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Research report

Complex sound processing during human REM sleep by recovering information from long-term memory as revealed by the mismatch negativity (MMN)

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Abstract

Perceptual learning is thought to be the result of neural changes that take place over a period of several hours or days, allowing information to be transferred to long-term memory. Evidence suggests that contents of long-term memory may improve attentive and pre-attentive sensory processing. Therefore, it is plausible to hypothesize that learning-induced neural changes that develop during wakefulness could improve automatic information processing during human REM sleep. The MMN, an objective measure of the automatic change detection in auditory cortex, was used to evaluate long-term learning effects on pre-attentive processing during wakefulness and REM sleep. When subjects learned to discriminate two complex auditory patterns in wakefulness, an increase in the MMN was obtained in both wake and REM states. The automatic detection of the infrequent complex auditory pattern may therefore be improved in both brain states by reactivating information from long-term memory. These findings suggest that long-term learning-related neural changes are accessible during REM sleep as well.

Theme: Neural basis of behavior

Topic: Neural plasticity

Keywords: Neural plasticity; Mismatch negativity; Complex auditory pattern; Perceptual learning; REM sleep; Human

1. Introduction

One necessary requirement for the brain is the automatic detection of changes in a relative constant environment. Behavioral and electrophysiological evidence suggests that the sleeping brain is able to detect not only the presence of an auditory input but also variations in a constant sequence of auditory stimuli [1,2,6,32]. This is possible because several capabilities of sensory analyzers to process information are preserved during sleep [e.g. 15]. However, the majority of previous studies that have demonstrated active neural processing during sleep used only simple stimuli. Considering that the external environment is much more complex than a sequence of tones, it is worth while to determine if the brain is able to discriminate changes in complex signals during sleep.

It is well known that training on a task improves the performance possibly as consequence of neural changes that evolve over a period of several hours or even several days. This is evident in the auditory [4,5,55,57,60], visual [22,25,53], and somatosensory [11,18,21] systems, as well as for motor skills [46]. Furthermore, results from animal studies suggest that the same neuronal activity patterns associated with learning of spatial behavioral tasks in rats [31,39,41,47,48,58] or vocal learning in birds [10] may be spontaneously replayed during the following sleep period. This has been interpreted as representing signs of the consolidation process, which is presumably initiated during the training session and results in more prolonged neural

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changes that continue when stimulation is absent. As a consequence, behavioral improvements are shown several hours after the training session and retained for several years [23], implicating storage in the long-term memory system. However, there are no experimental data indicating whether the information acquired during wakefulness can be accessed from long-term memory during sleep, allowing the detection of changes in a complex auditory environment. This, indeed, would serve an adaptive function by enabling the sleeping organism to recognize a stimulus that may be potentially important for its survival.

Animal studies have shown that neuronal activity in the auditory cortex is altered during tone-signaled learning. This neural plasticity has been observed in the primary [5,42,56] and secondary areas [12–14,26] of the auditory cortical system. Likewise, human event-related potential (ERP) studies have demonstrated that auditory perceptual learning is associated with changes in neurophysiological responses [27,37,51] preceding changes in behavior [52]. These learning-dependent neurophysiological changes indicate an improvement in automatic information processing. It is conceivable that similar improvement on pre-attentive processing could occur during human sleep once the consolidation process has been initiated. This hypothesis is strongly supported by animal studies reporting the conditioned enhancement of the neuronal response in the dorsal hippocampus [33] and medial geniculate body of the thalamus [20] to a tone delivered during paradoxical sleep (the equivalent of human REM sleep). This conditional response enhancement has also been observed in the auditory cortex under deep general anesthesia [57].

