Decay time of the auditory sensory memory trace during wakefulness and REM sleep

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Abstract
In a repetitive auditory stimulus sequence, deviant infrequent tones typically elicit a component of auditory event-related potentials termed mismatch negativity (MMN). The elicitation of MMN is assumed to reflect the existence of a memory trace of the standard stimulus that has a decay time of about 10 s and is strengthened by repetition of the standards. The main aim of the present study was to test the decay time of the sensory memory trace during rapid-eye movement (REM) sleep vs. wakefulness, as indexed by the MMN. Subjects were presented 10 tone trains, separated by 3, 6, or 9 s of silence, during waking and REM sleep. Each train consisted of 9 standards of 1000 Hz and 1 deviant of 2000 Hz that occurred at position 1, 2, 4, or 6. The waking deviants elicited a frontocentral negativity with a scalp topography equivalent to the MMN component. During REM sleep, the negative component showed the same scalp distribution only for the 3-s intertrain interval (ITI). In this brain state, the MMN amplitude was smaller and decreased with prolongation of the ITI. These results suggest a weaker sensory memory trace formation and a premature decay time of such a memory trace during REM sleep as compared with wakefulness.

Descriptors: Auditory event-related potentials, Auditory sensory memory, REM sleep, Memory trace, Mismatch negativity, Neuronal representation, Sleep, Humans

The infrequent changes that burst into a sequence of homogeneous repetitive auditory stimuli cause mismatch responses, which can be studied using event-related potentials (ERPs). These changes typically elicit a negative ERP component known as mismatch negativity (MMN) (Näätänen, Gaillard, & Mäntysalo, 1978, 1980; Näätänen & Michie, 1979). Although the MMN usually peaks around 150–250 ms from stimulus onset, its amplitude increases and its latency shortens as a function of the stimulus deviation magnitude (Tiitinen, May, Reinikainen, & Näätänen, 1994). This component shows its maximum amplitude over frontocentral regions and inverts polarity at postero-temporal leads. Accordingly, its main generators have been located in the auditory cortex on the superior temporal plane (for a review, see Alho, 1995; see also Alho et al., 1998; Woldorff, Hillyard, Gallen, Hampson, & Bloom, 1998).

The MMN is thought to reflect the outcome of a mismatch process automatically registering the deviation of the current input from the neuronal representation of a repetitive stimulus in sensory memory (Näätänen, 1990, 1992). This deviance detection mechanism uses not only information contained in the transient sensory memory but also information maintained in long-term memory. Cowan, Winkler, Teder, and Näätänen (1993) presented stimulus trains separated by long silent intervals, and found that only the deviants delivered from position 2 on elicited an MMN. The authors suggested that the memory trace left by repetitive stimulus, which was deactivated between each two consecutive trains, is reactivated by one reminder of the standard stimulus at the start of the train. Such a reactivation process is only possible if the information has been maintained in a long-term memory (Cowan et al., 1993; see also Winkler, Cowan, Csépe, Czigler, & Näätänen, 1996). Some results suggest that what is being reactivated is a separated representation of individual features of stimuli (Ritter, Gomes, Cowan, Sussman, & Vaughan, 1998). However, the change detection mechanism indexed by MMN seems to operate on both specific and gestalt representations of features of stimuli (for a review, see Ritter, Deacon, Gomes, Jawitt, & Vaughan, 1995).

On the other hand, it has been suggested that the MMN also represents a triggering signal for the involuntary attention capture. Several lines of evidence support such hypothesis. First, if the physical differences between standard and deviant stimuli are large, the MMN is followed by the P3a component (Näätänen, Simpson, & Loveless, 1982; Sams, Paavilainen, Alho, & Näätänen, 1985). This electrophysiological component is usually elicited by novel stimuli and is thought to be associated to an automatic orienting of attention toward the deviant stimulus (Alho, Paavilainen, Reinikainen, Sams, & Näätänen, 1986; Näätänen et al., 1982; Sams et al., 1985; Snyder & Hillyard, 1976; Squires, Squires, & Hillyard, 1975). Second, the activity of the frontal cortex, related with attention switching, has also been shown to contribute to MMN generation (Giard, Perrin, Pernier, & Bouchet, 1990). Third, the MMN is occasionally followed by changes in the autonomic nervous system responses, suggesting that an involuntary switching of atten-
tion has occurred (Lyttinen, Blomberg, & Näätänen, 1992). And finally, the most important support of the hypothesis that the MMN triggers attention switching is provided by studies finding that the task-irrelevant deviants prolonged reaction times and decreased performance accuracy in auditory and visual discrimination tasks (Escera, Alho, Winkler, & Näätänen, 1998; Schröger, 1996).

