Odd Sound Processing in the Sleeping Brain

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Abstract

■ How does the sleeping brain process external stimuli, and in particular, up to which extent does the sleeping brain detect and process modifications in its sensory environment? In order to address this issue, we investigated brain reactivity to simple auditory stimulations during sleep in young healthy subjects. Electroencephalogram signal was acquired continuously during a whole night of sleep while a classical oddball paradigm with duration deviance was applied. In all sleep stages, except Sleep Stage 4, a mismatch negativity (MMN) was unquestionably found in response to deviant tones, revealing for the first time preserved sensory memory processing during almost the whole night. Surprisingly, during Sleep Stage 2 and paradoxical sleep, both P3a-like and P3b-like components were identified after the MMN, whereas a P3a alone followed the MMN in wakefulness and in Sleep Stage 1. This totally new result suggests elaborated processing of external stimulation during sleep. We propose that the P3b-like response could be associated to an active processing of the deviant tone in the dream's consciousness. ■

INTRODUCTION

Although it was thought for a long time that the sleeping brain is disconnected from the external world, many studies in the end of the last century have revealed that it is not the case. As an example, it was found in the late 1980s that, during sleep, the brain produces stimulus-related activity in the primary auditory cortex in response to simple sounds (Deiber, Ibanez, Bastuji, Fischer, & Mauguière, 1989). Nowadays, the sleeping brain is less and less considered as a passive and isolated resting organ but more and more as an active processor (generating dreams), with a modified functional organization (e.g., with visual information processing flow going from associative to primary visual areas; Maquet et al., 2004; Braun et al., 1998), and still interacting with the external world (e.g., processing auditory stimulations up to their semantic dimension; Bastuji, Perrin, & Garcia-Larrea, 2002; Perrin, Bastuji, & Garcia-Larrea, 2002; Perrin, Garcia-Larrea, Mauguière, & Bastuji, 1999). But to what extent is the sleeping brain responsive to the environment? Which sensory and cognitive processes are maintained?

Given the elaborated processing of external stimuli during sleep evidenced by the results of Bastuji et al. (2002) and Perrin et al. (1999, 2002), one would expect that basic mechanisms such as sensory memory are also preserved during sleep. These memory traces may indeed be considered as a prerequisite for further and more complex processing, as discussed by Näätänen and Winkler (1999). Sensory memory is a short-lasting process which can be investigated in humans using electrophysiology. It was often investigated in the auditory modality using an oddball paradigm in which trains of repetitive identical sounds (standards) are occasionally interspersed with slightly different sounds (deviants). The potential evoked by the rare sound was shown to be more negative than the one evoked by the frequent sound so that difference between the two was labeled mismatch negativity (MMN) (Näätänen, Gaillard, & Mantysalo, 1978). This negative wave appears at fronto-central electrodes around 150 msec and is considered to be an electrophysiological correlate of a comparison mechanism indicating a mismatch between a stored representation in sensory memory and an incoming auditory event (Näätänen, 1985). The MMN can therefore be used to probe auditory sensory memory representations (Ritter, Deacon, Gomes, Javitt, & Vaughan, 1995).

MMN was described to be an automatic wave, which can be elicited even though the subject is not attending to the irregularities eliciting it (Woldorff, Hackley, & Hillyard, 1991; Giard, Perrin, Pernier, & Bouchet, 1990). It seems to be associated with triggering the orienting response (for a recent review, see Kujala, Tervaniemi, & Schröger, 2007). Actually, according to the extent of stimulus change and to the task involved, the MMN can sometimes be followed by other event-related potential (ERP) components such as P300 waves. When subjects are involved in a distracting task and do not pay attention to the tones, the MMN tends not to be followed by any P300 components. However, in these unattended conditions, a P3a component (the early and fronto-central component of the P300) or a N2b–P3a complex happens to be detected when the extent of

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deviance is large enough to trigger a switch of attention (Escera, Alho, Winkler, & Näätänen, 1998). In active paradigms, when the deviant tones are to be drawn to the subject's attention, a task-relevant target P3b (the late and parietal component of the P300) is obtained (Squires, Squires, & Hillyard, 1975a). A P3b can even arise in passive paradigms if the extent of deviance is very large (Polich, 1989; Näätänen, Simpson, & Loveless, 1982).

In an attempt to investigate sensory memory during sleep, several studies have used oddball paradigms in sleeping healthy subjects. They resulted in divergent conclusions as revealed by the review of the literature presented in Table 1, so that the issue of a preserved ability of the sleeping brain to evoke an MMN in response to a deviant tone is still under debate. Some authors concluded to the absence of MMN in all sleep stages tested (Sleep Stages 1 to 4 in Paavilainen et al., 1987), whereas, more recently, Sabri, Labelle, Gosselin, and Campbell (2003) detected a deviant-related negativity (DRN) in each of these stages. However, because they used a rapid rate of stimulus presentation, it is quite difficult to conclude whether this DRN is a mere N1 enhancement effect, a genuine MMN, or a combination of the two. During paradoxical sleep (PS; also called rapid eye movement [REM] sleep) several authors (Atienza & Cantero, 2001; Atienza, Cantero, & Gomez, 1997, 2000; Nashida et al., 2000; Loewy, Campbell, & Bastien, 1996), although not all of them (Loewy, Campbell, de Lugt, Elton, & Kok, 2000; Sallinen, Kaartinen, & Lyytinen, 1996), found an MMN. This absence of clear positive results, suggesting a loss or an attenuation of sensory memory function during sleep, is quite puzzling given that an MMN can be detected in some comatose patients. In this context, the positive detection of this wave was further shown to be a very efficient predictive factor of awakening and recovery, even in deeply comatose patients (Fischer, Luauté, Adeleine, & Morlet, 2004; Fischer et al., 1999). These results, demonstrating the possibility of a spared auditory sensory memory in a pathological altered state of consciousness, lead to predict that such ability should also be preserved in a physiological altered state of consciousness such as sleep.

To explain the apparent inconsistency between the results reported in Table 1, many reasons could be invoked such as differences in the protocol used (including sound duration, frequency, intensity, interstimulus interval [ISI], percentage of rare stimuli), significance threshold for statistical analysis, Electroencephalographic (EEG) recording duration (e.g., 40 min, Nielsen-Bohlman, Knight, Woods, & Woodward, 1991; 3 hr, Nittono, Momose, & Hori, 2001; 4 hr, Nashida et al., 2000; the whole night, Sallinen et al., 1996), and circadian periods (daytime, Nielsen-Bohlman et al., 1991; Winter, Kok, Kenemans, & Elton, 1995; or night-time). The objective of the authors and the sleep stage elected for investigation may also contribute to the variability of the results in these studies (subjects were awakened repeatedly in Sabri et al., 2003; Sabri, De Lugt, & Campbell, 2000, in order to investigate sleep onset; subjects were awakened as soon as they entered in Sleep Stage 3 in Nittono et al., 2001, in order to investigate Sleep Stage 2; Sallinen et al., 1996 focused on the comparison between phasic and tonic PS).

Given the lack of convincing data regarding the possibility to obtain an MMN during sleep with classical oddball paradigms (with ISI typically around 600 msec), Sabri and Campbell (2005) and Sabri et al. (2003) hypothesized that, during non-rapid eye movement sleep, MMN generators remain active but a rapid memory decay prevents the brain to detect the deviance. In order to test this hypothesis, they used a faster rate of stimuli presentation (i.e., every 150 msec; Sabri et al., 2003). With this noncanonical paradigm they managed to evidence significant DRN in response to large frequency deviants, in all sleep stages (Sabri & Campbell, 2005). However, the authors stated that the DRN probably reflects a contribution of both the N1 and MMN intracranial sources (Sabri & Campbell, 2005) so that their study did not fully solve the issue of the possibility to detect a ''true'' MMN during sleep. Hence, we cannot say today, based on the results in the literature, whether an MMN can be elicited during each stage of natural sleep.

