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Auditory Processing across the Sleep-Wake Cycle: Simultaneous EEG and fMRI Monitoring in Humans

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Summary

We combined fMRI and EEG recording to study the neurophysiological responses associated with auditory stimulation across the sleep-wake cycle. We found that presentation of auditory stimuli produces bilateral activation in auditory cortex, thalamus, and caudate during both wakefulness and nonrapid eye movement (NREM) sleep. However, the left parietal and, bilaterally, the prefrontal and cingulate cortices and the thalamus were less activated during NREM sleep compared to wakefulness. These areas may play a role in the further processing of sensory information required to achieve conscious perception during wakefulness. Finally, during NREM sleep, the left amygdala and the left prefrontal cortex were more activated by stimuli having special affective significance than by neutral stimuli. These data suggests that the sleeping brain can process auditory stimuli and detect meaningful events.

Introduction

The degree of cognitive activity taking place in a sleeping brain is a current matter of interest (e.g., Cote and Campbell, 1999; Perrin et al., 1999). Although it is generally accepted that sensory inputs are consciously perceived only during wakefulness, sensory information can be, under certain circumstances, integrated in the sleeper's mental activity (Burton et al., 1988). Since sleep occupies almost one-third of human life, it seems important to investigate the degree of sensory processing achieved during this state. In this study, we investigate the effect of auditory stimuli during nonrapid eye movement (NREM) sleep, which represents 80% of the total sleeping time (Carskadon and Dement, 1994).

Sensory stimulation during NREM sleep evokes the appearance in the electroencephalogram (EEG) of a large biphasic waveform named the K complex (Roth et al., 1956). Studies of auditory-evoked potentials have shown that early-latency responses are present during NREM sleep (Celesia and Puletti, 1969; Amadeo and Shagass, 1973; Mendel and Kupperman, 1974; Bastuji et al., 1988). These early auditory-evoked potentials are generated in the acoustic nerve and in the brainstem (Jewett and Williston, 1971; Chiappa, 1982; Buchwald, 1983). Thus, it is possible that early stages of sensory processing are unaffected during sleep. Results from middle-latency auditory potentials are more controversial. Several investigators found that the middle-latency potentials were altered in some or all of their components during NREM sleep (Erwin and Buchwald, 1986; Deiber et al., 1989). Middle-latency potentials reflect a generator with its origin in the primary auditory cortex (Wolpaw, 1979; Kaga et al., 1980; Buchwald et al., 1981) and in the auditory thalamus (McGee et al., 1992; Fischer et al., 1995). Finally, late responses (cortical in origin), reflecting complex cognitive processes (Donchin et al., 1984; Giard et al., 1988), are sometimes present but delayed during NREM sleep. For example, the P300, a late potential associated with attention and discrimination, is often preserved during NREM sleep (Wesensten and Badia, 1988; Brualla et al., 1998; Cote and Campbell, 1999; Perrin et al., 1999). Thus, the auditory potentials more affected are the ones generated at the thalamocortical level. In support of this notion, electrophysiological studies in cats showed specific decline in the firing rate of neurons in the parietal association cortex (Steriade et al., 1978) and the thalamus (Steriade and Hobson, 1976) during NREM sleep. Hence, it is possible that decreased efficiency in input processing in the thalamus and association cortices may be responsible for the lack of conscious perception during sleep. This possibility is consistent with data showing a relationship between conscious perception and activity in association cortices in humans (Lumer et al., 1998; Kleinschmidt et al., 1999; Portas et al., 2000).

Although the electrophysiological studies described above show that some aspects of sensory processing are preserved during NREM sleep, they lack the spatial resolution to identify the neuroanatomical substrates underlying this process. In the present study, we used functional magnetic resonance imaging (fMRI) combined with EEG to investigate "if" and "how" the brain responds to sensory processing across different levels of consciousness. First, we tried to establish to what extent auditory stimuli presented during sleep are associated with brain activity. We were also interested in comparing hemodynamic changes associated with auditory processing in sleep and wakefulness. Second, we considered whether, during NREM sleep, the brain may differentially process stimuli having special affective significance. To test this hypothesis, we presented two types of auditory stimuli, matched for their intensity and

