Human Thalamic Medial Pulvinar Nucleus is not Activated during Paradoxical Sleep

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Wakefulness and paradoxical sleep (PS) share a similar electrophysiological trait, namely, a more elevated level of high-frequency activities at both thalamic and cortical levels relative to slow wave sleep (SWS). The spatio-temporal binding of these high-frequency activities within thalamo-cortical networks is presumed to generate cognitive experiences during wakefulness. Similarly during PS, this phenomenon could be at the origin of the perceptual experiences forming dreams. However, contents of dreams often present some bizarre features which depart from our cognitive experiences in waking. This suggests some differences in processing and/or integration of brain activities during waking and PS. Using intracranial recordings in epileptic patients we observed, specifically during PS, the presence of unexpected delta frequency oscillations, as well as a surprisingly low amount of high-frequency activities, in a posterior region of the thalamus, the medial pulvinar nucleus (PuM). This discrepancy between activities in a thalamic nucleus and its related cortical areas may compromise the spatio-temporal binding of the high-frequency activities, resulting in altered perceptual experiences during dream periods.

Keywords: cortex, dreaming, electrophysiology, human, paradoxical sleep, thalamus

Introduction

First described in the middle of the last century, the fluctuations of the electroencephalographic activity allowed a heuristic description of the different states of vigilance (Aserinsky and Kleitman, 1953; Dement and Kleitman, 1957). Since then, a great deal of progress has been made in the understanding of the biochemical and electrophysiological processes at the origin of these vigilance states (for reviews, see Steriade, 2000; Hobson and Pace-Schott, 2002; Pace-Schott and Hobson, 2002). It can be briefly summarized as follows: wakefulness is the result of facilitating neuromodulatory influences at both thalamic and cortical levels, originating from monoaminergic and cholinergic cells located in the brainstem and the basal forebrain. A decrease in the firing rate of these cells leads to a progressive hyperpolarization of thalamic and cortical neurons, a state favourable to the development of slower and slower oscillating activities, which characterize the different stages composing the slow wave sleep (SWS or non-REM sleep: stages 3 and 4). This sleep state is interrupted by recurrent episodes of a brain activated state, the so-called paradoxical sleep (PS or REM sleep). PS episodes are consecutive to the specific increase in firing rate of cholinergic neurons localized in the mesopontine junction and basal forebrain. The release of their neurotransmitters at the thalamic and cortical levels leads to a depolarizing effect disrupting the generation of the SWS low-frequency activities, thus restoring a brain activated state resembling wakefulness in several aspects (Steriade *et al.*, 1969; Steriade, 1978; Glenn and Steriade, 1982; Yamada *et al.*, 1988; Llinas and Paré, 1991; Gross and Gotman, 1999). Cognitive experiences in waking and PS are presumed to be supported by the spatio-temporal binding of high-frequency activities within thalamo-cortical networks (Rodriguez *et al.*, 1999; Jones, 2001). However, the cognitive contents of dreams are known to present some bizarre neuropsychological features, reminiscent of misidentification syndromes (Frégoli syndrome) or visual distortions (palinopsia, polyopia, achromatopsia) observed in brain-damaged patients during waking (Schwartz and Maquet, 2002). We may thus hypothesize that these oneiric vagaries are due to some incomplete processing and/or integration of brain activities during PS and that this deficiency could be revealed at an electrophysiological level by studying simultaneously thalamic and cortical activities.

Materials and Methods

Patients

Thalamic and cortical recordings were obtained from 11 patients. All of them presented with refractory temporal lobe epilepsy and necessitated a stereotactic EEG (SEEG) presurgical evaluation before functional surgery. All patients gave informed consent for the implantation of intracerebral electrodes and the recordings performed for this study. They presented with seizures suggesting a rapid propagation of epileptic discharges between limbic areas and posterior temporal neocortex, based on non-invasive video-scalp EEG recordings performed prior to intracerebral implantation of recording electrodes.