One direction to ensure reliable results may be found in the use of a robust procedure in ecological conditions. To the best of our knowledge, only one study (Nashida et al., 2000) looked for MMN in all sleep stages, however, their results (no significant detection of MMN in Sleep Stages 2, 3, and 4) were issued from only 4 hr of EEG recordings. In addition, most of the studies, which looked for an MMN during sleep, used frequency deviants. Tervaniemi et al. (1999), however, showed that among frequency, intensity, and duration, the deviance in duration elicited the MMN with the most replicable amplitude and latency. Duration deviance protocols also have a number of advantages with regard to potential confounds of the MMN. The traditional deviant-minus-standard ERP can indeed be contaminated by a number of other negativities overlapping the MMN. Most particularly, differences in the evoked sensory responses (such as the N1) for the standard and deviant tones might artificially enhance measures of the MMN. Such N1 differences may be due to both physical differences between the stimuli and differential states of refractoriness of the underlying neural generators. Such issues are most critical when using a large difference between the standard and deviant tones when these tones recruit different neuronal populations (e.g., tones of different frequencies due to the tonotopic organization of auditory areas), and when using short ISIs. Jacobsen and Schröger (2003) demonstrated that the descending duration MMN (shorter deviants, i.e., with less physical energy than standards and an identical frequency) was not overestimated as compared with a duration MMN

Table 1. MMN during Sleep: A Review of the Literature

	Stage 1	*Stage 2*	*Stage 3*	*Stage 4*	*PS*
Deviance in Sound Frequency					
Paavilainen et al., 1987 (SD = 50 msec; ISI = 510 msec; SI = 75 dB SPL; SF-Std = 1000 Hz; SF-Dev = 1050 Hz)	−	−	−	−	
Nielsen-Bohlman et al., 1991 (SD = 50 msec; ISI = 1000 msec; SI = 50 dB SPL; SF-Std = 1000 Hz; SF-Dev = 1500 Hz)		−	−	−	
Sallinen, Kaartinen, & Lyytinen, 1994 (SD = 50 msec; ISI = 625 msec; SI = 45 dB; SF-Std = 1000 Hz; SF-Dev = 1200 Hz)		+			
Winter et al., 1995 (SD = 50 msec; ISI = 1000 msec; SI = 65 dB(A); SF-Std = 1000 Hz; SF-Dev = 1200/2000 Hz)	+	−			
Loewy et al., 1996 (SD = 55 msec; ISI = 600 msec; SI = 80 dB SPL; SF-Std = 1000 Hz; SF-Dev = 1050/2000 Hz)		−		−	+
Sallinen et al., 1996 (SD = 50 msec; ISI = 625 msec; SI = 50 dB; SF-Std = 1000 Hz; SF-Dev = 1100/2000 Hz)					−
Atienza et al., 1997 (SD = 50 msec; ISI = 600 msec; SI = 80 dB SPL; SF-Std = 1000 Hz; SF-Dev = 2000 Hz)					+
Sabri et al., 2000 (SD = 50 msec; ISI = 600 msec; SI = 60 dB HL; SF-Std = 1000 Hz; SF-Dev = 1100/2000 Hz)	−	+	−	−	
Nashida et al., 2000 (SD = 50 msec; ISI = 450 msec; SI = 60 dB; SF-Std = 1000 Hz; SF-Dev = 2000 Hz)	+	−	−	−	+
Nittono et al., 2001 (SD = 50 msec; ISI = 450 msec; SI = 60 dB; SF-Std = 1000 Hz; SF-Dev = 1050/1200 Hz)	+	−			
Atienza & Cantero, 2001 (SD = 365 msec; ISI = 975 msec; SI = 70 dB SPL; SF-Std = complex sound of 8 segments with different frequencies. SF-Dev = frequency increase in the segment 6 of the standard sound [15%])					+
Sabri et al., 2003 (SD = 55 msec; ISI = 150 msec; SI = 80 dB SPL; SF-Std = 1000 Hz; SF-Dev = 1100/2000 Hz)	DRN	DRN	DRN	DRN	
Sabri & Campbell, 2005 (SD = 55 msec; ISI = 150 msec; SI = 80 dB SPL; SF-Std = 1000 Hz; SF-Dev = 1100/2000 Hz)		DRN	DRN	DRN	DRN
Deviance in Sound Intensity					
Loewy et al., 2000 (SD = 55 msec; ISI = 600 msec; SF = 1000 Hz; SI-Std = 70 dB SPL; SI-Dev = 80/60 dB SPL)		−			−

The characteristics of the stimuli (SD = sound duration; SF = sound frequency; SI = sound intensity; and ISI = interstimulus interval) are described for each quoted article. + = MMN was detected; − = MMN was not detected; DRN = deviant-related negativity, supposed to be a mixture of N1 enhancement and/or MMN (Sabri et al., 2003); PS = paradoxical sleep; dB = decibel; SPL = sound pressure level; HL = hearing level; Std = standard (frequent) sound; Dev = deviant (rare) sound.

controlled for the physical differences of the stimuli or for N1 refractoriness effect. This stands in contrast to other first-order feature MMNs (e.g., location, Schröger & Wolff, 1996; frequency, Jacobsen & Schröger, 2003), for which an overestimation of pure MMN processes is likely to happen. Hence, the use of a large duration difference between deviants and standards enables to obtain a robust and ''pure'' MMN (with deviants shorter than the standards). Such considerations led Fischer et al. (1999) to choose an oddball paradigm with deviance in duration to investigate MMN preservation in comatose patients. To increase sensitivity of the wave detection, these authors used a large deviance (the standard lasted 75 msec and the deviant 30 msec). Such protocol induced in awake healthy subjects a large MMN and a subsequent P3a component in response to the deviant tone.

The aim of the present study was to investigate how the healthy sleeping brain processes auditory information and, more precisely, to identify which steps of auditory stimuli analysis are preserved, suppressed, or modified during each sleep stage. We focused our investigation on both low-level mechanisms such as sensory memory and more cognitive/elaborated processing of auditory information. To do so, we used an oddball paradigm to determine in which sleep stages an MMN and putative subsequent positive waves can be detected in response to an unattended deviant tone. We were especially interested in amplitude and latency modifications of the elicited waves during sleep. In order to increase the sensitivity of the investigation, we acquired EEG (23 scalp electrodes) and polysomnographic recordings (electrooculogram [EOG] and electromyogram [EMG], in addition to EEG) during a whole and undisturbed night of sleep (and presleep wakefulness), and we used the duration oddball paradigm designed by Fischer et al. (1999), known to be sensitive and robust, to elicit an MMN.

METHODS

Subjects

Twelve (6 men and 6 women) healthy, right-handed subjects volunteered to participate in the study. They were between the age of 19 and 26 years (22 ± 2 years). All were self-reported good sleepers with neither ongoing medication nor history of hearing disorders. Prior to testing, each subject signed an informed consent in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Subjects were paid for their participation.

Two subjects were excluded from data analysis: one because EEG recordings contained an unacceptable level of 50 Hz interference, and another one because ERP analysis revealed an immature N1 component (a 19-year-old subject).

Stimulation

Tone bursts of 800 Hz were presented at a level of 50 dB above each subject's own hearing threshold (50 dB SL), with a stimulus onset asynchrony (SOA) of 610 msec. Frequent stimuli (p = .86) lasted 75 msec (including 5 msec rise and fall times), whereas randomly distributed rare stimuli (p = .14) lasted 30 msec (including 5 msec rise and fall times). A minimum of two standards were presented between two consecutive deviants.

Procedure

Subjects slept a single night in the laboratory. They arrived at 7.30 p.m. Electrodes were stuck (using collodion) and insert earphones were placed in each ear and kept in place by means of an adhesive tape. Then the hearing threshold of the subject was determined and the baseline waking recording could start. It lasted around one hour, during which subjects were instructed to read a self-chosen book while ignoring the tones (wakefulness condition). Around 11.00 p.m., subjects got into a bed installed in a soundproof room, and light was switched off for a 7- to 8-hr night recording (sleep conditions). Stimuli were presented continuously during the whole night, and data were recorded without any break.