The automatic nature conferred on MMN generator mechanisms is based on the fact that the elicitation of this ERP component is independent of attention (Näätänen, Paavilainen, Tiitinen, Jiang, & Alho, 1993). However, in several studies, the MMN amplitude appeared to be greater when the deviants were attended, suggesting that mismatch-registration processes reflected by MMN are only partially automatic (Trejo, Ryan-Jones, & Kramer, 1995; Woldorff, Hackley, & Hillyard, 1991; Woldorff et al., 1998).

An additional proof contrary to the exclusive preattentive nature of MMN generator mechanisms comes from studies that assessed this component in different brain states. MMN amplitude seems to be attenuated, at least over frontocentral regions, during objective and subjective drowsiness, for both small and large stimulus changes (Sallinen & Lyttinen, 1997). Moreover, most laboratories that recorded ERPs using the classic oddball paradigm in sleeping adult humans failed to show the MMN component (Paavilainen et al., 1987; Nielsen-Bohlman, Knight, Woods, & Woodward, 1991; Sallinen, Kaartinen, & Lyttinen, 1994; Winter, Kok, Kenemans, & Elton, 1995). In human non-rapid-eye-movement (NREM) sleep, a negative waveform similar to waking-MMN was observed in stage 2 only during the second half of the night (Campbell, Bell, & Bastien, 1992), or when K-complexes followed the deviant stimulus (Sallinen et al., 1994). In human REM sleep, an MMN-like waveform was elicited by large and small changes in frequency using both a repetitive stimulus sequence (Loewy, Campbell, & Bastien, 1996) and bursts of tone trains separated by a silence of 3 s (Atienza, Cantero, & Gómez, 1997). The negativity associated to the deviance has also been studied during phasic and tonic REM periods, but it failed to reach statistical significance in either period (Sallinen, Kaartinen, & Lyttinen, 1996). The low number of deviant stimuli (the authors presented the deviant tone with a \( p = 1.5\% \)) and the use of loudspeakers to present stimulation may explain the different results obtained by those authors.

The controversy about MMN generation during sleep may be attributed essentially to the different methodology used in each one of the studies. The manipulation of stimulation varied between the studies, and in some cases (Nielsen-Bohlman et al., 1991; Paavilainen et al., 1987) the experimental sessions were not even carried out during a full nocturnal sleep period. However, the negative waves associated to the deviant stimulus, recorded during sleep, shared a decrease of the amplitude, a lesser duration, and a shortening of the latency with respect to waking MMN. The amplitude attenuation was observed over frontocentral regions and mastoids, suggesting a state modulation of both the supratemporal and frontonal MMN components. The differences in amplitude may be due to

1. the different cortical arousal level, as follows from psychopharmacological studies (Born, Fehm-Wolfsdorf, Lutzenberger, Vogt, & Fehm, 1986; Born et al., 1987a, 1987b; Serra, Escera, Sánchez-Turet, Sánchez-Sastre, & Grau, 1996);

2. the different neuromodulation brainstem systems involved, because in waking, the brain is essentially aminergic and cholinergic, in NREM it is chemically intermediate between the two, and in REM sleep it is basically cholinergic (for a review, Kahn, Pace-Schott, & Hobson, 1997); or

3. the reduced availability of attentional resources, which are assumed to modulate the MMN amplitude during wakefulness (Trejo et al., 1995; Woldorff et al., 1991, 1998).

