations (parenthesis) of the difference waveforms at Fz for each 50 ms interval of the total 400 ms sweep

	1–50	*51–100*	*101–150*	*151–200*	*201–250*	*251–300*	*301–350*	*351–400*
Wake	0.17 (0.19)	0.30 (0.48)	−0.47 (0.84)	−0.69* (0.64)	−0.07 (0.53)	0.51† (0.45)	0.13 (0.57)	−0.64* (0.84)
Stage 2	−0.07 (0.28)	0.07 (0.43)	0.03 (0.50)	−0.12 (0.33)	0.00 (0.25)	−0.02 (0.22)	0.07 (0.30)	−0.05 (0.61)
SWS	−0.41 (1.56)	0.06 (0.77)	−0.20 (0.69)	−0.54 (1.06)	−0.08 (0.64)	−0.12 (0.75)	−0.15 (1.46)	−0.22 (1.00)
REM	0.15 (0.37)	0.17 (0.33)	0.03 (0.38)	0.01 (0.31)	0.20 (0.32)	0.05 (0.29)	0.02 (0.30)	0.22 (0.46)

For all conditions $n = 12$.
*Negative amplitude values significantly different from the baseline ($P < 0.05$).
†Positive amplitude values significantly different from the baseline ($P < 0.05$).

(1992) model, this requires a comparison of the incoming physical features of the deviant stimulus with the stored neuronal representation of the standard. The automatic detection of acoustic deviation is believed to occur preconsciously, prior to awareness that the deviant had indeed been presented. If the extent of deviance is sufficiently large, however, its detection may lead to an automatic attentional switch allowing the individual to possibly become aware of the acoustic environment. A number of researchers use the P3a as evidence of the actual attentional switch (e.g. Escera *et al*., 1998). In the present study, there was evidence in wakefulness of both the MMN and the P3a.

The scalp-recorded negativity that was observed in wakefulness following presentation of the large deviant probably reflects a contribution of both the N1 and MMN intra-cranial sources. Consistent with the finding that the amplitude of the MMN varies directly with the extent of deviance (Muller-Gass *et al*., 2001; Sams *et al*., 1985), a much reduced DRN was observed following the small deviant; this is probably a true MMN. In wakefulness, the amplitude of N1 following the standard stimuli was near baseline level. The amplitude of the N1 following the presentation of the small deviant also would have been expected to be near baseline because it should have activated the same neuronal population as the standard. The reduction of N1 is explained, in part, by the very rapid rate of stimulus presentation (Näätänen *et al*., 1987; Sussman *et al*., 1998). Moreover, even though subjects were awake, N1 declines in amplitude just prior to the sleep onset period, perhaps because of accumulated fatigue and sleepiness (Ogilvie *et al*., 1991), particularly when stimuli are presented rapidly (de Lugt *et al*., 1996).

Consistent with previous studies, a significant, but attenuated DRN was also apparent following the large deviant during REM sleep (Atienza *et al*., 1997, 2000; Loewy *et al*., 1996; Nashida *et al*., 2000). Again, this DRN may also reflect a composite of N1 and MMN activity. It is exceedingly difficult to determine the independent contribution of the N1 and MMN sources. Equally challenging is verifying whether the N1 or MMN sources were differentially activated within the waking and REM states. The small deviant failed to elicit a significant DRN. In the waking state, a relatively large amplitude positivity, within the 201–250 ms time window, was apparent following the large deviant. A similar positivity was apparent during REM sleep, although it failed to attain significance. The automatic detection of acoustic deviation is believed to occur preconsciously, prior to awareness that the deviant indeed had been presented. If the extent of deviance is sufficiently large, its detection may lead to an involuntary attentional switch allowing the individual to possibly become aware of the acoustic environment; this process is probably reflected by the P3a rather than the MMN. The P3a can peak as early as 200–250 ms, when simple tonal stimuli are used (as in the present study), and as late as 300–350 ms, when more complex stimuli are used (Escera *et al*., 1998). In this study, there was thus evidence of both the MMN which is involved in the detection of stimulus change and, the P3a which is involved in the subsequent attentional switch within the waking state and possibly within REM sleep.

In spite of the very rapid rate of stimulus presentation, the small deviant did not elicit a significant MMN during REM or NREM sleep. The most parsimonious explanation for this finding is that processing of the auditory stimuli was inhibited by the thalamic gating system prior to entry into the cortical MMN generating system, which resulted in a failure or degradation of the initial encoding of the standard stimulus. A sensory representation of the standard cannot therefore be formed in the temporal cortex. It is possible that this early inhibition was limited to the processing of the frequently presented standard stimulus. However, even if processing of the deviant stimulus did 'pass' the thalamic gating system and was successfully encoded in the temporal cortex, the poor or absent sensory representation of the standard would preclude memory comparison.