Data Recording

EEG, EOG, and EMG data were continuously recorded via a Neuroscan Compumedics system through Synamps DC-coupled amplifiers at a sampling rate of 1000 Hz. EEG data were recorded from 23 Ag–AgCl scalp electrodes placed according to the International 10-20 System: Fpz, Fz, Cz, Pz, Oz; F3, FT3, FC1, T3, C3, T5, P3, M1, OM1, and their counterparts on the right hemiscalp (EEG: amplification gain, 12,500; bandwidth, 0.1–200 Hz). ERP recordings were referenced to the nose (ground to the forehead). Polysomnographic data comprised two EEG channels (the C3 and C4 scalp electrodes referenced, respectively, to M1 and M2), one EMG channel (two electrodes attached to the chin; amplification gain, 12,500; bandwidth, 1–200 Hz) and one horizontal EOG channel (two electrodes at the outer canthi of both eyes; amplification gain, 2500; bandwidth, 0.1–30 Hz). Electrode impedances were kept below 5 kΩ.

Sleep Stages Scoring

Successive 30-sec epochs of polysomnographic data were classified double-blind into five different sleep/wake stages (wakefulness, Sleep Stage 1, Sleep Stage 2, Sleep Stage 3, Sleep Stage 4, and PS) by S.B. and C.D., according to the standard criteria of Rechtschaffen and Kales (1968). After this first double-blind scoring round, in a second round, both scorers revised together the

epochs for which they disagreed in the first round. When no consensus could be found between the two scorers in this second round, the epoch was excluded from the EEG analysis.

Event-related Potentials

EEG analysis was undertaken with the ELAN Pack software developed at the INSERM U280 (now U821) laboratory (Lyon, France). For each subject, ERP waveforms were obtained separately for the two stimulus types (frequent and rare sounds) and the six conditions (corresponding to the six states of consciousness studied: wakefulness and five sleep stages) by averaging epochs between 100 msec before and 400 msec after stimulus onset. The following trials were excluded from the averaging: (1) trials in which EEG exceeded 100 μV, (2) trials with standards immediately following a deviant. Occipital electrodes (OM1 and OM2) were excluded from the analysis because of a too noisy signal. The baseline was corrected according to the mean value of the signal during the 100 msec prior to the stimulus onset. A 30-Hz low-pass digital filter was applied after averaging. To detect the MMN and the putative following positive waves elicited by deviant tones, difference waveforms were calculated by subtracting the ERPs to frequent tones from the ERPs to rare tones.

Statistical Detection of the Deviance-related ERPs

Mismatch Negativity

This statistical analysis performed at Fz, Cz, M1, and M2 aimed at checking the presence of an MMN at the group level in each condition (wakefulness and all sleep stages). It relied on the expectation of a fronto-central negative wave associated with a polarity inversion at both mastoids. The mean value of the difference curve (deviant minus standard) in a fixed time window was computed for each subject in each condition at Fz, Cz, M1, and M2. For each of the six conditions, we used a time window of 50 msec centered on the maximum of the grand-average difference curve around the usual MMN latency (bounds: wakefulness, 135–185 msec; Sleep Stage 1, 125–175 msec; Sleep Stages 2, 3 and 4, 110–160 msec; PS, 115–165 msec). One-tailed *t* tests compared to zero the more negative values at Fz or Cz (negative difference expected) and the mean value at M1 and M2 (positive difference expected).

Post-MMN Positivity

A similar procedure was applied to test whether a positive wave followed the MMN in the different conditions. The mean value of the difference curve (deviant minus standard) at Cz in a fixed time window was computed for each subject in the candidate stages. For each condition considered, a time window of 40 msec centered on the maximum of the grand-average difference curve was used (bounds: wakefulness, 240–280 msec; Sleep Stage 1, 245–285 msec; Sleep Stage 2, 185–225 msec; PS, 280–320 msec). We compared to zero the values obtained at Cz with one-tailed *t* tests.

Topographic Analysis

To facilitate the interpretation of the voltage values recorded at multiple electrodes over the scalp surface, we qualitatively analyzed the topographic distributions of the scalp potentials (SPs) at MMN and post-MMN positivity (PMP) latencies. SP maps were generated using a spherical spline interpolation algorithm (Perrin, Pernier, Bertrand, & Echallier, 1989).

Equivalent Current Dipole Modeling

In order to assess to what extent intracerebral generators similar to that of the waking MMN could explain the activity observed on the scalp during sleep, we conducted a dipole modeling analysis. We first modeled the MMN in the awake state in the grand-average difference ERP using two equivalent current dipoles (ECDs) in the 135–185 msec time window (i.e., the time window used for MMN detection). A three-layer spherical head model was used, with a nonlinear iterative procedure (Marquardt algorithm) to estimate dipole parameters (see also Caclin et al., 2006; Giard et al., 1995). Location and orientation of the dipoles were constrained to be constant across time, whereas their amplitudes were time-variant. Further, we constrained the position and orientation of the two dipoles to be symmetrical. We then ran a dipole modeling analysis in the grand-average difference ERP for each of the five sleep stages in the time window used for MMN detection for this stage (see above). In this analysis, we modeled the putative MMN with the very same dipoles as those found in the modeling of the waking state MMN, and we assessed the residual variance in the data not accounted for by the model.

Peak Measurement of the Deviance-related ERPs

Mismatch Negativity

For each subject, and for each condition in which the wave was actually detected, the point with maximum negative value of the difference wave (deviant minus standard) was sought in the 115–200 msec time window at Fz and Cz electrodes. We retained the latency and the amplitude measured at the electrode where the larger negative amplitude was found. In the same time window, we also detected the point with maximum positive value at each of the two mastoids and retained the mean latency and the mean amplitude.

Post-MMN Positivity

In the case this wave was detected, for each subject and in each concerned condition, the maximum value of the difference wave at Fz, Cz, and Pz was sought in the difference wave in the 185–330 msec time window.

Statistical Analysis of the Influence of Sleep Stages on ERPs

We used repeated measures analysis of variance (ANOVA) to test the possible effect of sleep stages on amplitude and latency of the waves detected during sleep (MMN and PMP). Greenhouse–Geisser correction was applied, and epsilon and corrected *p* values are reported.

RESULTS

Sleep Stages Scoring

In average for the 10 subjects, double-blind scoring of the sleep stages (Rechtschaffen & Kales, 1968) resulted in 80% (±5) between-scorer concordance. After the two scorers revised together the tricky recordings, 3.9% (±1.6) of the 30-sec epochs scored were excluded because no consensus could be reached. Mean recording duration was 8 hr 52 min (±37 min), including 8 hr (±42 min) of sleep. The proportion of each sleep stage (Sleep Stage 2, 51 ± 8%; Sleep Stages 3 and 4, 23 ± 5%; PS, 20 ± 5%) matched the usual values recorded in a healthy population of young subjects with no sleep disorders (Sleep Stages 1 and 2, 50%; Sleep Stages 3 and 4, 30%; PS, 20%; Hirshkowitz, 2004; Benoit & Foret, 1992). Visual inspection of the data revealed some large K-complexes that were removed from the analysis by the automated artifact rejection procedure (in the time window between 100 msec before and 400 msec after the stimulus).

Event-related Potentials

For the rare (deviant) sounds, the averaged percentage of rejected responses and the average number of accepted responses in each condition were as follows: *Wakefulness*, rejected deviants = 25% (±13), accepted deviants = 739 (±502); *Sleep Stage 1*, rejected deviants = 9% (±5), accepted deviants = 288 (±340); *Sleep Stage 2*, rejected deviants = 11% (±5), accepted deviants = 2744 (±512); *Sleep Stage 3*, rejected deviants = 26% (±11); accepted deviants = 183 (±80); *Sleep Stage 4*, rejected deviants = 50% (±18), accepted deviants = 488 (±254); *PS*, rejected deviants = 6% (±2), accepted deviants = 1122 (±367).