The recording of ERPs is a non-invasive technique that supplies information about the temporal relationship between a stimulus event and the associated cerebral response in different temporal windows of information processing. The mismatch negativity (MMN) is an auditory ERP component that reflects the automatic cortical response to variations occurring in an otherwise relatively invariant auditory environment [36]. This brain response can be elicited varying single features of stimuli or abstract characteristics in the relationship between stimuli (for a review, see Ref. [40]). The MMN has been successfully used as an electrophysiological measure of plasticity in the central auditory system associated with the automatic discrimination of complex auditory patterns [37] and with speech discrimination [27,28], as well as with the learning of the native language in infancy [7], or a foreign language in adulthood [59]. In these studies, the MMN amplitude was found enhanced and/or its latency shortened as a consequence of training on a task or long-term experience. These results demonstrate that information contained in long-term memory may affect auditory sensory memory processing. Given that the MMN-generating system can be activated during human REM sleep [2,3,32,38], it is hypothesized that the learning-related long-term changes observed in MMN during wakefulness will be obtained during REM sleep. An enhanced MMN during REM sleep by variations in complex stimuli, as a result of a training period, would suggest that neural changes underlying the consolidation process can be accessed during REM sleep as well, possibly by reactivating information stored in long-term memory.

2. Methods

2.1. Subjects

Twenty healthy normal-hearing adult subjects (nine males and 11 females; age range 18–30 years) participated voluntarily in the present study after receiving a full explanation of the experimental procedure and giving informed consent. Data from four subjects were rejected from analysis for different reasons: two showed a clear MMN in the pre-training session, and in the other two cases, one of the earphones was not correctly inserted in the ear in the morning following sleep stimulation. All subjects were instructed to abstain from alcohol and caffeine during the 48-h prior to the first experimental session and during the whole experiment.

2.2. Stimuli

Subjects were presented with two complex auditory patterns in a classical oddball paradigm with an ISI of 975 ms. Stimuli used in the present experiment were modeled on those used in a previous study [37]. Each stimulus

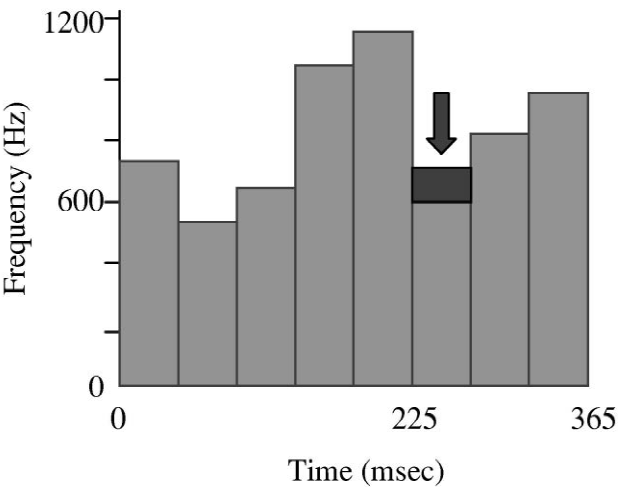

Fig. 1. Complex auditory pattern used in the present experiment. The down arrow signals the segment in which the frequency deviance (an increase of 15%) was introduced.

consisted of eight segments (50 ms each, including rise and fall times of 5 ms, with overlapping fall and rise of consecutive segments) of different frequencies. The overall duration of the stimulus was 365 ms. The only difference between the standard and deviant stimuli was a frequency contrast (an increase of 15%) in the sixth segment (see Fig. 1). Blocks of 200 stimuli each were presented. The deviant pattern was introduced within the block in a pseudorandom way (deviant patterns were always separated by a minimum of two standard patterns).

2.3. Procedure

Subjects were trained to differentiate between two complex auditory patterns. Stimuli were presented bilaterally via insert earphones (Etimotic Research®, Model ER-3A) with an intensity of 70 dB SPL. Subjects were instructed to make a keypress response as fast as possible only when they perceived a stimulus pattern that differed from the previous one. Therefore, two measures of performance were obtained. The number of correct responses to the target stimulus (for measuring the improvement in the detection of the difference), and reaction times (in order to test changes in the speed information processing). Previous studies have demonstrated changes in the performance to occur during the training session and from one session to the next [23]. Since subjects were required to achieve a high number of correct responses during the training session, further behavioral changes are expected to occur in the speed of information processing rather than in the number of correct responses.