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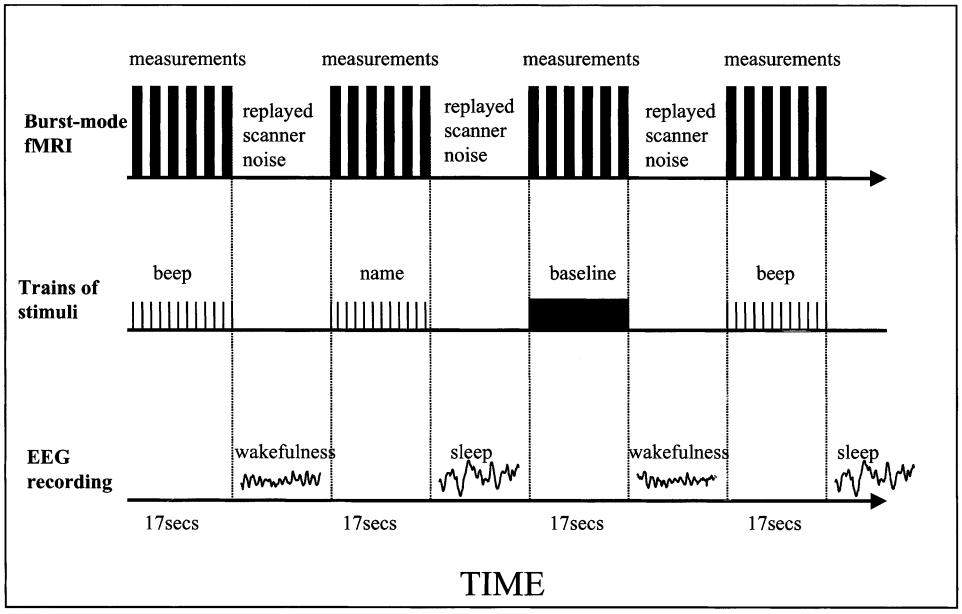

Figure 1. Schematic of the Experimental Design

The figure shows the time-relation between functional measurements, EEG recording, presentation of auditory stimuli, and replay of scanner noise.

duration but with different affective significance: pure tones (beep) and the subject's own first name.

Results

Figure 1 shows a schematic of the experimental design (see Experimental Procedures for more details). During the course of the experiment, subjects were presented with two types of auditory stimuli of equal length and intensity, a pure tone (beep) and the subject's own first name (name). Hypnograms showed in all subjects an alternation between wakefulness and sleep periods. NREM sleep will be referred to as "sleep." Most subjects fell asleep immediately after the start of the experiment and spent most of the sleeping time in stages II and III. An example of a subject's polygraphic recordings is shown in Figure 2.

The mean number of awakenings was 10 per subject and the majority was due to the presentation of the subject's own name (Figure 3). The most important finding of this study was that the pattern of brain activation associated with auditory stimulation was remarkably similar during wakefulness and sleep. In particular, processing of the auditory stimuli (name or beep) produced bilateral activation in auditory cortex (superior temporal gyrus, BA 41/42), thalamus, and caudate in wakefulness and sleep (Figure 4; Table 1).

However, when the stimuli-related brain activity during sleep was compared to stimuli-related brain activity during wakefulness, a decreased activation was found in the left parietal cortex (BA 7) and bilaterally in the prefrontal cortex (BA 47), thalamus, cingulate gyrus (BA23/24), and peri-amygdala regions (Figure 5; Table 1).

Direct comparison between the two event types (name versus beep) revealed higher activation of the middle temporal gyrus and orbitofrontal cortex bilaterally in response to the name in both wakefulness and sleep (Figure 6; Table 1).

Finally, we looked for activations associated with the interaction between stimulus type and state. That is, we contrasted name- versus beep-related brain activity during sleep with name- versus beep-related brain activity during wakefulness. Because we were interested in those brain regions that responded more to the presentation of the subject's own name, compared to beep, in sleep than in wakefulness, we masked the interaction with a contrast coding for the simple main effect of name versus beep in sleep (see Experimental Procedures). This comparison showed increased activation in the left amygdala and left prefrontal cortex (BA 46) (Figure 7; Table 1).

Discussion

This is the first fMRI study to investigate auditory processing as a function of the level of consciousness. The importance of understanding how sensory stimuli are processed in a state of reduced consciousness goes beyond the boundary of sleep physiology. Such knowledge would help us to comprehend how residual cognitive activity operates during states of "unconsciousness" other than sleep (e.g., anesthesia, comatose states, etc.).