Wakefulness

The grand-average ERPs elicited by frequent (standard) sounds, rare (deviant) sounds, and the difference between the two (deviant minus standard) in the wakefulness condition are shown in Figures 1 and 2. The auditory N1 wave can be seen on the curve showing ERP to the frequent sound. Both an MMN and a PMP were detected in wakefulness (see Tables 2 and 3). The MMN showed the largest amplitude at Fz. It peaked at 170 msec (±23) with an amplitude of 2.65 μV (±1.66). SP maps at the latency of the maximum of the MMN in wakefulness are displayed in Figure 3

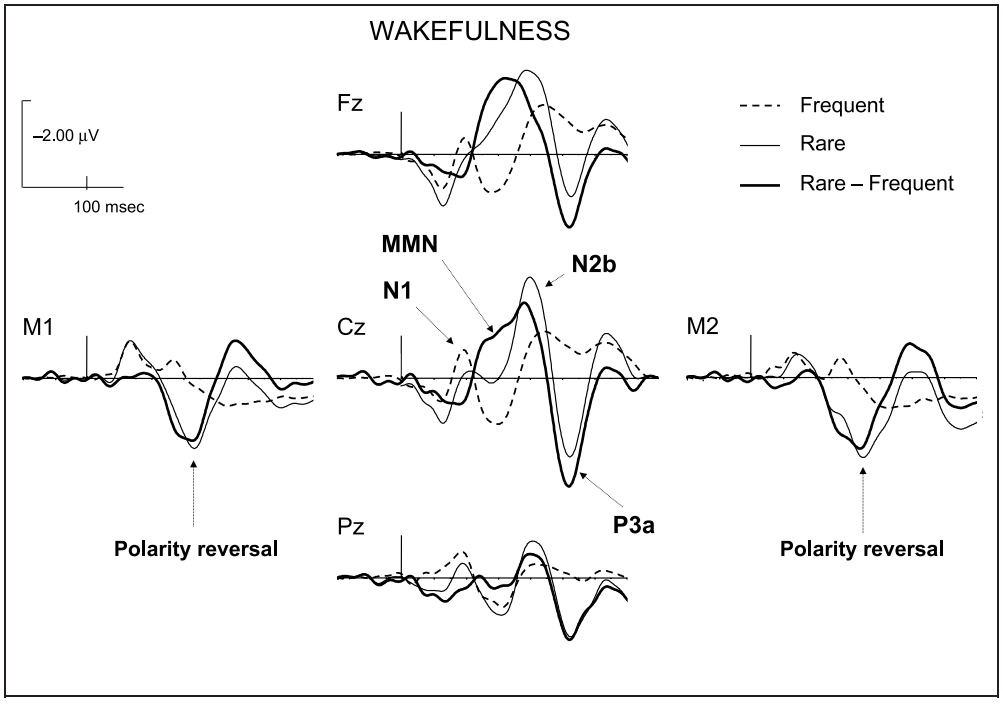

Figure 1. Grand-average ERPs (10 subjects) at Fz, Cz, Pz, M1, and M2 in wakefulness are shown for the frequent sound, the rare sound, and for the difference between the two.

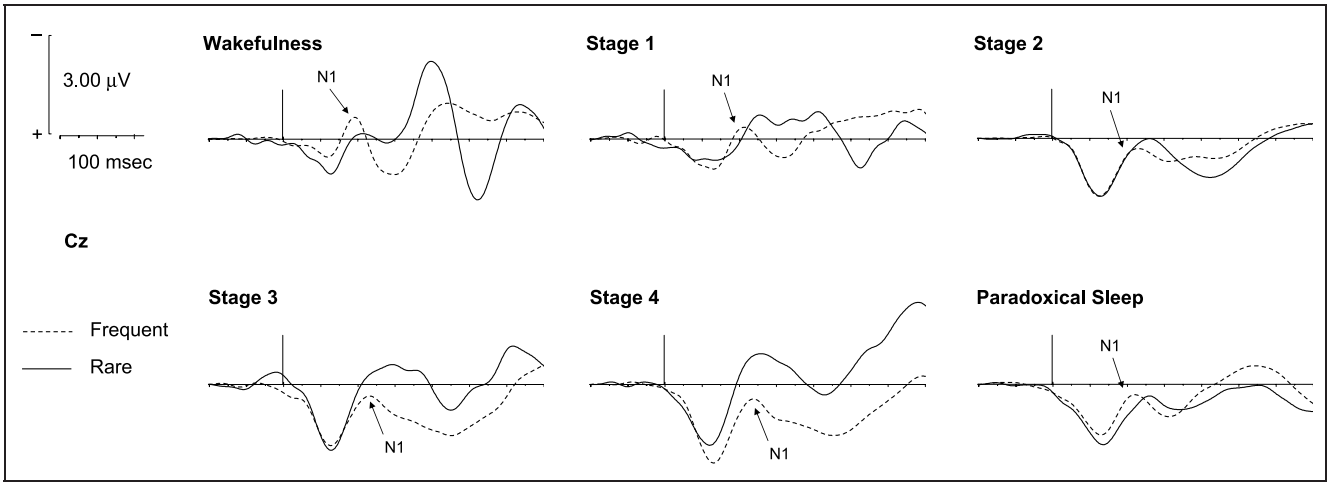

Figure 2. Grand-average ERPs (10 subjects) for the frequent (standard) and for the rare (deviant) sounds in the six states of consciousness at Cz.

(first column). They show polarity reversal at the mastoids as expected with a nose reference, indexing activity in both supratemporal auditory cortices. MMN was objectified by a positive detection test at Fz–Cz ($p < .01$) and at M1–M2 ($p < .001$). A PMP wave was also detected ($p < .001$ at Cz) in the difference curve and was maximum (2.78 ± 1.57 μV) at Cz at 262 msec (±7.7). An SP map at the latency of the maximum of the PMP in wakefulness is displayed in Figure 3 (first column).

Sleep Conditions

The ERPs at Cz for the standard and deviant tones in all conditions are presented in Figure 2. Well-defined auditory ERPs for standards and deviants, including a

Table 2. MMN Detection and Measurements in the Six States of Consciousness at Fronto-central Sites (Fz–Cz) and at the Mastoids (M1–M2)

	Wakefulness	*Stage 1*	*Stage 2*	*Stage 3*	*Stage 4*	*Paradoxical Sleep*
Fz–Cz						
Detection	**	**	**	*	**	*
Latency (msec)	170 ± 23	154 ± 21	139 ± 9	153 ± 24	NM	147 ± 21
Comparison with wake	/	$p = .074$	***	$p = .057$	NC	**
Comparison with Stage 1	$p = .074$	/	$p = .080$	NS	NC	NS
Amplitude (μV)	−2.65 ± 1.66	−1.94 ± 1.29	−0.68 ± 0.45	−2.97 ± 2.13	NM	−0.62 ± 0.49
Comparison with wake	/	NS	**	NS	NC	**
Comparison with Stage 1	NS	/	*	NS	NC	*
M1–M2						
Detection	***	**	*	$p = .084$	NS	$p = .092$
Latency (msec)	159 ± 14	149 ± 20	140 ± 24	139 ± 25	NM	141 ± 14
Amplitude (μV)	1.88 ± 0.65	1.27 ± 0.83	0.30 ± 0.31	1.20 ± 1.51	NM	0.26 ± 0.22
Comparison with wake	/	NS	***	NS	NC	***
Comparison with Stage 1	NS	/	**	NS	NC	**

For each site, the first row shows the result of the statistical detection of the MMN (one-tailed *t* test). The mean ± *SD* latencies and amplitudes of the waves are reported with between-states comparisons (Fisher test) presented below. NS = not significant; NM = not measured; NC = not calculated.

*$p < .05$.