The amplitude of the mismatch response in wakefulness is presumed to reflect the strength of the neural trace left by the repetitive stimulus. Increasing both the deviant-stimulus probability (Näätänen, Sams, Järvilehto, & Soininen, 1983) and the stimulation rate (Böttcher-Gandor & Ullsperger, 1992; Czigler, Csirba, & Csontos, 1992; Mäntysalo & Näätänen, 1987; Näätänen, Paavilainen, Alho, Reinkainen, & Sams, 1987), or introducing some temporal or physical variations in the standard stimulus (Winkler et al., 1990) attenuates the MMN amplitude. This attenuation suggests a weakening in the strength of the stimulus representation in the neuronal-trace system underlying the auditory sensory memory. According to this assumption, the decrease of the MMN during sleep could be interpreted in the same terms. Thus, if the sensory memory trace is weaker during sleep, its decline should also begin earlier. The estimated time that the repetitive stimulus information is maintained in the auditory sensory memory during wakefulness is about 10 s, as deduced from electrophysiological (Böttcher-Gandor & Ullsperger, 1992) and neuromagnetic studies (Sams, Hari, RIF, & Knautila, 1993), or up to 20 s, according to behavioral data (reviewed by Cowan, 1984). The present work aims at determining the presence and duration of the auditory sensory memory during REM sleep vs. wakefulness in human subjects as reflected by frequency MMN.

The duration of the memory trace has typically been studied by varying the interval between stimuli. Contrary to what is expected, the MMN amplitude seems not to be much affected as a product of this manipulation (Böttcher-Gandor & Ullsperger, 1992; Czigler et al., 1992; Mäntysalo & Näätänen, 1987; Näätänen et al., 1987; Sams et al., 1993; Schröger, 1996; Schröger & Winkler, 1995). Imada, Hari, Loveless, McEvoy, and Sams (1993) suggested that the different temporal probability of deviants for each interstimulus interval (ISI) might explain the small effect of ISI on the MMN amplitude. Those authors observed larger mismatch responses as the interval between deviants was longer (with a constant ISI). However, this result could also be due to the increased number of standards for the longer interdeviant intervals (Imada et al., 1993). Because the repetitive stimulation paradigm has not been demonstrated to be sensitive to the progressive deterioration of sensory memory trace as a function of ISI, an alternative might be the use of stimulus trains separated by different silent intervals. This experimental paradigm shows several advantages over the former. Figure 1 shows an example of repetitive stimulation (A) and another for trains of tone bursts (B). In Case A, the shortest interval between two deviants was 15 s (for the 3-s ISI) and the longest interval was 135 s (for the 9-s ISI). Thus, although the interdeviant interval affected the MMN amplitude (Imada et al., 1993), such an effect should be much less in Case B, in which the range was 5.5–17.5 s. On the other hand, the fact that the ISI remains constant within the tone train guarantees the memory trace formation, independently of changes in the intertrain interval. Consequently, the weakening of the neuronal representation in sensory memory could be examined after the silent interval between tone trains. Finally, the ISI used in Case B results in an increased number of stimuli to include in subsequent analyses, enhancing the signal-noise ratio in Case B with respect to Case A.
Memory-trace decay during wakefulness and REM

A. Repetitive Stimulation

![Diagram A](image)

Figure 1. Schematic illustration of two different experimental paradigms to measure the decay time of sensory memory trace as indexed by mismatch negativity (MMN) component of event-related potentials (ERPs). Bars represent the auditory tones for the standard stimulus of 1000 Hz (empty bars) and the deviant stimulus of 2000 Hz (filled bars). (A) Repetitive stimulation: the interstimulus interval (ISI) is kept constant within a trial block (each row represents a trial block), but is different between blocks (3, 6, or 9 s). Thus, the interdeviant interval varies between 15 s (for the shortest ISI) and 135 s (for the longest ISI). (B) Trains of stimulus bursts: the ISI (600 ms) is kept constant within the stimulus train in all trial blocks and the intertrain interval (ITI) is different between blocks (3, 6, or 9 s). In this case, the interval between deviants (which can occur in position 1, 2, 4, or 6 within the train) varies from 5.5 s (for the shortest ITI) to 17.5 s (for the longest ITI). Note: The experimental paradigm presented in Case B was used in the present study. The ITI was examined in three different groups of subjects (nine subjects per group).

In view of the advantages mentioned previously, the stimulation in tone trains was chosen for studying the memory trace decay time during REM sleep vs. wakefulness. As indicated in Figure 1B, trains of tone bursts were presented, in both waking and REM sleep, with a constant ISI. Three different intertrain intervals (3, 6, and 9 s) were examined in three separate groups of human subjects. A frequency-shift deviant was made to occur in various positions (P1, P2, P4, or P6) within each stimulus train to address, on the one hand, the hypothesis of the memory-trace reactivation proposed by Cowan et al. (1993), and on the other, the effect of the number of consecutive standards on the strength of the memory trace left by them.