Implantation of SEEG electrodes

The electrode implantation procedure was carried out using multiple contact electrodes introduced into the brain perpendicular to the midsagittal plane, according to the stereotactic technique of Talairach and Bancaud (1973). Coordinates of relevant targets were determined on the patient's brain magnetic resonance (MR) images according to previously described procedures (Frot and Mauguière, 1999, 2003; Ostrowsky *et al.*, 2002). The medial pulvinar nucleus (PuM) was one of the targets of stereotactic implantation because, due to its reciprocal connections with cortical areas involved in seizures, it was suspected to be an important relay in the building of epileptic discharges. Moreover, intracortical exploration of target temporal neo-cortical areas and of the PuM nucleus was possible using stereotactic implantation of a single multi-contact electrode, so that PuM exploration did not increase the risk of the procedure by adding one further electrode track specifically devoted to the study of PuM activity. Anatomical localization of the thalamic and cortical electrode contacts was counterchecked using fusion of skull X-ray after electrode implantation with the appropriate coronal MR slice of the patient's brain. The placement of two to four contacts within the PuM was assessed using the Morel atlas of the human thalamus (Morel *et al.*, 1997).

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Recording Conditions

Night recording under video-EEG monitoring was conducted after a minimum delay of 5 days after electrode implantation. At that time, anticonvulsant drug intake had been drastically reduced for at least 1 week in order to record spontaneous epileptic seizures. Bipolar EEG signals and electro-oculograms were amplified, filtered (band pass: 0.33–300 Hz) and stored with a sampling frequency of 128 Hz. The different states of vigilance were visually identified according to the criteria of Rechtschaffen and Kales (1968). In each patient, the thalamic PuM activity was recorded simultaneously with 3–12 cortical derivations selected for absent or limited interictal epileptic activities. In each state (i.e. waking, stage 2, SWS and PS), periods of 3–4 min were selected after discarding the remaining interictal epileptic activities. These periods were further subdivided in 4 s epochs, the power spectra of which were calculated using a fast Fourier transform (10% tapered-cosine window; frequency resolution 0.25 Hz) and averaged. Cortical and thalamic spectra were then normalized and the average relative power of each standard electroencephalographic frequency band [slow oscillation (SO), 0.5–1.25 Hz, delta, 1.5–4.5 Hz, theta, 4.75–7.75 Hz, alpha, 8–12 Hz, sigma, 12.25–15 Hz, beta, 15.25–30 Hz, gamma, 30.25–60 Hz] was calculated. Finally, a grand average of the relative power of each frequency band was obtained by pooling the 11 thalamic PuM and 91 cortical (temporal lobe, 53; frontal lobe, 16; parietal lobe, 10; insula, 7; occipital lobe, 5) recordings and submitted to statistical analysis.

Results

Qualitative Analysis

Striking preponderant oscillations in the delta (1.5–4.5 Hz) frequency band were apparent on rough recordings in PuM during PS, without any counterpart during the three other vigilance states (Fig. 1*a*). A few sporadic cycles of these delta oscillations were occasionally present in the final decay of sleep stage 4 (Fig. 1*b*). They were interspersed in, but distinct from, the previously described SO (<1.25 Hz) frequency oscillation characteristic of this sleep stage (Steriade *et al.*, 1993; Achermann and Borbély, 1997; Simon *et al.*, 2000). As cortical activity became desynchronized, indicating the beginning of a PS period, PuM delta oscillations occurred more and more frequently before becoming stable (Fig. 1*b*). Nevertheless, all