**$p < .01$.

***$p < .001$.

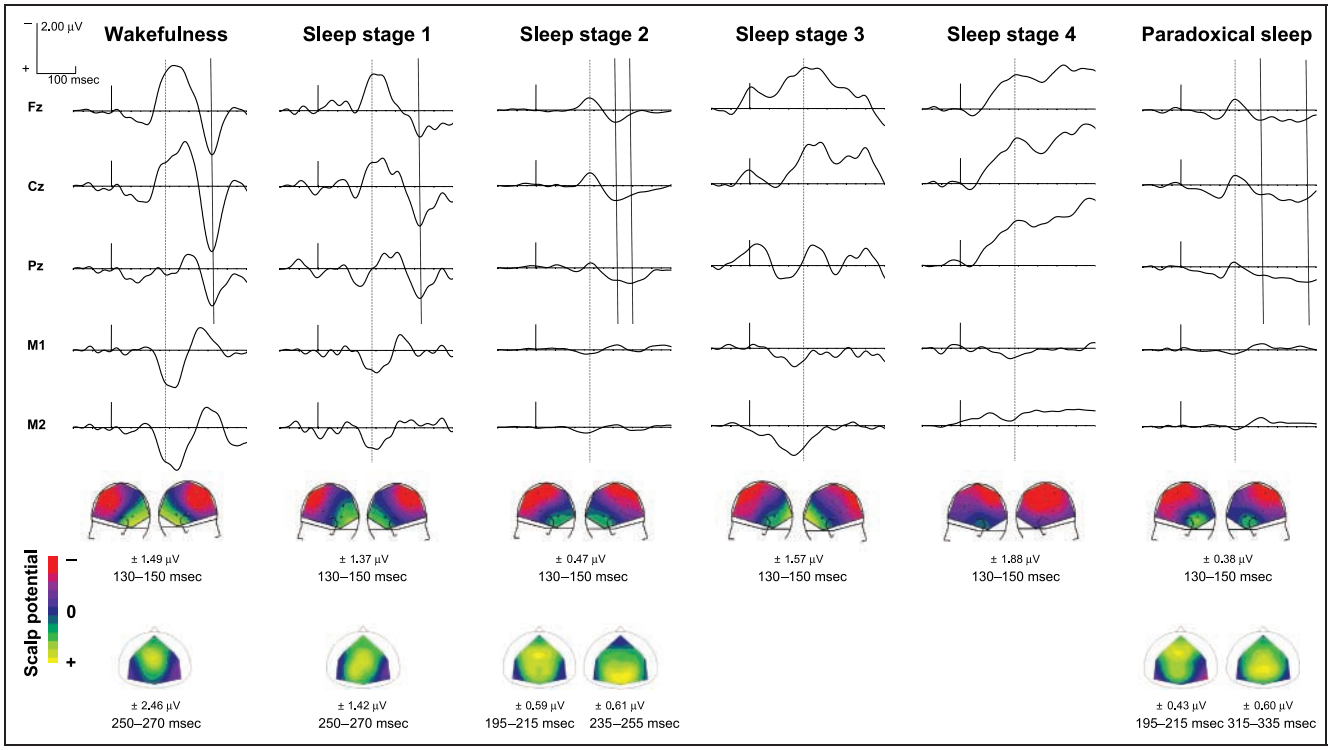

Figure 3. Grand-average difference ERPs (rare minus frequent sound), recorded at three midline electrodes (Fz, Cz, Pz) and at the mastoids (M1 and M2), in the different states of consciousness. Scalp potential topographies at MMN and PMP latencies are presented below in two rows: The time window used and the range of the color scale are given below each map. The vertical lines on the ERP curves localize the middle of the time windows chosen for scalp potential maps.

P50, N1, and P2, were recorded in all conditions. In accordance with previous work (for a review, see Bastuji & Garcia-Larrea, 1999), the N1, known to reflect mainly activity in the auditory cortex, showed some modification in sleep, in particular, with more positive potentials in the P50 and N1 latency range during the sleep conditions, and with the Stage 1 ERP most resembling the awake ERPs (see Figure 2).

Mismatch Negativity

Statistical Detection

Grand averages of the difference waves (deviant minus standard) at Fz, Cz, Pz, M1, and M2, and SP maps in the 130–150 msec time window are displayed for all sleep stages in Figure 3. The results of the statistical detection of the MMN component are shown in Table 2. In Sleep Stages 1 and 2, one-tailed *t* tests were significant at Fz–Cz and M1–M2, and SP maps exhibited a topography very similar to the topography of the MMN in wakefulness. In Sleep Stage 3 and in PS, one-tailed *t* tests were significant at Fz–Cz and tended to be significant at M1–M2, and SP topographies were also very similar to the maps of the MMN in wakefulness. In Sleep Stage 4, one-tailed *t* test was significant at Fz–Cz and was not significant at M1–M2, and the SP map poorly resembled the usual MMN topography in wakefulness. Hence, according to these criteria, a true MMN was detected in all sleep stages except Sleep Stage 4.

Equivalent Current Dipole Modeling

In the awake state, using two symmetrically positioned and oriented dipoles to model the MMN in the 135–185 msec time window, the residual variance in the data not accounted for by the model was 1.39%. The model therefore provided a very good fit of the data. When using these two dipoles to model the difference ERPs obtained in the different sleep stages, the residual variance not accounted for by the model was 5.60% in Sleep Stage 1 (125–175 msec time window), 7.22% in Sleep Stage 2 (110–160 msec time window), 10.66% in Sleep Stage 3 (110–160 msec time window), 63% in Sleep Stage 4 (110–160 msec time window), and 16.29% in PS (115–165 msec time window). Thus, the fit of the model was good in Sleep Stages 1 to 3 and acceptable in PS, but poor in Sleep Stage 4.

Influence of Sleep Stages on the MMN

The influence of sleep on the MMN is illustrated in Figures 3 and 4. Amplitude and latency of the MMN in the conditions where it was detected are presented

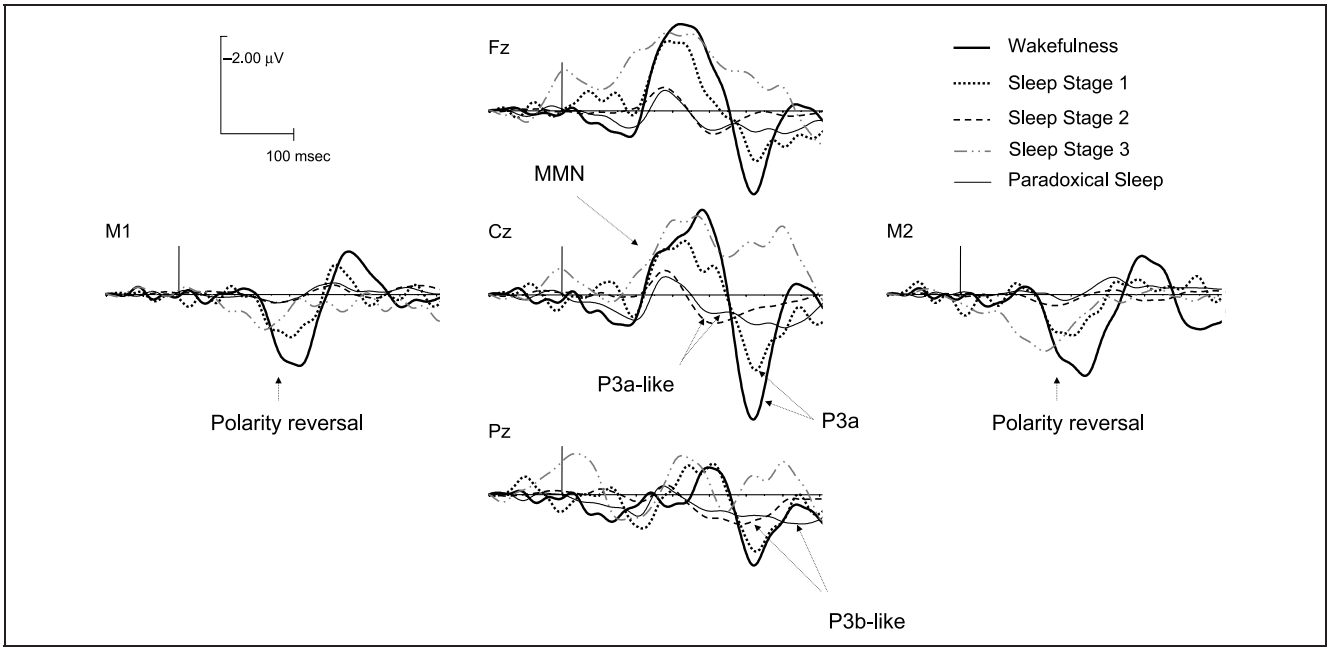

Figure 4. Grand-average ERPs obtained at Fz, Cz, Pz, M1, and M2 for the difference between the rare and frequent sounds in wakefulness; Sleep Stages 1, 2, 3; and paradoxical sleep.