Methods

Subjects

Recordings were obtained from 27 healthy volunteers (13 women) ranging in age between 18 and 27 years. All subjects were screened for neurological and audiological abnormalities. Most of the participants (18 subjects) had participated several times previously in other sleep studies. In cases in which the subjects had no previous experience, an adaptation night was required to overcome the first-night effects.

Experimental Procedure

Recordings were conducted in an acoustically and electrically shielded room while the subjects slept throughout the night, and during the following morning, while they read a book of their own choice, thus ignoring the auditory stimuli. Subjects were presented trains of 10 pure tones binaurally via insert earphones (Etimotic Research) at an intensity of 80 dB SPL. Tones lasted 60 ms including a rise-fall time of 5 ms. ISI was kept constant within the stimulus train (600 ms), and three intertrain intervals (ITI) of 3, 6 and 9 s were examined in three separate groups of subjects (nine subjects per group). Each stimulus train included nine tones of 1000 Hz (standard) and the other one of 2000 Hz (deviant). The deviants could occur pseudorandomly at position 1, 2, 4, or 6 in the stimulus sequence, at the same proportion (25%) of deviants for each position.

Stimulus blocks consisted of 64 tone trains each. In the reading session, six train blocks were delivered at an ITI of 3 s and five blocks at the other two ITIs. Identical sequences of tones occurred in each block, lasting about 70–90 min depending on the ITI condition. The number of tone trains during REM sleep varied from 392 to 784 depending on stage duration. Auditory stimulation during sleep started just after the first oculomotor activity that occurred in the REM period, and was stopped when the arousal level changed (presence of K-complexes, continuous alpha activity, increasing of electromyogram [EMG] level), or when bodily movements, and/or signals indicating a sleep stage change occurred. The first stimulus train of each block and the stimulation presented during the first REM period of the night were rejected from analysis, because of the frequent fluctuations in the arousal levels.

Recording

The electroencephalogram (EEG) was recorded along the midline at Fz, Cz, Pz, and Oz. In addition, six lateral electrodes were placed on the two hemispheres connecting mastoids through Fz. These electrodes will be referred to as L1, R1 (1/3 of the distance from Fz to each mastoid), L2, R2 (2/3 of the distance from Fz to each mastoid), and L3, R3 (mastoids). An electrode placed on the tip of the nose was used as reference. Electrooculogram (EOG)-derivation electrodes were placed 1 cm above and 1 cm below the right and left eye, respectively. EMG was recorded from muscles beneath the chin. Interelectrode impedance was always kept below 5 kΩ for EEG electrodes. EEG data were bandpassed between 0.1 and 100 Hz (3 dB points of a 24 dB/octave roll-off curve), then digitized continuously at 250 samples/s (sampling period 4 ms), and stored on computer disk for offline averaging. Epochs of 600 ms including a 100-ms prestimulus baseline were selected in each trial. Trials with an EEG- or EOG-amplitude change exceeding ±75 μV were rejected, as well as those containing excessive eye movements, blinks, enhanced muscle activity, amplifier clipping,
or other extracerebral artifacts. After averaging, frequencies higher than 30 Hz were digitally filtered (~3 dB). ERPs were averaged for each experimental condition and stimulus type, separately. At least 50 deviant tones were averaged for each subject in each condition, and the mean number of deviants averaged in waking and REM sleep was 63 and 75, respectively.

Three experienced sleep technologists visually scored the sleep according to the standard criteria (Rechtschaffen & Kales, 1968). Total REM sleep was distributed in three to five periods through the night, after rejecting the first, with duration varying from 9 to 47 min.

**Data Analysis**

The experimental design used in the present work included the brain state (waking and REM sleep), deviant stimulus position within tone trains (P1, P2, P4, and P6), and electrodes of the midline (Fz, Cz, Pz, Oz) as within-factors, and the ITI (3, 6, and 9 s) as the between-factor.