Information about the characteristics of stimuli was provided. Subjects also were informed about the infrequent appearance of the target stimulus and the fact that a minimum of two standard stimuli would separate a target stimulus from the next. One block of 25 stimuli was presented as probe. Subjects were required to reach a hit-percentage of 80% and no more than three errors in each of two consecutive blocks. The total number of blocks varied between 6 and 22 (mean=9.45, S.D.=4.78). The training phase lasted no more than 2 h. Stimuli were embedded in six different blocks, which were counterbalanced. Subjects were informed about the hit and error percentage after each block.

ERPs were recorded in an acoustically and electrically shielded room just before and after the training phase. Nine blocks of 200 stimuli each were presented during the ERP recording phase, with 2 min of rest between blocks. Subjects read a book and were asked to ignore the auditory stimuli. ERPs (nine stimulus blocks) were recorded again 12, 24, 36, and 48 h following the training phase, just before testing performance for one stimulus block. In this case, no feedback was given. These sessions lasted about 1 h each. Half of the subjects were trained in the morning (09:00 h) and the other half at night (21:00 h) to control for circadian effects on the alertness level.

All subjects spent three consecutive nights in an acoustically and electrically shielded room from 24:00 h (lights-off) to 08:00 h (lights-on). In the first two nights, subjects slept with the same electrode montage used in the experimental night, but no data were recorded. In this way, subjects became familiar with the sleep lab environment. Auditory stimulation was presented only during the REM sleep periods of the third night, just after the appearance of the first rapid eye movement burst. REM sleep was scored according to standard criteria [43]. Stimulation was stopped when signals of arousal, wakefulness, or transition to another sleep stage were detected. The results reported in the present study correspond to ERPs recorded during pre- and post-training phases, before and after the night in which stimulation was presented (pre- and post-sleep phases), as well as ERPs obtained during REM sleep.

2.4. Electrophysiological recordings

Electrophysiological activity was recorded, amplified, digitized, and filtered with a MEDICID® 4 system (Neuronic). Electroencephalographic (EEG) activity was measured from 19 derivations according to the 10–20 system (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2). An electrode placed on the tip of the nose was used as reference. Horizontal and vertical ocular movements were also recorded, as well as submental electromyography (EMG). All electrophysiological parameters were amplified and digitized on-line at 250 Hz. Both EEG and EOG were low- and high-bandpass filtered at 0.1 and 40 Hz, whereas EMG was filtered at 5 and 70 Hz. Impedance of electrodes was kept below 5000 Ohms in all derivations. The same recording protocol was used in all wake and sleep sessions.

For each artifact-free trial, an epoch of 800 ms, including a 100-ms pre-stimulus baseline, was selected. Trials with an EEG- or EOG-amplitude change exceeding ± 100 μV were rejected. Trials immediately following deviant stimuli were always rejected. Stimuli presented in the first REM period were not analyzed because of frequent changes in the arousal level. The first five trials of each stimulus block were also excluded from analyses. After averaging, the signals were digitally filtered with a cutoff frequency of 30 Hz (-3 dB). ERPs to standard and deviant stimuli were analyzed separately for each experimental session and subject.

2.5. Statistical analysis

For each subject, the difference wave was obtained by subtracting the ERPs elicited by the standard pattern from

those obtained to the deviant pattern. In each phase of the experiment, and for each individual subject, the maximum peak of the MMN was obtained at Fz between 375 and 475 ms from the stimulus onset (150–250 ms from the introduction of the frequency deviance). MMN amplitude at Fz, Cz and Pz were then measured as the mean voltage within a temporal window of 50 ms (25 ms before and after the maximum negative peak) minus the mean voltage value obtained between the stimulus onset and the introduction of the frequency deviance (225 ms). MMN latency was defined as the time from deviance onset to the maximum negative peak.

One-tailed *t*-tests were used to determine whether the mean amplitudes within the temporal window of MMN differed significantly from zero. Differences in amplitude and peak latency in each condition were assessed using an mixed-model analysis of variance (ANOVA) including phases (pre-training, post-training, pre-sleep, REM sleep, and post-sleep) and electrodes (Fz, Cz, and Pz) as within-factors, and the time of the day which subjects were trained (09:00 and 21:00 h) as between-factor. Since no significant differences were found between the two conditions of the between-factor, the MMN amplitude and latency value for both subject groups were collapsed. Therefore, data were analyzed using a two-way ANOVA of repeated measurements with phases and electrodes as within-factors. Significance levels of the F ratios were adjusted with the Greenhouse–Geisser correction where appropriate. Post-hoc analyses (Newman–Keuls test) were carried out to assess the main effects.