in Table 2. An ANOVA on the MMN latency measured at Fz–Cz (one within-subject factor, condition, with five levels: wakefulness, Sleep Stages 1, 2, 3, and PS) revealed a significant influence of sleep stages [$F(4, 36) = 3.62$, $\varepsilon = 0.685$, $p = .03$]. Fisher tests (presented in Table 2) further showed that the MMN latency in wakefulness tended to be different from the MMN latency in all the sleep stages tested. Fisher tests also revealed that the MMN latency did not differ between sleep stages, except for a tendency of Sleep Stage 1 to exhibit a later MMN than Sleep Stage 2. However, there was no significant influence of sleep stages on the MMN latency measured at the mastoids [$F(4, 36) = 2.24$, $\varepsilon = 0.85$, $p = .10$]. Another ANOVA (one within-subject factor, condition, with five levels) revealed a significant influence of sleep stages on the MMN amplitude measured at Fz–Cz [$F(4, 36) = 6.20$, $\varepsilon = 0.385$, $p = .01$]. Fisher tests (presented in Table 2) further showed that the MMN amplitude was not significantly different between wakefulness, Sleep Stage 1, and Sleep Stage 3 on the one hand and between Sleep Stage 2 and PS on the other hand. Fisher tests also revealed that the MMN amplitude in Sleep Stage 2 and PS was smaller than in wakefulness and in Sleep Stage 1. At the mastoids also, the MMN amplitude was influenced by sleep stages [$F(4, 36) = 8.09$, $\varepsilon = 0.501$, $p = .003$]. Fisher tests showed that, as for fronto-central sites, the MMN amplitude at the mastoids was not significantly different in wakefulness, Sleep Stage 1, and Sleep Stage 3, and it was smaller in Sleep Stage 2 and PS than in wakefulness and in Sleep Stage 1 (Table 2).

Post-MMN Positivity

Statistical Detection

The results of the statistical detection of the PMP component are shown in the first row of Table 3. A significant positivity was detected at Cz after the end of the MMN and before 320 msec in Wakefulness, Sleep Stage 1, Sleep Stage 2, and PS.

Influence of Sleep Stages on the Post-MMN Positivity

To illustrate the influence of sleep on PMP, ERPs at Fz, Cz, Pz, M1, and M2 are shown in Figure 3 for each sleep stage as well as SP maps at the latency of the PMP (second row). Latency and amplitude of the PMP maximum at Fz, Cz, and Pz for each condition where it was detected are presented in Table 3. An ANOVA (two within-subject factors: electrode, with two levels: Fz, Pz; Condition, with four levels: wakefulness, Sleep Stage 1, 2, and PS) revealed significant effects neither of the electrode factor nor of the condition factor on the PMP latency. However, the interaction effect between electrodes and conditions was significant [$F(3, 27) = 3.49$, $\varepsilon = 0.866$, $p = .04$]. Between conditions comparisons (Fisher tests presented in Table 3) showed that the PMP latency at Fz in Sleep Stage 2 was shorter than in all the other conditions (wakefulness, Sleep Stage 1, PS). The PMP latency at Fz in PS was also shorter than in Sleep Stage 1. Within condition, that is, between electrodes, comparisons (Fisher tests presented in Table 3) revealed that in wakefulness and Sleep Stage 1, the PMP latencies at Fz and Pz were not significantly different. In

Table 3. Post-MMN Positivity Detection and Measurements

	Wakefulness			*Stage 1*			*Stage 2*			*Paradoxical Sleep*		
	Fz	*Cz*	*Pz*	*Fz*	*Cz*	*Pz*	*Fz*	*Cz*	*Pz*	*Fz*	*Cz*	*Pz*
Detection at Cz		***			**			**			*	
Latency (msec)	262 ± 8.8	262 ± 7.7	257 ± 24	272 ± 38	274 ± 23	277 ± 25	228 ± 39	249 ± 51	246 ± 38	249 ± 45	263 ± 50	285 ± 35
Within-states comparison between Fz and Pz		NS			NS			$p = .06$			***	
Between-states comparison with wake at Fz		/			NS			**			NS	
Between-states comparison with Stage 1 at Fz		NS			/			***			*	
Between-states comparison with Stage 2 at Fz		**			***			/			*	
Amplitude (μV)	1.95 ± 1.00	2.78 ± 1.57	1.77 ± 1.18	1.53 ± 1.18	2.15 ± 1.14	1.78 ± 1.61	0.60 ± 0.44	0.81 ± 0.42	0.80 ± 0.57	0.86 ± 0.63	1.10 ± 0.73	1.10 ± 0.53
Within-states comparison between Cz and Pz		***			NS			NS			NS	
Between-states comparison with wake at Cz		/			*			***			***	
Between-states comparison with Stage 1 at Cz		*			/			***			***	

The first row shows the result of the statistical detection at Cz of a PMP wave (one-tailed *t* test). The mean ± *SD* latencies and amplitudes of the PMP waves in the time window 185–330 msec at Fz, Cz, and Pz are presented in the states of consciousness where it was detected. Below latency and amplitude values, some within- and between-conditions comparisons (Fisher test) are reported. NS = not significant.

*$p < .05$.

**$p < .01$.

***$p < .001$.

contrast, during Sleep Stage 2 and PS, the PMP latency was shorter at Fz than at Pz.

Another ANOVA (two within-subject factors: electrode, with two levels: Cz, Pz; condition, with four levels) revealed a significant effect of the electrode factor [$F(1, 9) = 7.41$, $\varepsilon = 1$, $p = .02$] and the condition factor [$F(3, 27) = 4.60$, $\varepsilon = 0.683$, $p = .02$] on the PMP amplitude. The interaction effect between electrode and condition was also significant [$F(3, 27) = 4.21$, $\varepsilon = 0.707$, $p = .03$]. Between-conditions comparisons (Fisher tests presented in Table 3) showed that the PMP amplitude at Cz was larger in wakefulness than in Sleep Stage 1, Sleep Stage 2, and PS. They also revealed that the amplitude of the PMP in Sleep Stage 1 was smaller than in wakefulness and larger than in Sleep Stage 2 and PS. No PMP amplitude differences were found between Sleep Stage 2 and PS. Within-condition, that is, between-electrodes, comparisons (Fisher tests presented in Table 3) revealed that the PMP amplitude was larger at Cz than at Pz during wakefulness. No such difference between Cz and Pz was found in Sleep Stage 1, Sleep Stage 2, or PS.

To recap (1) in wakefulness and in Sleep Stage 1, PMP peaks at the same latency at Fz and Pz and its amplitude is maximum at Cz, and (2) in Sleep Stage 2 and in PS, PMP peaks first at Fz and, subsequently, at Pz, and its amplitude is similar at Cz and at Pz.

DISCUSSION

This study aimed at investigating how external stimuli are processed during the different sleep stages, by assessing both the putative maintenance of sensory memory and possible more complex cognitive mechanisms using ERPs in response to an auditory deviance. In order to increase the sensitivity of our investigations, we used a robust procedure, that is, an oddball paradigm with a large duration deviance (Fischer et al., 1999) and we recorded EEG during a whole and undisturbed night of sleep in 10 healthy young subjects.

The analysis of the presleep recordings reproduced previous results (Fischer et al., 1999) obtained with the same paradigm in awake healthy subjects. During wakefulness, as expected, a large MMN with a typical polarity inversion at the mastoids and a subsequent P3a component were detected in response to the deviant tone (Figure 1). The detection of a P3a component suggests that this protocol elicits an involuntary orientation of attention toward the deviant sound due to its

large salience (Polich & Criado, 2006; Polich, 1989; Näätänen et al., 1982).