For each subject, the difference waveform was obtained by subtracting the ERPs elicited by standard tones from those elicited by the deviants. In each experimental condition, and for each individual subject, the deviance-related negativity (DRN) amplitudes were measured from all electrodes as the mean amplitude in the ±20-ms period around the most negative peak at Fz. The range latency in which the peak reached maximum was different depending on the brain state: 85–170 ms (waking) and 75–150 ms (REM sleep) from stimulus onset. The latency of this component was measured at Fz as the peak latency in the temporal windows mentioned above.

For each latency window, one-sample *t* tests were performed to determine whether the mean values of DRN amplitudes across the subjects were significantly different from zero at all electrodes. Differences in amplitude for each one of these components in relation to ITI (3, 6, and 9 s), arousal state (waking and REM sleep), position (P1, P2, P4, and P6), and electrode location (Fz, Cz, Pz, and Oz) were assessed using a mixed-model analysis of variance (ANOVA). The ANOVA for the differences in latency included the same factors excepting the electrode location variable. Significance levels of the *F* ratios were adjusted with the Greenhouse–Geisser correction where appropriate. The Newman–Keuls procedure for repeated measures was used for unplanned comparisons (Keppel, 1982).

The topographic distribution of the DRN was studied by performing a three-way ANOVA with ITI, arousal state, and electrode location (all EEG electrodes) as factors. Amplitude values were normalized by dividing the absolute amplitude at each electrode site by the square root of the sum of the squared amplitudes of all leads to avoid artificial interactions between the effects of different experimental conditions and the electrode location (McCarthy & Wood, 1985).

**Results**

In wakefulness, the negative waveform associated to frequency deviance was significantly different from zero in all conditions over frontocentral regions and inverted polarity in mastoids, above all for the 3-s ITI. In contrast, the negativity elicited during REM sleep was significantly different from zero level almost exclusively when the ITI was 3 s. This deflection also reached its maximum at frontal and central locations and showed a tendency toward polarity reversal in mastoids, but when compared with the baseline, the inversion failed to reach statistical significance. Table 1 displays amplitudes and latencies of DRN measured from the difference waveforms at Fz, L3, and R3 electrodes for each condition, as well as the statistical significance obtained with one-sample *t* tests. Figure 2 shows the grand-average ERPs to standard and deviant stimuli for each condition at Fz. The difference waves (deviant minus standard) at Fz and right mastoid are presented in Figure 3.

The four-factor mixed-model ANOVA allowed us to examine the effects of the different experimental manipulations on the amplitude of the negative component. The DRN amplitude was significantly affected by the brain state, *F*(1,24) = 15.03, *p < .001, the electrode location, *F*(3,72) = 156.62, *p < .001, *e* = 0.623, and the ITI, *F*(2,24) = 3.38, *p < .05. This deflection appeared to be larger in waking, at electrodes Fz and Cz, *F*(3,72) = 62.24, *p < .0001, and for 3- and 6-s ITIs, *F*(2,24) = 3.48, *p < .047. ANOVA also disclosed a significant interaction between the effects of the ITI and the arousal state, which was examined with a one-way ANOVA in each brain state. No ITI effect was found for deviant tones in wakefulness. However, the negativity associated to the frequency deviance showed significantly smaller amplitudes for the longest ITI during REM sleep, *F*(2,24) = 6.17, *p < .007.

**Table 1. Mean (SD) MMN Amplitudes Measured at Fz, Left, and Right Mastoids (L3 and R3, Respectively) From Difference Waveforms (Deviant Minus Standard) for all Levels of the Factors Intertrain Interval, Arousal State, and Position**