The first significant result of this study is that the pattern of brain activation associated with auditory stimulation was strikingly similar in wakefulness and sleep, suggesting that sensory processing occurred in both conditions. However, we found qualitative differences in brain activation associated with auditory processing during sleep compared to wakefulness. The reduced

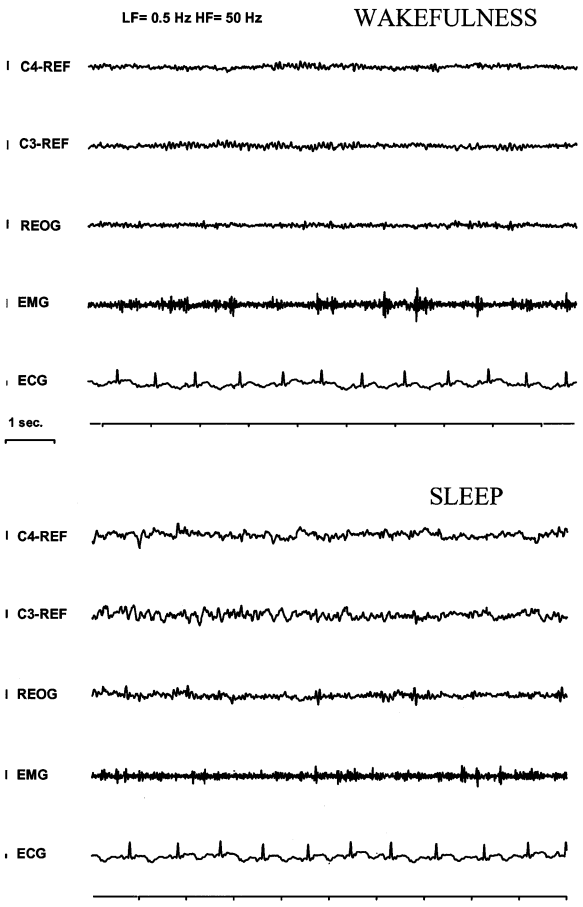

Figure 2. Example of Polygraphic Recording in a Subject

Note α activity in the EEG channels characteristic of quiet wakefulness (upper panel) in contrast with slow, high-amplitude activity characteristic of sleep (lower panel). Also note the decrease in heart frequency in wakefulness compared to sleep. Calibration bar used for EEG, EOG, EMG channels corresponds to 50 μV, for the ECG channel corresponds to 500 μV.

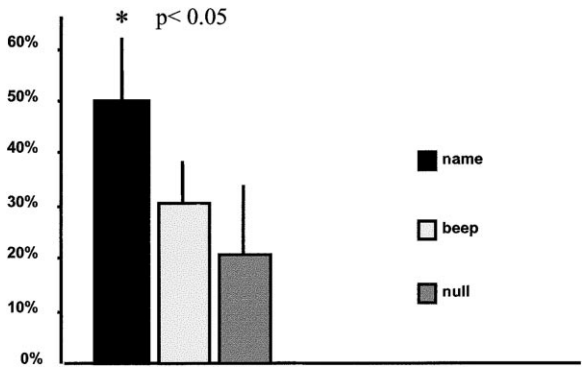

Figure 3. Percentage of Awakenings in Relation to Stimuli Plus SD

The affective saliency of the stimuli was estimated as percentage of awakenings in relation to the type of stimulation. The graph shows the percentage of awakenings in relation to the type of auditory stimulation. Name is significantly more arousing than beep (ANOVA followed by post-hoc comparison $p < 0.05$).

regional activity during sleep, compared to wakefulness, in the left parietal and, bilaterally, in the prefrontal cortex, thalamus, and cingulate gyrus (part of the limbic system) suggests that these areas may be involved in the further processing and perceptual integration of sensory inputs likely to occur during wakefulness only. Indeed, a role for frontal and parietal regions (Kleinschmidt et al., 1999; Lumer et al., 1998; Portas et al., 2000) and the thalamus (Hugdahl et al., 1991; Portas et al., 2000) in conscious perception has previously been proposed.

Recent positron emission tomography (PET) studies of vegetative patients showed that their primary auditory cortex responds to auditory stimulation (Laureys et al., 2000). However, a significant alteration in functional connectivity between the auditory cortex and multimodal (parietal cortex) and limbic areas was reported. The authors suggested that these "functional" disconnections restrict cortical processing and prevent perceptual integration in vegetative patients. In this respect, Laureys's study is entirely consistent with our observations. Residual input processing in vegetative patients in relation to other sensory modalities has also been shown (Owen et al., 1999). Furthermore, a selective decrease of activity in association cortices (parietal and prefrontal regions) during REM sleep in healthy volunteers has been reported (Maquet et al., 1996). We note that REM sleep is a state in which the brain is highly aroused and the activity in the thalamocortical system is similar to wakefulness (Llinás and Ribary, 1993). However, sensory awareness is rarely achieved (Burton et al., 1988) and the threshold for awakening is as high during REM sleep as in delta sleep (Rechtschaffen et al., 1966). It is conceivable that the dampened activity in association regions during REM sleep is sufficient to prevent awareness and contextualization of sensory stimuli despite the high degree of brain arousal. Despite the intrinsic difference between REM and NREM sleep (Llinás and Pare, 1991), it seems that a similar decrease in association cortices activity may occur in the two states. This might explain the common perceptual impairment. The present findings argue in favor of this hypothesis.