The cortical areas involved in the MMN generating system during the different wakefulness phases and REM sleep were examined by a phase×electrode interaction in a separate ANOVA. In this case, the values corresponding to the pre-training phase were not included because the negative wave in the MMN window was not significantly different from zero. A significant interaction effect would suggest that different brain generators elicit this negative wave in different experimental phases. For assessing the topographic distribution, the voltage for each electrode and experimental condition was scaled by dividing by the square root of the sum of the squares of the voltage values at all electrodes [35].

3. Results

3.1. Behavioral results

Fig. 2 shows the number of correct responses to the target stimulus for each individual subject and superimposed the mean of correct responses achieved in the first and last three stimulus blocks of the training session, as well as the results obtained before and after the night in which ERPs were measured (left). Reaction times obtained in the last block of the training phase and during pre- and post-sleep phases are also shown (right).

All subjects reached the behavioral criteria for learning during the training session (80% of correct responses to the target stimulus and no more than three errors in each of two consecutive blocks), but the number of blocks differed between subjects. Two subjects reached the criteria in the second block, but in both cases, six blocks were needed before showing the percentage required in two consecutive blocks. In the remaining wakefulness phases the performance was maintained or improved. The differences in the number of hits to the target stimulus were not significant. The reaction time measures were, however, significantly shorter in the pre- and post-sleep phases as compared with the values obtained in the training phase ($F(2,30)=7.736$, $P<0.005$, $\epsilon=0.749$; post-hoc test: $F(2.45)=3.332$, $P<0.045$).

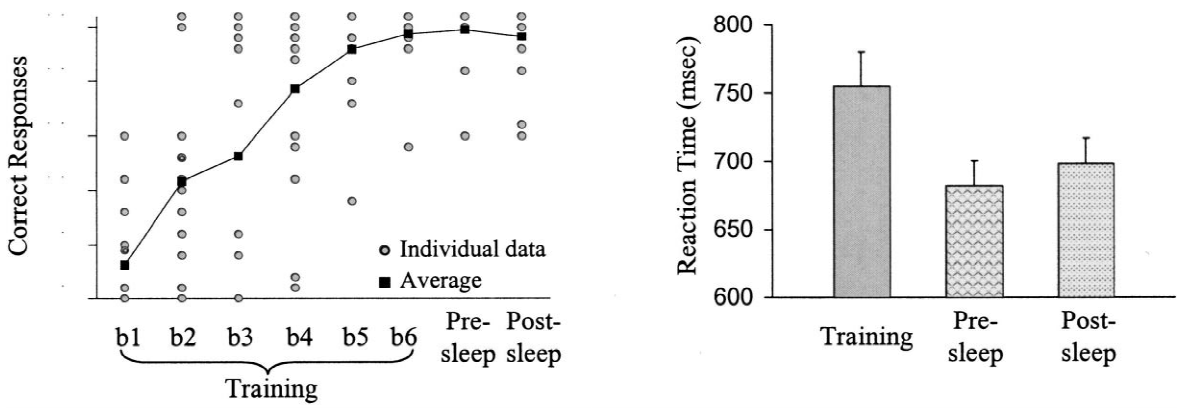

Fig. 2. Left: Number of correct responses to the target stimulus obtained for each subject ($n=16$) (gray circle) and mean of correct responses (black square) in the first and last three stimulus blocks of the training phase, as well as during the pre- and post-sleep sessions. Right: Mean of reaction times achieved for the target stimulus during the training, pre- and post-sleep phases.

3.2. Neurophysiological results

Fig. 3 shows superimposed grand-average waveforms for ERPs recorded from Fz, Cz, and Pz to standard and deviant patterns, as well as the difference waves (deviant minus standard) obtained in each phase of the experiment. ERPs to standard and deviant patterns showed two clear negative waves in all conditions, one at about 100 ms related to the stimulus onset, the N1 potential, and the second at about 350 ms after stimulus onset, related to the sudden decrease in frequency in the sixth segment of the pattern.