<table>
<thead>
<tr>
<th>Electrode</th>
<th>Intertrain interval (ITI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 s</td>
</tr>
<tr>
<td>Fz electrode</td>
<td></td>
</tr>
<tr>
<td>Waking</td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>−3.1 (1.8)**</td>
</tr>
<tr>
<td>P2</td>
<td>−2.2 (1.3)**</td>
</tr>
<tr>
<td>P4</td>
<td>−2.9 (1.5)**</td>
</tr>
<tr>
<td>P6</td>
<td>−1.9 (1.2)**</td>
</tr>
<tr>
<td>REM sleep</td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>−1.5 (1.1)**</td>
</tr>
<tr>
<td>P2</td>
<td>−1.9 (1.3)**</td>
</tr>
<tr>
<td>P4</td>
<td>−1.6 (0.9)**</td>
</tr>
<tr>
<td>P6</td>
<td>−1.8 (1.1)**</td>
</tr>
<tr>
<td>Left mastoid</td>
<td></td>
</tr>
<tr>
<td>Waking</td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>0.84 (1.0)*</td>
</tr>
<tr>
<td>P2</td>
<td>1.50 (1.1)**</td>
</tr>
<tr>
<td>P4</td>
<td>1.61 (0.9)**</td>
</tr>
<tr>
<td>P6</td>
<td>1.45 (1.7)*</td>
</tr>
<tr>
<td>REM sleep</td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>−0.07 (1.0)</td>
</tr>
<tr>
<td>P2</td>
<td>0.31 (0.6)</td>
</tr>
<tr>
<td>P4</td>
<td>0.34 (0.6)</td>
</tr>
<tr>
<td>P6</td>
<td>0.17 (0.5)</td>
</tr>
<tr>
<td>Right mastoid</td>
<td></td>
</tr>
<tr>
<td>Waking</td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>0.76 (1.5)</td>
</tr>
<tr>
<td>P2</td>
<td>1.05 (0.8)**</td>
</tr>
<tr>
<td>P4</td>
<td>0.91 (1.2)*</td>
</tr>
<tr>
<td>P6</td>
<td>1.34 (0.9)**</td>
</tr>
<tr>
<td>REM sleep</td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>−0.29 (0.9)</td>
</tr>
<tr>
<td>P2</td>
<td>0.15 (0.6)</td>
</tr>
<tr>
<td>P4</td>
<td>0.24 (0.6)</td>
</tr>
<tr>
<td>P6</td>
<td>0.19 (0.4)</td>
</tr>
</tbody>
</table>

The mean amplitudes were compared with zero using one-sample *t* tests. MMN = mismatch negativity.

*p < .05, **p < .01, ***p < .001.*
Across the nine subjects, averaged event-related potentials (ERPs) at Fz to standard tones (dashed lines) and deviant tones (solid lines) in all levels of the factors arousal state (waking, rapid-eye movement [REM] sleep), intertrain interval (3, 6, and 9 seconds), and position (P1, P2, P4, and P6).

**Figure 2.**

Difference waves obtained by subtracting grand-average event-related potentials (ERPs) to standard tones from grand-average ERPs to deviant tones at Fz and R3 (right mastoid) for waking (solid lines) and rapid-eye movement (REM) sleep (dashed lines) in all levels of the factors intertrain interval (3, 6, and 9 s) and position (P1, P2, P4, and P6).

**Figure 3.**
Finally, no effect of the deviant position within stimulus trains on the DRN amplitude was found. According to these results, the DRN amplitude displayed no variation with the number of standards previous to the deviant tone in either brain state, but it decreased with the prolongation of ITI during REM sleep.

The DRN latency was affected by the brain state, showing a later onset latency in waking (127.54 ± 19.06 ms) than in REM sleep (109.95 ± 31.76), F(1,24) = 22.82, p < .001. ANOVA yielded a significant ITI × Arousal interaction, F(2,24) = 4.38, p < .05, due to latencies being shorter for the 9-s ITI in waking, F(2,24) = 4.31, p < .05.

To rule out a possible standard tone habituation during REM sleep across the night for the 3-s ITI, a two-sample t test was carried out, comparing the peak amplitude of negativity to repetitive stimuli delivered in the first versus the second half of the night. This analysis showed no differences between the two halves of the night.

The negative waveform recorded in wakefulness and REM sleep showed a different scalp topography, as the significant Arousal × Electrode interaction confirmed by the three-way ANOVA using scaled data, F(9,216) = 11.42, p < .001, $\eta^2 = 0.392$. The interaction between the effects of ITI and electrode was also statistically significant, F(18,216) = 4.45, p < .001, $\eta^2 = 0.479$. To examine this interaction effect, two-way ANOVAs were carried out for each level of ITI. These analyses yielded significant Arousal × Electrode interactions only for the 6- and 9-s ITIs, F(9,72) = 6.46, p < .003, $\eta^2 = 0.299$; F(9,72) = 4.82, p < .015, $\eta^2 = 0.280$, whereas for the shortest ITI the negative component showed a similar scalp distribution in the two brain states. Figure 4 shows the scaled scalp amplitude distributions of DRN in waking and REM sleep for each ITI condition. This result suggests that the same brain generators remained active during waking and REM sleep when the ITI was 3 s. Therefore, the REM-associated negativity, at least for the shortest ITI, could be considered as equivalent to the waking-MMN component.