An extended DRN continued to be apparent in NREM following the large deviant. The morphology of the difference wave was remarkably similar in both wakefulness and NREM sleep; however, it represents a composite of the MMN and other negativities. The DRN began earlier in NREM sleep relative to wakefulness. In NREM sleep, it is unlikely that N1 contributed to this DRN. Most studies indicate that N1 falls to near-baseline level during NREM sleep, even when stimuli are presented as slowly as every 12 s (Armitage *et al*., 1990). Thus, even though the large deviant was presented relatively slowly (on average, every 4.5 s), N1 probably did not contribute to the scalp-recorded DRN during NREM sleep. The DRN might, however, reflect the activity of the later sleep-N350. Consistent with other studies, the deviant elicited a significant late negativity 300–400 ms after stimulus onset (Atienza *et al*., 2000; Loewy *et al*., 1996; Nittono *et al*., 2001). The amplitude of N350 (about 25–50 μV) is much larger than that of the

MMN (often < 1 μV). Although N350 peaks much later than the MMN, it is possible that its initial activation might have temporally overlapped the MMN source activity.[2] Similarly, Sallinen *et al*. (1994) have reported that the MMN is visible in stage 2 sleep but only when a K-Complex is also elicited by the deviant. When the K-Complex was not elicited, the MMN was not observed. The N350 forms part of the component structure of the K-Complex. It is unlikely, however, that the K-Complex was elicited by the deviant stimulus in the present study. K-Complexes are most often elicited when stimuli are presented slowly. Very few K-Complexes can be elicited when deviant stimuli are presented every 4.5 s (Bastien and Campbell, 1994). Nevertheless, the vertex sharp wave can be elicited by stimuli presented at this rate during an oddball sequence (Colrain *et al*., 2000), although it may not be elicited on every trial. While N350 is maximum over central areas of the scalp (Colrain *et al*., 2000), its frontal dispersion may overlap with the fronto-central MMN. The DRN that was observed in stage 2 and SWS did have a distinct central distribution, which is more consistent with a N350 than the fronto-central MMN. Moreover, although the DRN was relatively large in NREM sleep, only a very small inversion in polarity was observed at the mastoids. A small inversion of the later N350 was also apparent. Unfortunately, sleep studies have not extensively examined the inferior scalp distribution of the N350 thus precluding an explicit conclusion.

A large negative wave peaking at about 350 ms was also observed in wakefulness and during REM sleep replicating findings by Nittono *et al*. (2001). The NREM sleep-related N350 cannot be elicited in either of these states (Bastien *et al*., 2002). In addition, the scalp distributions of the late negative waves were different in NREM sleep and in the waking/REM states. The late negativity in the waking state may reflect a need for additional processing (Otten *et al*., 2000) or a call for reorientation back to the to-be-attended task following distraction by an obtrusive deviant (Schröger and Wolff, 1998). The late negativity observed during cortical arousal (waking, REM states) therefore appears to be functionally different from the NREM N350, and moreover, reflects the activity of different intra-cranial generators.

In summary, a statistically significant DRN was observed in the waking state and during both REM and NREM sleep following the large deviant. These scalp-recorded DRNs do not necessarily reflect the activity of the same intra-cranial sources nor do they share functional significance. In wakefulness and REM sleep this negativity might be a composite of N1 and MMN, whereas in NREM sleep it might be a composite of MMN and a later N350 component. This N350 occurs only in NREM sleep. The DRN was, however, absent following the small deviant in REM and NREM sleep supporting the hypothesis that acoustic information, unless highly salient, is gated prior to entry into the change detector system.

Can the ambiguity between the DRN and MMN be resolved? Unfortunately, it would appear that if acoustically simple pure tone deviants are employed, they will need to be physically quite distinct from the standards for a possible MMN to be elicited during either REM or NREM sleep. But, more complex deviants may not need to be as distinctive. Atienza and Cantero (2001) employed acoustically complex standards and deviants. These formed a long duration, complex spatiotemporal pattern in which the deviance pattern was introduced only 225 ms after stimulus onset. Importantly, in the waking state, the acoustic pattern of the deviant was often perceived as not being different from that of the standard. Once subjects did learn to distinguish between the stimuli, the presentation of the deviant elicited the MMN. Another advantage of this paradigm is that the delay in presentation of deviance also bypassed the overlap of the MMN and N1 potentials. In spite of the fact that the standard and deviant were quite similar, the deviant did elicit an MMN during REM sleep (stimuli were not presented during NREM), which is highly unlikely to be a result of an N1 overlap. Such an elegant paradigm may not help to resolve the NREM controversy. The long duration complex stimuli used by Atienza *et al*. had to be presented relatively slowly. A failure to elicit the MMN in NREM might then again be explained by a rapid fading of sensory memory. Ideally, acoustically complex but short duration stimuli should be rapidly presented to help resolve this controversy.

[2]It might also be argued that the N350 peaks much too late to influence the DRN. There is, however, very strong evidence that in the waking state, another late negativity can overlap and summate with the MMN. The MMN is usually recorded when subjects ignore the auditory channel and attend to another task (for example, in the present study, subjects were asked to read a book and ignore the auditory stimuli). This is because when subjects attend to the auditory channel, detection of the rare deviant (or 'target') is associated with the elicitation of another late negativity, the N2b. N2b (the MMN was initially labeled as the N2a, but this label is now rarely used) peaks 250–300 ms after stimulus onset. The N2b has been demonstrated to overlap with the MMN. Thus, the MMN appears to be larger when subjects attend to the auditory channel. Näätänen (1992) has pointed out that this apparent increase in the amplitude of the MMN is actually due to the initial overlapping influence of the N2b.

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