Our second aim was to investigate if, during sleep, the brain responds in a different fashion to different stimuli as a function of their significance. Behavioral and electrophysiological evidence support this possibility. For example, some auditory stimuli produce more awakenings than others regardless of their intensity; e.g., young mothers are woken up by their infants' lightest movements (Nishihara and Horiuchi, 1998). In addition, a waveform called "mismatch negativity" elicited by deviant tones in wakefulness is also present during sleep (Nordby et al., 1996; Pratt et al., 1999). Similarly, other electrophysiological studies suggested that certain processes of attention and memory-related operations involved in auditory processing remain operative during sleep (Bastuji et al., 1995; Nordby et al., 1996; Brualla et al., 1998). Of particular interest is the recent study by Perrin et al. (1999) reporting that, during REM and NREM sleep, presentation of the subject's own name elicited a cognitive response comparable to that occurring during wakefulness as shown by enhancement of the P300 component. Such responses were not shown for presentation of other first names. Taking advantage of the higher spatial resolution of fMRI compared to event-

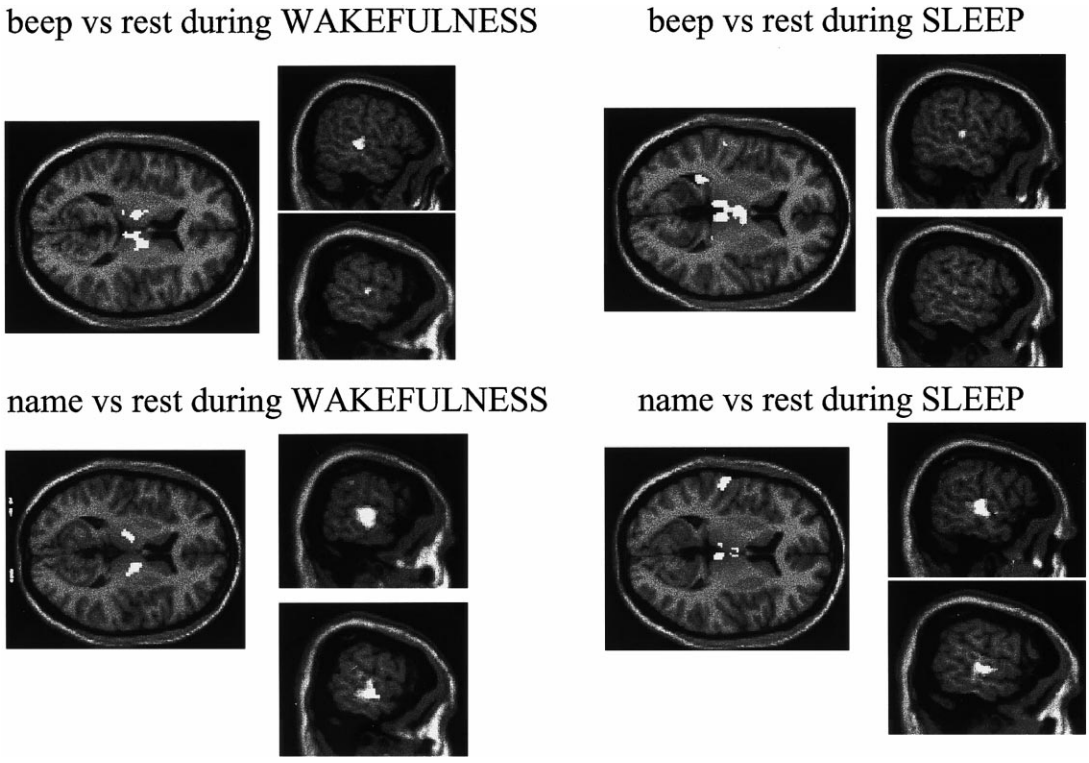

Figure 4. Effect of Auditory Stimulation in Wakefulness and in Sleep

Brain activation associated with beep (upper panels) or name presentation (lower panels) in wakefulness (left panels) or sleep (right panels). Note bilateral activation in the superior temporal gyrus and thalamus in both wakefulness and sleep.

related potentials, we were able to identify selective areas of brain activation associated with processing of significant (subject's own name) and neutral (beep) auditory stimuli across the sleep-wake. Presentation of beep or the subject's own name induced a similar pattern of activation in the auditory cortex, thalamus, and caudate bilaterally. However, when name- was compared to beep-related brain activity, higher activation was present in the middle temporal gyrus and orbitofrontal cortex bilaterally both in wakefulness and sleep. This difference is likely to reflect complex semantic processing (Binder et al. 1997) essential for name processing only.