A clear MMN was observed in the difference waves, peaking 150–200 ms after the introduction of the frequency deviance in the sixth segment (Fig. 3). This deviance-related negativity was significantly different from zero in all phases after the training on the task (Table 1). A main effect of the phase factor on the MMN amplitude was

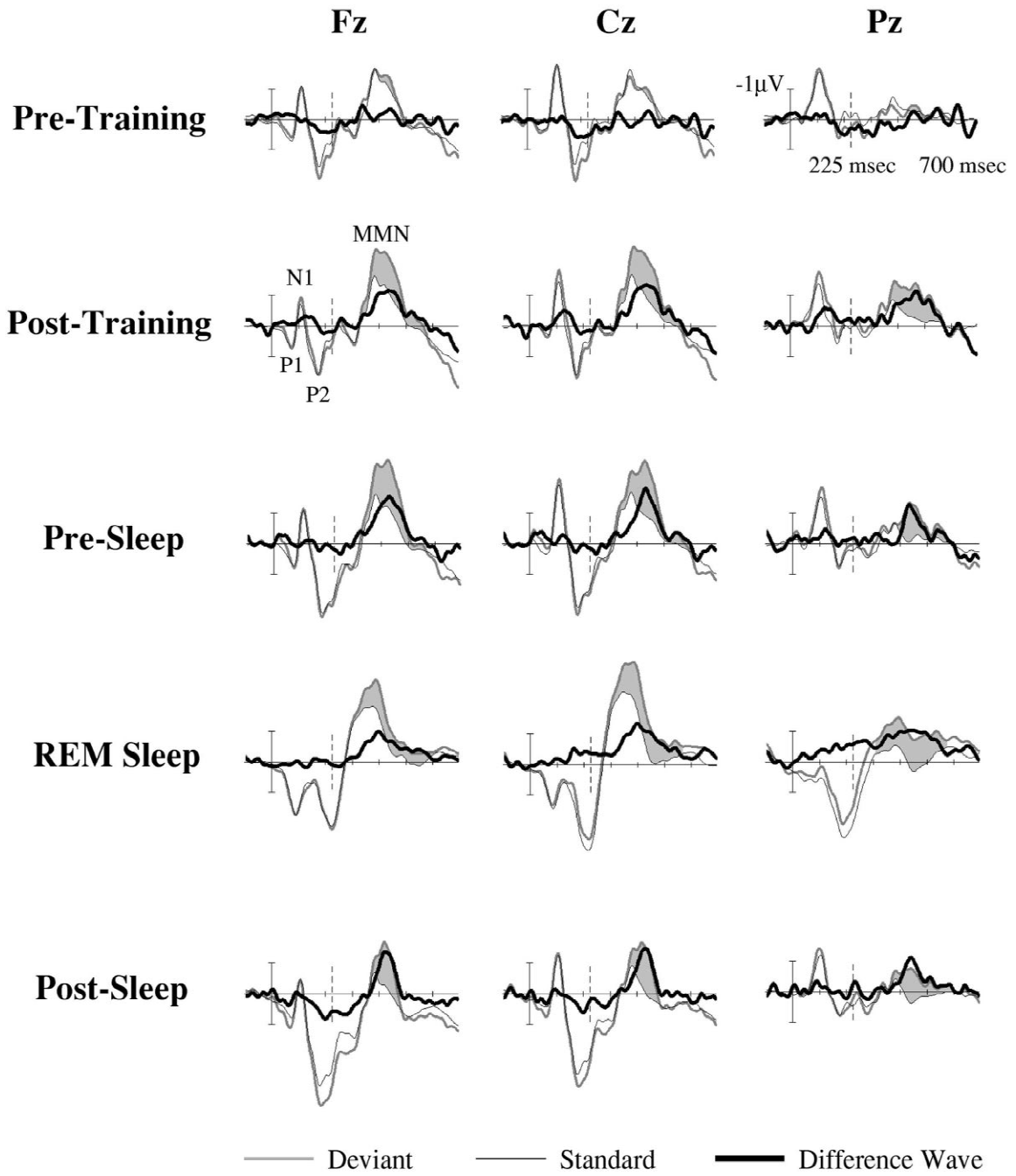

Fig. 3. Grand averages event-related potentials. Event-related potentials (n=16) were obtained at electrodes of midline (Fz, Cz, Pz) to standard and deviant stimuli in the different phases of experiment. The difference waves (deviant minus standard) are shown superimposed in each condition. The vertical dotted line indicates the introduction of the frequency deviance within the pattern. μV=microvolts; msec=millisecond; MMN=mismatch negativity.

Table 1
MMN mean amplitudes (μV) and standard deviation (S.D.) measured in the difference wave (deviant minus standard) at Fz, Cz, and Pz, during a latency-window of 150–250 ms from the introduction of the frequency deviance within the auditory pattern, for each experimental phase

Phases	Electrodes	Mean	S.D.	*t*	*P*
Pre-training	Fz	−0.0452	0.5160	−0.35	0.7319
	Cz	0.1529	0.6116	0.99	0.3332
	Pz	0.2811	0.7778	1.45	0.1688
Post-training	Fz	−1.0983	0.9362	−4.69	0.0003
	Cz	−1.2212	1.0005	−4.88	0.0002
	Pz	−0.6711	0.9557	−2.81	0.0132
Pre-sleep	Fz	−1.7923	1.0758	−6.66	0.0001
	Cz	−1.8227	1.1600	−6.28	0.0001
	Pz	−1.0334	1.2009	−3.44	0.0036
Post-sleep	Fz	−1.7938	0.7685	−9.34	0.0001
	Cz	−1.7890	1.0275	−6.96	0.0001
	Pz	−1.0643	0.8825	−4.82	0.0002
REM sleep	Fz	−1.0459	0.8917	−4.69	0.0003