**Discussion**

The negative waveform obtained from the difference wave during wakefulness showed the typical brain topography of the MMN component. The fact that the negativity obtained in REM sleep, at least for the shortest ITI, displayed an identical scalp distribution suggests that this component, associated to frequency deviance during REM sleep after a silence of 3 s, could be equivalent to the waking MMN. As was expected, the MMN amplitude was significantly smaller and decreased with prolongation of the ITI during REM sleep, suggesting a weakening of stimulus representations in the neuronal-trace system underlying auditory sensory memory and a premature decay time of such a memory trace during this sleep stage in comparison with wakefulness.

The deviant stimuli delivered while the subjects read elicited frontally peaking MMNs between 85 and 170 ms, showing polarity reversal in mastoids. The large frequency deviance resulted in a shortening of the MMN latency and consequently in an overlapping of MMN and N1 components (Lavikainen, Huotilainen, Ilmoniemi, Simola, & Näätänen, 1995; Näätänen & Gaillard, 1983; Scherg, Vjasar, & Picton, 1989). As in previous studies (Atienza et al., 1997; Loewy et al., 1996), the DRN during REM sleep showed a smaller amplitude and a shorter latency than in wakefulness. This result may be interpreted as an activation of nonreentrant neurons in the N1 generator for the frequency of the deviant stimulus but not for that of the standard stimulus (Näätänen, Paavilainen, Alho, Heinikainen, & Sams, 1989). Contrary to this hypothesis, the negativity elicited by deviant tones presented when the ITI was 3 s showed a similar topographic distribution in both brain states (Figure 4). Additionally, the analysis of standards delivered in the first versus the second half of the night suggested that the negativity observed during REM sleep, at least for the shortest ITI, was not the result of a long-term habituation effect. According to these results, the frontally negative waveform recorded during REM sleep was assumed to be the equivalent to MMN in wakefulness.

The MMN attenuation during REM sleep as compared with the waking state was especially remarkable over mastoids, indicating that the supratemporal MMN component was sensitive to the brain state. The MMN duration as well as its latency were also shorter during REM sleep, which could be explained by disappearance of the frontal component that is typically observed at between 150 and 200 ms (Loewy et al., 1996). These results are consistent with several psychopharmacological studies showing the dependence of MMN amplitude on the brain activation state (Born et al., 1986, 1987a, 1987b; Serra et al., 1996). The MMN frontal generator appears to be the most affected by the arousal level. In fact, the MMN polarity inversion in mastoids, which is thought to be an

**Figure 4.** The scalp distribution of the negativity associated to deviant stimuli in waking (black circles/solid lines) vs. rapid-eye movement (REM) sleep (white circles/dashed lines) for the three levels of the factor intertrain interval (3, 6, and 9 s). Mean voltages ($\mu$V) within the component measurement ranges were scaled.
index of the supratemporal origin when the nose is used as reference (Näätänen & Alho, 1995; Paavilainen, Alho, Reinikainen, Sams, & Näätänen, 1991), was hardly affected by decrements in alertness during sleepiness versus the notable attenuation observed in frontocentral regions (Sallinen & Lyytinen, 1997). Recent positron emission tomography (PET) studies have disclosed a deactivation of the dorsolateral prefrontal cortex during REM sleep (Braun et al., 1997; Maquet et al., 1996; for a review, Hobson, Pace-Schott, Stickgold, & Kahn, 1998), which seems to be involved in generation of the frontal MMN component (Alho, Woods, Algazi, Knight, & Näätänen, 1994). In the present study, not only were the frontal generators probably affected by the brain state but also the supratemporal MMN generator activity was attenuated during REM sleep—as suggested by the attenuation of this deflection in mastoids. In contrast, an increase in activation of the auditory cortex was reported during REM sleep in PET studies (Braun et al., 1997). An explanation for the divergence between the two brain states could be that the cortical–cortical networks might be differentially activated during REM sleep and wakefulness.