More importantly, when we specifically tested the effect of name versus beep in sleep compared to wakefulness, we found higher activation in the left amygdala and left prefrontal cortex. These responses to the presentation of subjects' own names were unrelated to the physical difference between the stimuli and only present during sleep. Thus, the results suggest that when subjects were listening to their own name during sleep some brain regions were selectively more responsive than in any other condition. The evidence that the amygdala may play a role in mediating the response to auditory stimuli with affective significance is not surprising. The role of the amygdala in detection of stimuli with affective content is well established (e.g., LeDoux, 1996), and amygdala responses to behaviorally relevant stimuli can occur without awareness (Morris et al., 1998; Whalen et al., 1998). The present study extends these findings to the unconscious state represented by sleep. The lateral nucleus of the amygdala receives profuse projections from the auditory thalamus and auditory cortex (Romanski et al., 1993). Information from the lateral nucleus flows to the central nucleus and from here to several cortical and subcortical areas. We suggest that following the detection of relevant emotional stimuli during sleep, the amygdala may activate the dorsolateral prefrontal cortex, inducing arousal and sustaining a basic level of sensory awareness (Armony and LeDoux, 2000). Although the amygdala is not directly connected to the dorsolateral prefrontal cortex, it projects to the mediodorsal thalamic nucleus, one of the major areas feeding into the prefrontal cortex. The amygdala also projects to nonspecific systems involved in the regulation of cortical arousal (Amaral et al., 1992).

The prefrontal cortex would then determine the consequences of the "alarm effect." Such effect may progress to full awakening and acknowledgment of the input or to sensory neglect. The role of the prefrontal cortex in "selection" is well established (Frith et al., 1991; Hyder et al., 1997).

In summary, we have demonstrated that the sleeping brain is able to process auditory stimuli. In addition, we postulate the existence of a functional network capable of detecting and facilitating processing of emotionally relevant inputs during sleep.

Experimental Procedures

Subjects

A total of 12 healthy volunteers (10 males and 2 female, age 23–34) participated in the study. They had negative history for neurological, psychiatric disorders or sleep abnormalities. Three subjects were

Table 1. Coordinates of Maxima and Z Scores of Brain Activations[a]

Brain Areas	Left Hemisphere				Right Hemisphere			
Planes	x	y	z	Z Score	x	y	z	Z Score
Beep − rest during wakefulness								
Sup. temporal gyrus	−54	−26	0	(5.40)	66	−18	6	(4.55)
Thalamus	−6	−22	8	(6.58)	6	−22	12	(6.58)
Caudate nucleus	−16	−24	14	(5.74)	22	−30	12	(5.42)
Beep − rest during sleep								
Sup. temporal gyrus	−56	−22	6	(5.48)	62	−24	4	(4.42)
Thalamus	−6	−24	10	(>10)	6	−22	10	(>10)
Caudate nucleus	18	−24	14	(6.56)	−16	−26	12	(6.59)
Name − rest during wakefulness								
Sup. temporal gyrus	−62	−22	2	(>10)	66	−20	4	(>10)
Thalamus	−10	−12	12	(5.88)	16	−10	10	(6.65)
Caudate nucleus	—				—			
Name − rest during sleep								
Sup. temporal gyrus	−58	−22	4	(7.77)	64	−18	−2	(6.95)
Thalamus	−4	−24	12	(>10)	6	−24	4	(>10)
Caudate nucleus	−22	−24	24	(4.99)	22	−22	24	(5.22)
Beep + name during wakefulness − beep + name during sleep								
Frontal cortex	−36	32	2	(3.37)	52	30	2	(3.81)
Parietal cortex	−28	−54	32	(3.97)	—			
Cingulate gyrus	−16	−28	36	(4.29)	14	−28	32	(3.31)
Thalamus	−14	−20	8	(4.26)	14	−2	4	(4.24)
Peri-amygdala	−36	0	−28	(4.36)	34	4	−26	(3.41)
Name − beep during wakefulness								
Middle temporal gyrus	−58	−34	−4	(5.41)	54	−22	−8	(6.22)
Orbitofrontal cortex	−46	24	−4	(5.44)	48	30	−6	(3.00)
Name − beep during sleep								
Middle temporal gyrus	−58	−12	−6	(5.61)	64	−24	−6	(7.31)
Orbitofrontal cortex	−46	20	−6	(3.54)	32	28	−16	(3.82)
Name − beep during sleep vs name − beep during wake (+ inclusive masking)								
Prefrontal crotex	−36	40	36	(3.81)	—			
Amygdala	−24	4	−26	(3.77)	—			

[a] Coordinates are in millimeters according to Talairach and Tournoux (1988), based on spatial normalization to a template provided by the Montreal Neurological Institute (Evans et al., 1994).

used in a pilot study to test the experimental procedure. Two more subjects had to be excluded from the group analysis due to severe movement artifacts present in the data acquired. Thus, results from 7 subjects (5 males and 2 females) were used in the data analysis. Subjects gave written informed consent and all procedures were approved by the local hospital ethics committee.