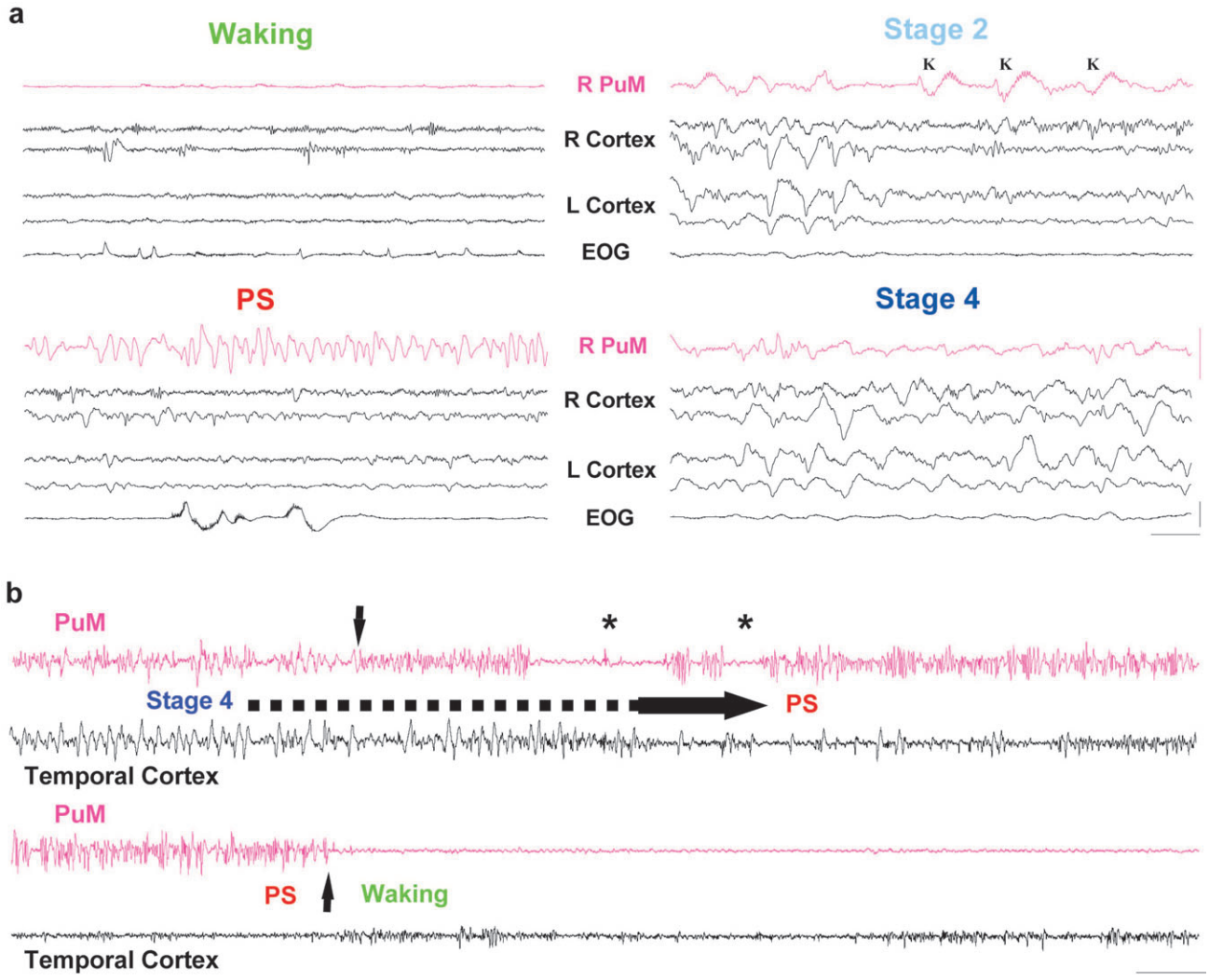

Figure 1. PuM and cortical electrical activities during different vigilance states. (*a*) The four sets of rough intracranial recordings and electro-oculograms (EOG) illustrate the bilateral (R, right; L, left) temporal cortical and concomitant right (R) PuM activities. In PuM, note the occurrence of K complexes followed by a spindle sequence during stage 2 and, during PS, the presence of well-structured delta frequency oscillations. (*b*) Cortical and PuM activities during the transition from stage 4 to PS and from PS to waking. Note that delta oscillations appear in PuM (arrow) before the cortical activity exhibits a stereotyped PS activity. Asterisks: during PS, PuM delta oscillations are interrupted by few recurrent periods of activity similar to that of waking. Note the abrupt disappearance (arrow) of the delta oscillations in PuM when waking is occurring. Scales: PuM, 250 μV; other traces, 500 μV. Time: 2 s (*a*) and 10 s (*b*).

along a PS period, they were interrupted by ~20 short (2–20 s) periods of rapid activity similar to that observed in wakefulness. At the end of the PS period, the delta oscillations ceased abruptly to be replaced by an activity corresponding to the next state of vigilance (Fig. 1*b*). This phenomenon was observed in the 11 patients without exception, during all recorded PS periods, although the amplitude of these delta oscillations showed a high degree of interindividual variation.