	Cz	−1.0420	0.9089	−4.58	0.0004
	Pz	−0.5042	0.8688	−2.32	0.0348

confirmed by a two-way ANOVA ($F(4,60)=11.007$, $P<0.001$, $\epsilon=0.765$), and post hoc analyses indicated that the MMN was significantly smaller in the pre-training phase than in any other phase ($F(4,75)=10.657$, $P<0.001$). The MMN recorded in wakefulness showed an enhanced amplitude in the pre- and post-sleep phases, although these differences did not reach statistical significance. Although the MMN showed a smaller amplitude during REM sleep when compared with the remaining post-training conditions, no significant differences were found.

During wakefulness, the MMN showed its peak latency at about 200 ms from the frequency-deviance introduction within the pattern, and significantly earlier during REM sleep (Fig. 4). ANOVA yielded significant differences in the MMN latency among phases ($F(3,45)=5.936$, $P<0.006$, $\epsilon=0.709$), and the Newman–Keuls test confirmed the shorter latency during REM sleep ($F(3,60)=4.093$, $P<0.01$).

The frontocentral distribution of the negative wave and its latency in relation to the introduction of the frequency deviance clearly suggest the activation of MMN generators. These brain generators were equally activated during wakefulness and REM sleep, since no interaction effect between electrode and phase was shown by ANOVA with scaled data (Fig. 5).

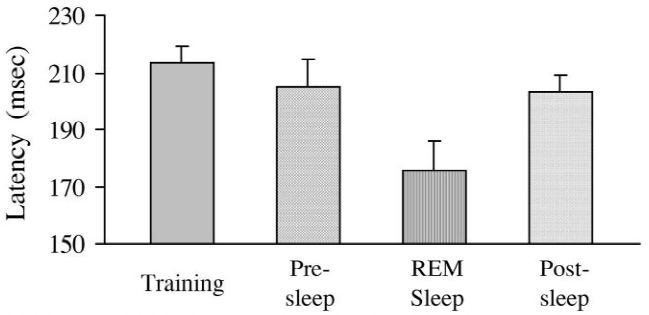

Fig. 4. Mean peak latency of mismatch negativity. The latency was measured at Fz, and the mean value obtained from 16 subjects is presented for each experimental phase.