Experimental Protocol

To ensure that subjects would sleep in the uncomfortable and noisy MRI environment, we increased sleep propensity by sleep depriving the subjects for 24 hr prior to the experiment, under continuous supervision. On the day of the experiment, subjects were prepared for polygraphic recording and then placed inside the scanner (8:00 a.m.). To minimize movement artifacts due to sleep, the subject's head was immobilized with special pads. During a 2 hr scanning period (including wakefulness and sleep), subjects were presented binaurally, using a headphone, with trains of auditory stimuli of two types alternated with periods of silence (baseline condition). In the baseline condition, there was no auditory stimulation other than the scanner noise (Figure 1). A pure tone (beep, 1400 Hz sine waves, 500 ms duration, 80 db intensity) was used as neutral stimulus and presentation of the subject's own name (500 ms duration, 80 db intensity) was used as stimulus having special affective significance. Previous studies have shown that a person's own name is an intrinsically meaningful stimulus (Brain, 1958; Oswald, 1960; McDonald et al., 1975; Fischler et al., 1987; Voss and Harsh, 1998), and its saliency stands out against presentation of other first names (Berlad and Pratt, 1995; Perrin et al., 1999). In addition, the subject's own name offers the same level of affective saliency across subjects. Finally, when presented during sleep, it produces more awakening responses compared to other stimuli (trains of beep) of the same intensity and duration (see Results). A total number of 160–180 "events" (prerecorded trains of stimuli or baseline) were presented in random order during matching bursts of functional measurements (see section below). In the gaps between bursts of fMRI measurements, the recorded scanner noise was replayed in order to produce a constant background noise through the duration of the experiment (Figure 1).

Functional Data Acquisition and Analysis

To detect brain activation associated with processing of auditory stimuli across the sleep-wake cycle, we used burst-mode fMRI (Josephs et al., 1999). This technique involves the acquisition of short "bursts" of measurements (6 measurements per burst in this study). In the gaps between bursts, it is possible to monitor behavior and/or electrophysiological parameters (e.g., EEG recording). During a 2 hr experimental session, 160–180 bursts (matching the number of events) were acquired for each subject (corresponding to ~1000 volumes). Each volume consisted of 34 slices (2 mm thickness). With this procedure, each volume covered the whole brain (with the exception of the lowest part of the cerebellum); the voxel size was $3 \times 3 \times 3$ mm, and the acquisition time (TA) was 2.88 s. Each burst had ~17 s duration (same as the gaps) (Figure 1). Before proceeding to fMRI data analysis, all volumes were realigned, motion corrected, normalized (Friston et al., 1995) to a standard template (Montreal Neurological Institute; Evans et al., 1994), and smoothed using a 6 mm FWHM Gaussian kernel. Statistical inference was obtained using statistical parametric mapping (SPM) 99 (http://www.fil.ion.ucl.ac.uk/spm/spm99.html). Data were analyzed by modeling the evoked hemodynamic responses for the different stimuli as boxcars con-