A possible alternative to the influence of brain state is the modulation of MMN generator mechanism by attention. Several studies have reported an attenuation of MMN amplitude to deviants occurring in the unattended channel (Alain & Woods, 1994, 1997; Alho, Woods, Algazi, & Näätänen, 1992; Oades & Dittmann-Balcăr, 1995; Schröger, 1995; Trejo, Ryan-Jones, & Kramer, 1995; Woldorff et al., 1991, 1998; Woods, Alho, & Algazi, 1992). On the basis of these results, the REM-associated decrease in MMN amplitude might be due to deficient attentional resources in this sleep stage, modulating either the amplification of the mismatch signals or the quality of the sensory traces (Schröger, 1997). Therefore, the processes underlying the deviance detection system reflected by MMN seem to be partially automatic.

If we accept that the MMN attenuation during REM sleep is the reflection of a weak neuronal representation of the repetitive stimulus, as a result of either the arousal level or insufficient attentional resources, the ITI modulation observed in the present study is easy to understand. No effect on the MMN was observed varying the ITI in wakefulness, but it was observed in REM sleep. Therefore, it could be concluded that the decay time of the sensory memory trace depends on the brain functional state that modulates the memory trace formation.

No previous study modifying the ISI in wakefulness has reported differences in the MMN amplitude (Böttcher-Gandor & Ullsperger, 1992; Czigler et al., 1992; Mäntysalo & Näätänen, 1987; Näätänen et al., 1987; Sams et al., 1993; Schröger, 1996; Schröger & Winkler, 1995). The lack of influence of the ISI on the MMN was attributed to interrelation between the deviant temporal probability and the ISI. Thus, an increased ISI weakens the strength of the sensory traces, but the consequent increase of the interdeviant interval gives novelty to the infrequent stimulus, originating a larger MMN (Imada et al., 1993). However, in the current experiment, the ISI was kept constant and the interval between deviants hardly changed from one condition to another as a function of the ITI (Figure 1B). An alternative possibility to account for the lack of the ITI effect on the waking MMN is that the standard stimulus at the start of the train reactivated the memory trace remaining “dormant” during the silent interval (Cowan et al., 1993).

As a consequence of this reactivation, deviants delivered in position 2, 4, and 6 within the train would elicit an MMN even after an ITI of 9 s. If we assume this to be so, and the reactivation mechanism is an automatic process (Winkler et al., 1996), why was the auditory sensory memory not reactivated during REM sleep? The present experiment cannot answer this question. Because the existence of a neuronal trace for the repetitive stimulus is a prerequisite for activating the deviance detection system underlying MMN (Winkler & Näätänen, 1995), it is possible that the reactivation is a process dependent on the strength of such a neuronal trace.

Finally, because the repetition of standards is thought to reinforce the neuronal trace in the auditory sensory memory (Imada et al., 1993; Näätänen et al., 1987; Sams, Alho, & Näätänen, 1983), the differences in the MMN amplitude could be predicted when tones are delivered at position 1 and 2, due to decay of sensory memory trace with the increase of ITI. Tones presented at position 6, however, were expected to elicit MMN, independently of brain state and ITI. However, the MMN amplitude was not affected by the deviant position within the stimulus train. It is likely that a higher number of standard tones between deviants was necessary to see a clear effect of position on the MMN amplitude, at least during REM sleep, during which the sensory memory trace seems to be dependent on the silent interval between stimulus sequences.

The main results obtained in this study suggest, first, that the negativity elicited by deviants during wakefulness and REM sleep, at least after a silence of 3 s, is equivalent to MMN, because the scalp distribution of this deflection was similar in the two brain states. Second, the decrease of MMN amplitude during REM sleep could be reflecting a weaker neuronal-trace formation of the standard stimulus with respect to the waking state. Third, the REM-associated memory trace weakens faster in REM sleep than in wakefulness. Finally, because the reactivation of the standard representation failed to occur in REM sleep, it is likely that the contents of sensory memory cannot be stored in the long-term memory during this brain state. Therefore, according to the present results, it can be concluded that the formation, maintenance, and reactivation of the auditory sensory memory trace seem to be modulated by the functional brain state characteristic of the human REM sleep.

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