4. Discussion

The present study demonstrates that the information acquired in wakefulness by training in an auditory perceptual task can be recovered during REM sleep 2 days later, as revealed in the activation of the MMN generating system by changes in complex auditory patterns. These data may represent the activation of neurophysiological mechanisms during human REM sleep that enable the brain to access information encoded and stored in the long-term memory system.

In the present experiment, subjects were able to differentiate two complex auditory patterns only after a training period. Electrophysiological data showed no MMN in the pre-training phase but did in the post-training phases, complementing the behavioral data. These results indicate a striking neurophysiological change associated with auditory discrimination learning which was maintained across the subsequent wakefulness sessions. However, the most remarkable result was that the neural changes initiated in wakefulness appeared to be accessible during REM sleep.

These results support the relationship previously found between the MMN amplitude and the improvement in the sensory processing of complex sounds after a training period [27,37,51,52]. In the present study, the MMN system was activated only after subjects learned to behaviorally discriminate the two patterns. This result indicates that, at least at the time of encoding, attention is critical for the establishment of perceptual learning. During this process, a neural representation of the standard pattern

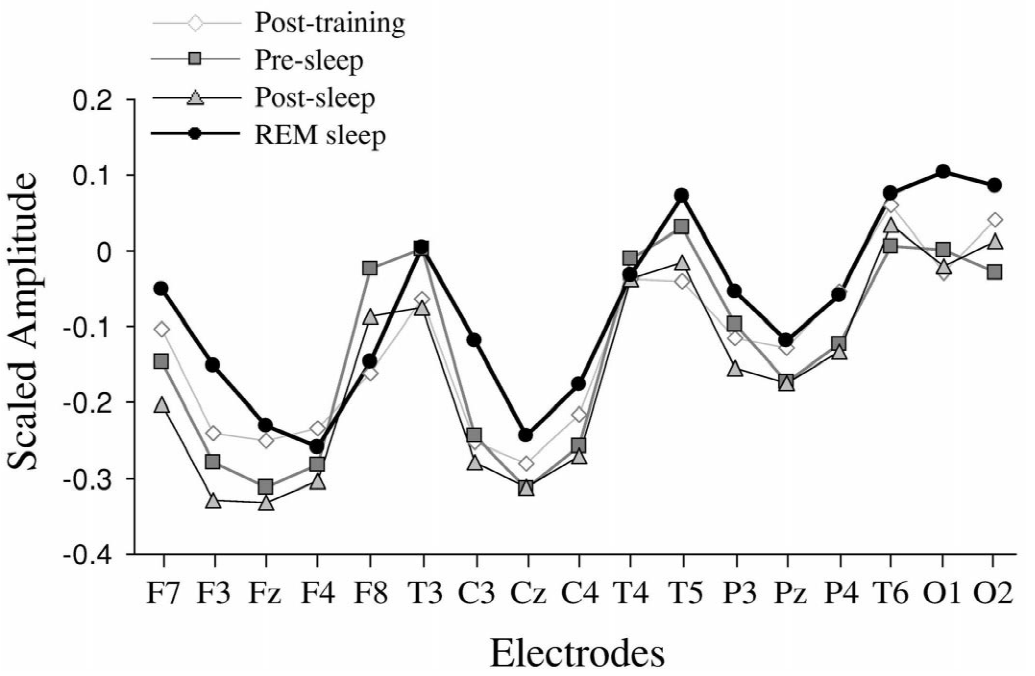

Fig. 5. Topographical distribution of the negative wave in each experimental phase. The voltage values represented in the temporal window of mismatch negativity (MMN) at each electrode for each phase of experiment were previously scaled according to the method proposed by McCarthy and Wood [35].

may develop. Presumably, this would facilitate the subsequent automatic change detection. Consistent with this, Näätänen et al. [37] have previously reported no change in the MMN amplitude when subjects were presented with the same stimuli with no intervening discrimination tests. Nonetheless, once a sufficient number of cells fire synchronously and differentially to the two stimuli (standard and deviant), this plastic firing pattern can be automatically reactivated in a previously non stimulated brain state even in the absence of attention, as revealed by the elicitation of MMN during REM sleep. These results are supported by previous findings showing that receptive field plasticity in the auditory cortex of guinea pig can be determined as late as 8 weeks after training, even under general anesthesia [57].