Mismatch Negativity

Given that we used a protocol that limits potential confounds of the MMN (see Introduction), our results suggest that we evidenced a genuine MMN in Sleep Stages 1, 2, 3, and in PS. Indeed, in all these sleep stages, the difference between ERPs in response to rare and to frequent sounds was significantly negative at fronto-central sites, positive at the mastoids, and the topography of the wave was close to the topography of the wakefulness MMN around 150 msec (Figures 3 and 4). In addition, the results of the dipole modeling analysis showed that the intracerebral generators of the MMNs observed in wakefulness and in Sleep Stages 1, 2, 3, and PS are fairly similar, suggesting that the same types of mechanisms are operating in all these conditions. It is to note that Sleep Stage 1 may be a mixed stage at the limit between wakefulness and sleep. For this reason, it cannot be excluded that the wave recorded in Sleep Stage 1 is overestimated due to a contamination by wakefulness data. Regarding, in particular, Sleep Stage 2 results, we also want to stress that it was beyond the scope of this study to explore the link between the MMN and possible subsequent K-complexes. Sallinen et al. (1996) have proposed that an MMN was only elicited in trials were an evoked K-complex was recorded. This could also be the case in our study. This interpretation is, however, unlikely given that (i) at least a significant part of trials with a K-complex should have been rejected by our automated artifact rejection procedure, and (ii) dipole modeling revealed that MMN sources were similar in wakefulness and Sleep Stage 2, suggesting that additional negative sources did not significantly contribute to the negativity observed during Sleep Stage 2. Whether an MMN can be elicited in Sleep Stage 4 is less clear but cannot be excluded. We detected a deviance-related negativity at fronto-central sites, but it was not accompanied by a clear polarity reversal at the mastoids (see Table 2 and Figure 3). Dipole modeling results confirmed this altered morphology of the recorded deviance-related ERP in the latency range of the MMN in Sleep Stage 4. Yet it remains possible that an overlap with large deep sleep slow waves may ''hide'' the MMN in this sleep stage.

At Fz–Cz, results revealed a slightly later MMN during wakefulness as compared to sleep, whereas the latency of the polarity reversal at the mastoids did not show any significant influence of sleep stages. This suggests an overlap of the MMN with the N2b component in wakefulness and, to a lesser extent, in Sleep Stage 1, which is confirmed by an inspection of the morphology of the waveforms (Figure 3). The N2b is, indeed, characterized by a sharp fronto-central or central negative peak superimposed on the late part of MMN (Näätänen et al., 1982). Relative to the MMN, the N2b has a more posterior topography (Sams, Paavilainen, Alho, & Näätänen, 1985) and, with a nose reference, the MMN typically inverts polarity at the mastoids, whereas the N2b does not (Novak, Ritter, Vaughan, & Wiznitzer, 1990). We thus suggest that the latency of the MMN at Fz–Cz in wakefulness (and also to a lesser degree in Sleep Stage 1) could have been overestimated due to an overlap of the MMN by an N2b component. Interestingly, this secondary N2b peak disappears in Sleep Stage 2, Sleep Stage 3, and PS, which results in similar latencies of the MMN in these three stages. Thus, one cannot exclude a rather preserved latency of MMN during wakefulness, Sleep Stage 1, Sleep Stage 2, Sleep Stage 3, and PS. Our results then tend to demonstrate that the latency of the change detection process reflected by the MMN may remain constant under physiological modifications of the level of consciousness in healthy subjects. What would be actually or mainly modified would be the MMN amplitude and later cerebral processes (associated to more delayed waves such as N2b and P300). Two groups of conditions were indeed segregated according to the MMN amplitude: wakefulness, Sleep Stage 1, and Sleep Stage 3 showed similar large MMN amplitudes, whereas, in Sleep Stage 2 and PS, the wave demonstrated a much smaller amplitude (Figures 3 and 4). In the awake state, it is fairly well established that the amplitude of the MMN after a change along one auditory dimension is correlated with the perceptible dissimilarity between the standard and the deviant (Toiviainen et al., 1998; Tiitinen, May, Reinikainen, & Näätänen, 1994). Although any extrapolation of this result to sleep conditions should be taken with care, the smaller MMN amplitudes observed in Stage 2 and PS might reflect a decreased perception of the distance between sounds. However, our results cannot disentangle between the two following interpretations: an attenuated discriminative process or a modified perceptual content.

Why we managed to detect significant MMN during sleep with a classical oddball paradigm, whereas other teams did not, is certainly explained for a big part by the large amount of data collected in the present study, and also by the use of large duration deviants. Our results thus extend those of Sabri and Campbell (2005) and Sabri et al. (2003) by showing that not only a DRN but a ''true'' MMN can be elicited during sleep, and that an MMN can be obtained with a classical procedure used to elicit MMN in wakefulness. These results argue against a shortening of sensory memory duration during sleep hypothesized by Sabri and Campbell, and Sabri et al. to explain the lack of results of previous studies (Table 1). All together, these results demonstrate that sensory memory mechanisms are not extinguished during sleep, at least during Sleep Stages 1, 2, 3, and PS. This conclusion is congruent with previous results which showed that semantic processing of auditory stimuli was also preserved during Sleep Stage 2 and PS (Bastuji

et al., 2002; Perrin et al., 1999). Sensory memory appears, indeed, to be a prerequisite for elaborated cognitive processing such as semantic extraction from auditory stimulation.

P300

In the present study, a post-MMN positive wave (PMP) was detected around 250 msec in wakefulness, Sleep Stage 1, Sleep Stage 2, and PS. During wakefulness, this positivity is centrally distributed (Figure 3) with synchronous maxima at Fz and Pz and shows the largest amplitude at Cz (Table 3). Immediately following the N2b component and peaking at 262 msec, it has the typical characteristics of the fronto-centrally distributed ''P3a'' described by Squires, Squires, and Hillyard (1975b) (see Figure 4). This N2b–P3a complex most likely reflects automatic orienting of the subjects' attention toward the quite salient deviant. Because such deviant tones were not attended by the subjects (reading a book) in this ''passive paradigm,'' a subsequent posteriorly distributed ''P3b'' was neither expected nor detected.

During Sleep Stage 1, as it was reported by Bastuji, Garcia-Larrea, Franc, and Mauguière (1995), the PMP was similar to the wave detected in wakefulness (Figure 4). It showed a small decrease in amplitude and no latency modification in comparison to the wakefulness P3a (Table 3). Such results encourage to conclude that the P3a component is maintained during Sleep Stage 1.

In Sleep Stage 2, a PMP was also detected (Figures 3 and 4). However, in this stage, the wave exhibited a shorter latency at Fz and a reduced amplitude in comparison to the wakefulness P3a (Table 3). Of most interest, this PMP showed a different morphology in comparison to the P3a observed in wakefulness and Sleep Stage 1, with the succession of a frontal component peaking at 228 msec and a parietal component peaking at 246 msec (Table 3, Figures 3 and 4). Figure 3 further shows that the SP topographies of the two successive PMP components in Sleep Stage 2 resemble the scalp topographies of P3a and P3b components detected in active paradigms in wakefulness (Polich & Criado, 2006). Given the early latency of the first component (228 msec), it may correspond to an enhancement of the earliest component of the so-called evoked K-complex (the P220 in Yang & Wu, 2007, or the P250 in Sallinen et al., 1996), which peaks at fronto-central sites. An alternative explanation would be that this PMP is a P3a-like component peaking early because of the vanishing of the N2b component in this stage or simply because its amplitude is small in this stage. Anyhow, our data reveal that in Sleep Stage 2, a P300-like wave can be elicited by deviant tones, with both a P3a-like (peaking earlier and with a smaller amplitude than in wakefulness) and a P3b-like component (which was not detected in wakefulness). This result particularly captured our attention because a P300-like wave in response to a simple tone was rarely reported in Sleep Stage 2. For example, Bastuji et al. (1995), in an experiment dedicated to P300 detection during sleep, did not objectify this wave in Sleep Stage 2. Cote (2002), who reviewed several results of the literature, showed that many studies failed to detect a P300 in Sleep Stage 2 and that some others detected a delayed positive wave around 450 msec in response to deviant stimuli. In Sleep Stages 3 and 4, no PMP was present (see Figure 3).

Finally, as could be expected from previous results, a P300-like wave was recorded in PS (Cote, 2002; Perrin et al., 1999; Pratt, Berlad, & Lavie, 1999; Sallinen et al., 1996; Bastuji et al., 1995; Niiyama, Fujiwara, Satoh, & Hishikawa, 1994). The wave showed a reduced amplitude as compared to both wakefulness and Sleep Stage 1. The PMP latency in PS at Fz was not different than in wakefulness, shorter than in Sleep Stage 1 and longer than in Sleep Stage 2 (Table 3 and Figure 4). As in Sleep Stage 2, the PMP wave presented both a P3a-like and a P3b-like component (Figures 3 and 4).