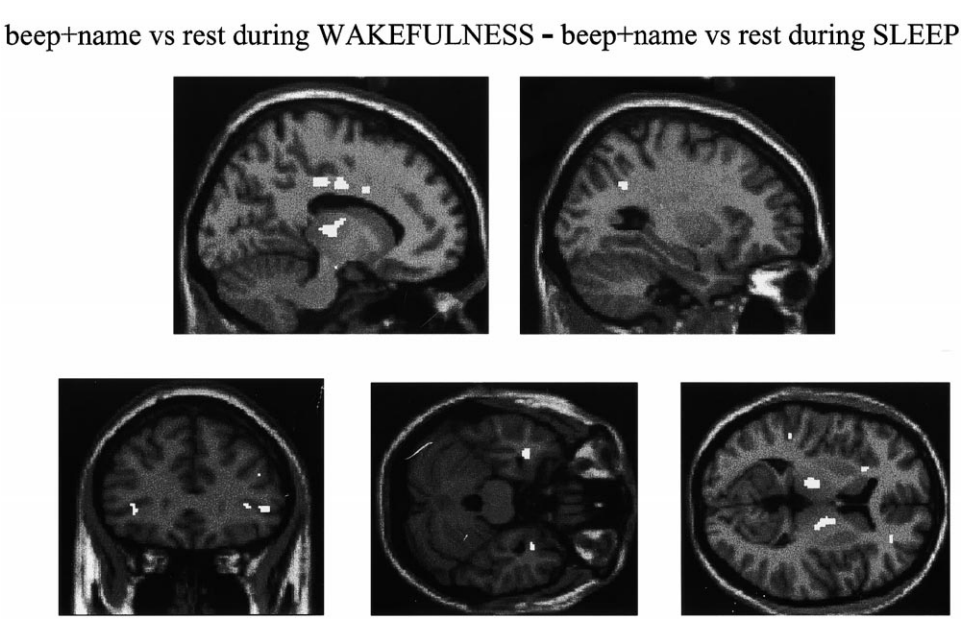

Figure 5. Differential Brain Activation in Relation to Auditory Stimulation in Wakefulness Compared to Sleep

The figure shows the brain areas more activated in wakefulness compared to sleep in relation to the same auditory stimulation: left posterior parietal cortex, prefrontal and cingulate cortices, thalamus, and peri-amygdala region bilaterally.

volved with a synthetic hemodynamic function (hrf), in the context of the general lineal model (Josephs et al., 1997). We defined six event types: name, beep, and rest in sleep and wake. Differential effects were tested by applying appropriate linear contrasts to the parameter estimates for the hrf regressors of each event, resulting in a t statistic for each voxel. These t statistics (transformed to Z statistics) constitute a statistical parametric map. The corresponding p values were corrected for multiple comparisons across the entire brain, in the context of Gaussian random field theory, except where otherwise indicated.

Data were first analyzed individually for each subject and then as a group. We used a fixed effects model to estimate the main effect of state (sleep or wakefulness) over each type of event (beep, name, baseline). We also looked at state by event interactions (e.g., auditory-related brain activity during sleep was compared to auditory-related brain activity during wakefulness), as well as state by event-type interactions (i.e., name- versus beep-related brain activity during sleep compared to name- versus beep-related brain activity during wakefulness; for a detailed review of interaction analysis, see Price and Friston, 1997). Because we were interested in whether the sleeping brain responds differently to stimuli with higher affective significance, we only looked at one side of the interaction

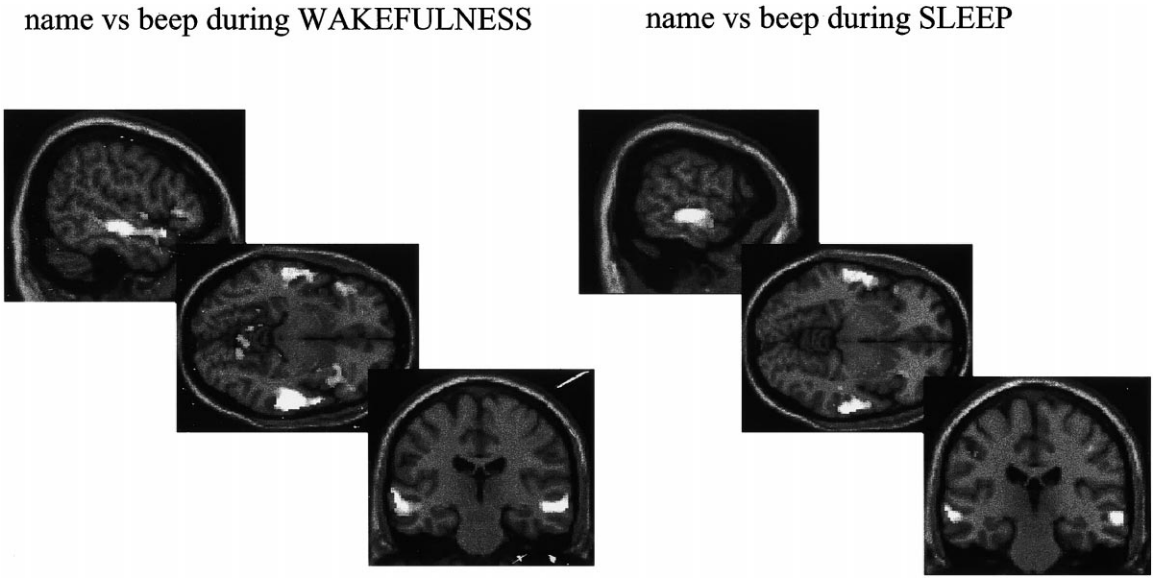

Figure 6. Differential Brain Activation for Name Compared to Beep Stimuli during Wakefulness and Sleep

Brain areas more activated in relation to name compared to beep presentation. The middle temporal gyrus and the orbitofrontal cortex is bilaterally more activated in both wakefulness and sleep.