The scalp distribution of the brain response elicited by the deviant pattern was identical in wakefulness and REM sleep, suggesting that the same brain generators were activated in both brain states. Although this finding is consistent with previous results [3], it represents the first time that the MMN has been recorded during human REM sleep without an overlapping N1 potential, due to the fact that the frequency deviance was introduced 225 ms after the stimulus onset within the pattern. In previous studies, the MMN was elicited by high frequency changes in single tones, which lead to a shortening of its latency, making difficult to differentiate MMN from N1. The other surprising result found in the present experiment was that, contrary to previous studies [2,3,32,38], the REM–MMN amplitude, though smaller, was not significantly different from that obtained in wakefulness. A possible explanation is that the on-line formation of a neural representation is quite difficult during REM sleep. If the neural representation already exists in the long-term memory, its reactivation during REM sleep might facilitate automatic sensory processing. Since the MMN was elicited in wakefulness during only the post-training phases, the activation of the MMN system during REM sleep appears to result mainly from experience-dependent neurophysiological changes that developed during wakefulness. These changes are presumed to occur in the non-primary auditory thalamocortical pathways [9,29,30,45], but it is also possible that the long storage of information occurs in the cortex, where the information is processed [49,54].

No changes in the MMN latency were found after training during wakefulness, which is supported by previous studies [27]. However, in agreement with previous results [2,3,32], this latency was significantly shortened during REM sleep. The shortening of the MMN latency during sleep is another unresolved question, but similar results in animal studies have been reported by Hennevin et al. [20] by using a tone conditioning paradigm. These authors found a shorter latency plastic response in paradoxical sleep than in wakefulness, with the excitation of neurons in the medial geniculate body occurring earlier in this sleep stage than in wakefulness (a difference of 20 ms). If this nucleus is involved in the neurophysiological changes associated with auditory learning, as suggested by other studies [16,17,29,30], it is possible that the subsequent cascade of subcortical and cortical processes is

also advanced, the final outcome being a shortening of the MMN latency.

The MMN elicited during human REM sleep by a deviant pattern after a period of learning suggests, in cognitive terms, that a neural representation including the integration of different frequencies within the standard pattern is maintained in long-term memory and reactivated during sleep, facilitating the automatic change detection. Our results support the hypothesis that information can be transferred in a top-down way from long-term memory to sensory memory in order to improve the quality of information that is provided by sensory memory to subsequent processing stages [44]. In a previous study [3], the duration of sensory memory during REM sleep was assessed by presenting single tone trains separated by different silent intervals (3, 6, or 9 s). A frequency deviant was introduced in each train but in different positions (1, 2, 4, or 6). A MMN was clearly generated independent of the deviant position, but only when the intertrain interval was 3 s. For the longer intertrain intervals, no MMN was elicited even when the deviant tone was presented late in the tone train. However, using a similar paradigm in wakefulness, Cowan et al. [8] demonstrated that MMN system could be activated to a deviant tone presented in position 2 within the train after 15 s of intertrain interval, even though the deviant in position 1 elicited no MMN. One possible explanation of the different results obtained in wakefulness and sleep in both studies is that the sleeping brain is not able to access information in long-term memory. An alternative explanation would be that the information was not transferred in a bottom-up way from sensory memory to long-term memory during REM sleep. The results obtained in the present study allow us to dismiss the first explanation but the second one remains to be tested.

In summary, the present study provides evidence that information acquired during wakefulness can be recovered during human REM sleep to detect minor changes in externally presented complex auditory patterns. Given that the stimulation was presented in the second night after the training, it is not possible to determine whether part of the neurophysiological changes associated with consolidation of the discrimination task happened during sleep. The present results suggest that MMN could be used as objective measure to test whether slow neural changes underlying perceptual learning take place during sleep, as has been proposed in recent studies [19,24,34,50]. Nevertheless, this interesting aspect must be addressed in subsequent studies.

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