Our data, showing a P3b-like component in Sleep Stage 2 and PS but not during wakefulness and Sleep Stage 1, appear somehow surprising given that such result was neither expected nor previously described in the literature. We are, however, inclined to believe in the possible elicitation of a P3b-like component in PS given that Bastuji et al. (1995) also reported a wave resembling such a component in response to deviant tones (deviance in frequency) in PS although the authors did not expect it. In addition, Perrin et al. (1999) reported results congruent with ours in a study which showed a P300-like both in Sleep Stage 2 and in PS in response to the subject's own name. The authors did not try to dissociate P3a and P3b components, however, their results showing the largest amplitude at Pz, in wakefulness, Sleep Stage 2, and PS is fairly compatible with our results. An explanation to conciliate previous positive and negative detection of P3 components during sleep may be that a P3b could be detected with especially salient deviant stimuli such as the own first name (Perrin et al., 1999), but could not always emerge from noise in studies using less salient stimuli such as simple tones (Sabri et al., 2000; Bastuji et al., 1995). A strength of our study was to increase the sensitivity of wave detection by collecting a large amount of data (2744 ± 512 and 1122 ± 367 deviants tones recorded in Sleep Stage 2 and PS, respectively). Such a strategy may have made it possible to objectify a P3b-like component usually too weak to be detected.

A puzzling result of the present study is, hence, to demonstrate the presence of a parietal P3b-like wave during some sleep stages when the very same paradigm elicited only a fronto-central P3a component during wakefulness. What is critical and very new here is to objectify, neither a suppression nor an attenuation of a component, but the arising of a new one during sleep. None of previous studies gathered all the required

conditions to show such an effect. For example, Bastuji et al. (1995) (active oddball with large frequency deviants) and Perrin et al. (1999) (passive oddball with the subject's own first name as deviants) used paradigms eliciting a P3b already during wakefulness so that they could not demonstrate that such a component arose during sleep only. Sabri et al. (2000) (passive oddball with large frequency deviant), on the other hand, did use a paradigm eliciting only a P3a component during wakefulness but they did not detect any P3 component during sleep.

As already mentioned, the topography of the positive wave recorded in Sleep Stage 2 and PS is very similar to that of the P3b wave observed in active paradigms during wakefulness. Although it cannot be excluded that the positive component detected during sleep reflects different cognitive operations than the waking P3b, it is worth examining the current results in light of the cognitive correlates usually attributed to the P3b. The P3b is considered to index an active processing of an attended target (Squires, Donchin, Herning, & McCarthy, 1977) and a widely accepted interpretation suggests that this wave is associated with a conscious processing of the stimulus (Sergent, Baillet, & Dehaene, 2005). How do we conciliate this interpretation with the arising of a P3b-like wave during a state where the subject is asleep, and thus, not conscious? Our proposition is that this wave, recorded in two sleep stages where dreams can arise (Dement, 1981; Foulkes, 1962; Dement & Kleitman, 1957), may sign the active processing of the deviant stimulus in the consciousness of the dream. Several studies reported external stimuli (be it auditory, somatosensory, or visual) incorporation into dream (Burton, Harsh, & Badia, 1988; Hoelscher, Klinger, & Barta, 1981; Saint-Denys, 1867/1977; Bradley & Meddis, 1974; Koulack, 1969; Dement & Wolpert, 1958; Maury, 1862). The painting of Salvador Dali ''One Second Before Awakening from a Dream Caused by the Flight of a Bee Around a Pomegranate'' (1944) is a famous illustration of such a phenomenon. Another example is provided by the well-known dream of Alfred Maury (1862) ''la guillotine,'' where the sleeper dreamt that his head was cut by a guillotine when he woke up and discovered that the top of his bed had just fallen on his neck. These examples illustrate how external stimuli are, indeed, in the focus of the attention of the dreamer when they are incorporated into dream. They also highlight that external stimuli are incorporated into the dream with respect to their meaning, that is, the external stimulus always induces a concomitant mental imagery congruent with its physical characteristics and possible meaning in the real world (a hit on the neck induces an image of a head cut by a ''guillotine'' and the ''Bzzz'' of a bee, an image of a sting, i.e., the blade of the bayonet on the arm of the character in the painting of Dali). Such phenomenon presupposes elaborated cognitive processing of the external stimulus by the asleep brain such as semantic analysis. Hence, external stimuli incorporation into dream provides an argument in favor of a possible complex cognitive processing of sounds during Sleep stage 2 and PS and makes it possible to suggest that the P3b-like recorded in these sleep stages is an electrophysiological correlate of an elaborated cognitive processing of the deviant.

Recapitulation of the Effects of Sleep on the Processing of Auditory Change

Our results reveal a strong modulation of the cerebral responses to deviant tones according to the sleep stage. The Sleep Stage 1 closely resembles wakefulness, exhibiting both a large MMN and a single consecutive positive component: a P3a associated with an N2b. Sleep Stage 2 marks the disappearance of the N2b component, a diminishing of the MMN amplitude, and the arising of a P3b-like component following the P3a-like wave. In Sleep Stage 3, the MMN is preserved with a large amplitude, but no later positive components were identified. In Sleep Stage 4, only basic processing of auditory stimuli, as reflected, for example, by the N1 (see Figure 1), resembles that observed in other sleep stages. The brain responses to the auditory deviance were indeed, if present at all, at least very different from those observed in other stages. Finally, in PS, even if delayed, brain responses to the deviant tones demonstrated a similar profile to the ones seen in Sleep Stage 2. This similarity between Sleep Stage 2 and PS is worth noticing and suggests similar cognitive processing of the deviance in these sleep stages. These two sleep stages seem to be associated to both a ''smoothed'' perception of external stimulation (a less acute ability to distinguish between two different sensory inputs) and a complex and elaborated cognitive processing of external stimuli, being possibly incorporated into dream. The results obtained in Sleep Stage 3 also demonstrated an interesting dissociation between the MMN and P3 components elicited by the very same deviance during different sleep stages: If a P3 component always follows an MMN, an MMN is not necessarily followed by a P3 component. This suggests that, in Sleep Stage 3, cognitive processing of the auditory deviance might not have gone beyond sensory memory. In this stage, the attention orienting trigger threshold might be higher than in other conditions. These very different patterns of electrophysiological responses in the different sleep stages highlight a future need for specific investigation of dream reports separately in each sleep stage, in order to test whether they are qualitatively different (i.e., to test whether cognitive activities in the different sleep stages can be dissociated).

Conclusion

Our results demonstrated that an MMN can be elicited during Sleep Stage 1, Sleep Stage 2, PS, and, for the first

time, Sleep Stage 3. In addition, this study showed that a P3b-like wave was elicited in response to the deviant tone in Sleep Stage 2 and PS, whereas it was not seen in wakefulness, Sleep Stage 1, or Sleep Stage 3. It is the first time that an MMN is objectified in so many sleep stages in the same study with a classical oddball paradigm. It is also the first demonstration that a P3b-like component can arise during sleep (Stage 2 and PS) when it is not elicited during wakefulness. These findings certainly originate in the use of a robust paradigm (oddball with sound duration deviance), the acquisition of a large amount of EEG data, and the concern to acquire data in as natural a condition as possible (whole and undisturbed night). The procedure used, increasing the sensitivity of ERP detection, allowed us to bring together in the same study many results scattered and controversial in the literature and to show new results.

These results provide a significant contribution to the understanding of the cerebral functional organization during sleep, revealing spared sensory memory processes in the sleeping brain and critical switches both from wakefulness to sleep and between sleep stages in subsequent cognitive processing of external stimuli. These results appear also of importance for our understanding of altered states of consciousness. It was, indeed, already demonstrated that an MMN can be elicited in comatose patients with this very same paradigm (Fischer et al., 1999, 2004). The results of the present study, hence, give opportunities for the future to compare these physiological and pathological altered states of consciousness regarding both basic and more complex levels of information processing.

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