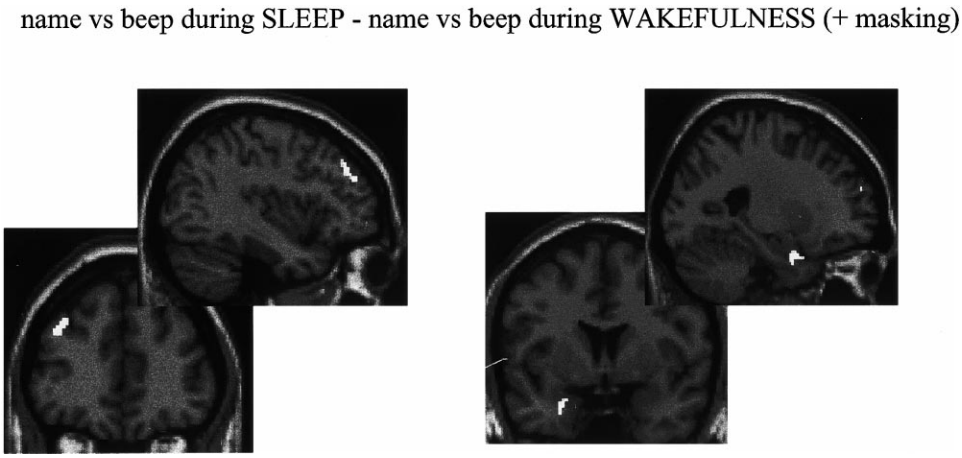

Figure 7. Activation in the Left Amygdala and Left Prefrontal Cortex for Name Presentation Compared to Beep during Sleep

The figure shows that during sleep there is a higher activation in the left amygdala and left prefrontal cortex for name presentation compared to beep.

name versus beep by sleep versus wake by masking the resulting SPM with the contrast associated with the simple main effect of name versus beep during sleep ($p < 0.05$ uncorrected). In other words, in the latter interaction, we only considered those voxels that also showed a differential activation to name, compared to beep, during sleep. Significance was accepted for $p < 0.001$ uncorrected or $p < 0.05$ corrected for multiple comparisons (Friston et al., 1994).

EEG Data Acquisition and Analysis

Sleep and wakefulness electrophysiological correlates were assessed by polygraphic recording obtained during bursts of measurements (Figure 1). Gold electrodes fitted with 12 kW carbon resistors were applied on the scalp (A1, A2, C3, C4) according to the International 10/20 system (Jasper, 1958) for EEG, on the outer canthus-external meatus for electrooculogram (EOG), and under the chin (submental muscles) for electromiogram (EMG). Silver chloride (Ag/AgCl) electrodes were applied in the precordial region for electrocardiogram (ECG). ECG recording was necessary in order to apply an online pulse artifact correction. This procedure accounts for a large EEG artifact due to pulsatile blood flow in subjects exposed to strong static magnetic fields (Allen et al., 1998). To reduce the EEG artifacts due to movement, electrode leads were grouped together in strips. A strict safety protocol for EEG recording in the MRI scanner was developed by O. J. and P. A. following previous indications (Lemieux et al., 1997). Electrodes were connected to a nonferrous head box placed at the entrance to the bore of the magnet. The box was connected to a Neurolink Patient Module that amplified, digitized, and transmitted the signal out of the scanner room via a fiber optic cable to a Neurolink Patient Monitor that reconstructed the analog EEG signals. The Neurolink System reference electrode (Pz in this experiment) is a driven ground, derived from the average of the EEG signals with respect to amplifier ground. Data were visually analyzed online and offline by two different raters (CP and KK) to distinguish sleep from wakefulness according to Rechtschaffen and Kales (1968) (Figure 2).

To increase the number of "events" in relation to the "state," we collapsed all NREM sleep stages into one. REM sleep epochs were too rare and short (due to the short scanning time and to the "total sleep deprivation" protocol) and were excluded from the data analysis. Epochs that included state transitions or combination of waking and sleep were also excluded from data analysis. Thus, only two states were considered: sleep and wakefulness.

For EEG-fMRI data matching, each EEG recording epoch was paired with the preceding burst of measurements and auditory event (Figure 1). We considered that because each train of auditory stimuli ended just before the outset of an EEG-epoch, such EEG-epochs would closely reflect the occurrence (or lack) of wakefulness during the preceding burst of measurements.

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