Quantitative Analysis

In all patients, power spectra of PuM activity during PS periods showed a clear peak in the delta frequency band (Fig. 2, solid arrow). This peak corresponded to the delta oscillations described above and its average frequency value was 2.38 ± 0.43 Hz. In 9 of the 11 patients, the power spectra exhibited a second peak in the SO (<1.25 Hz) frequency band (mean frequency: 0.84 ± 0.3 Hz; Fig. 2, open arrow). This phenomenon, when present, was highly variable in amplitude between patients. The average frequencies of the SO and delta peaks were statistically different (paired *t*-test, two-tailed $P < 0.0001$).

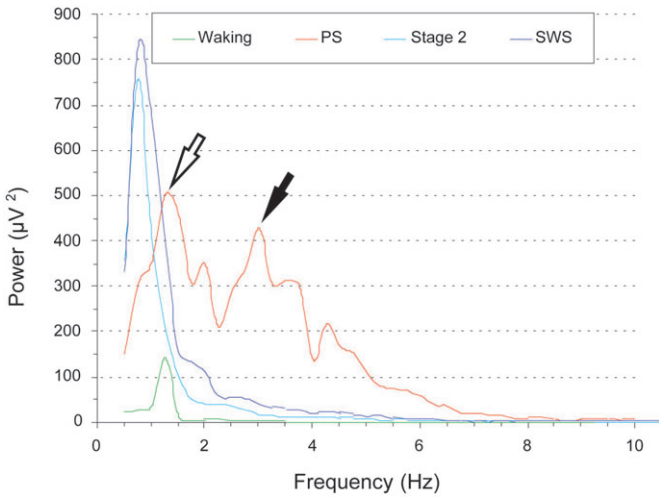

Figure 2. Spectrogram of PuM activities during the four vigilance states. An unexpected increase of power (arrows) is present in both the SO and delta frequency bands (open and solid arrows, respectively), specifically during PS.

Repeated-measures one-way analyses of variance (ANOVA) for the vigilance state effect were then performed with every frequency band as dependent variable, separately. Results indicated a significant effect of vigilance state on delta frequency activities [$F(3,10) = 28.11$, $P < 0.0001$]. *Post hoc* pairwise comparisons (Tukey–Kramer test) demonstrated a significant increase of the delta activity power during PS as compared to the three other vigilance states ($P < 0.001$; Fig. 3). A similar analysis of data obtained in the SO frequency band also showed a significant effect of vigilance state [$F(3,10) = 24.96$, $P < 0.0001$]. However, Tukey–Kramer *post hoc* pairwise comparisons specified that waking and PS did not differ significantly, while these two vigilance states exhibited significant lower power values with respect to stage 2 and SWS ($P < 0.001$).

At the cortical level, repeated-measures ANOVA analysis did not show any significant differences between the four vigilance states in the delta frequency band (Fig. 3). In the SO frequency band, a significant effect of vigilance state was present [$F(3,10) = 25.02$; $P < 0.0001$] exclusively due to a higher power value in SWS with respect to the three other vigilance states (Tukey–Kramer *post hoc* pairwise comparisons, $P < 0.001$)

Another interesting observation concerned the mean relative power of the beta and gamma frequency bands. At the thalamic PuM level, our data analysed with repeated-measures ANOVA revealed a marked vigilance state effect on power of the beta [$F(3,10) = 22.78$, $P < 0.0001$] and gamma [$F(3,10) = 9.65$, $P < 0.0001$] frequency bands due to a significant increased activity during waking with respect to the three other vigilance states (Tukey–Kramer *post hoc* pairwise comparisons: beta, $P < 0.001$; gamma, $P < 0.01$; Fig. 3). At the cortical level, statistical analysis showed a clear vigilance state effect for these two high-frequency bands [beta, $F(3,10) = 12.99$, $P < 0.0001$; gamma, $F(3,10) = 4.26$, $P < 0.01$] due to a selective decreased activity during SWS (beta, $P < 0.01$; gamma, $P < 0.05$; Fig. 3).

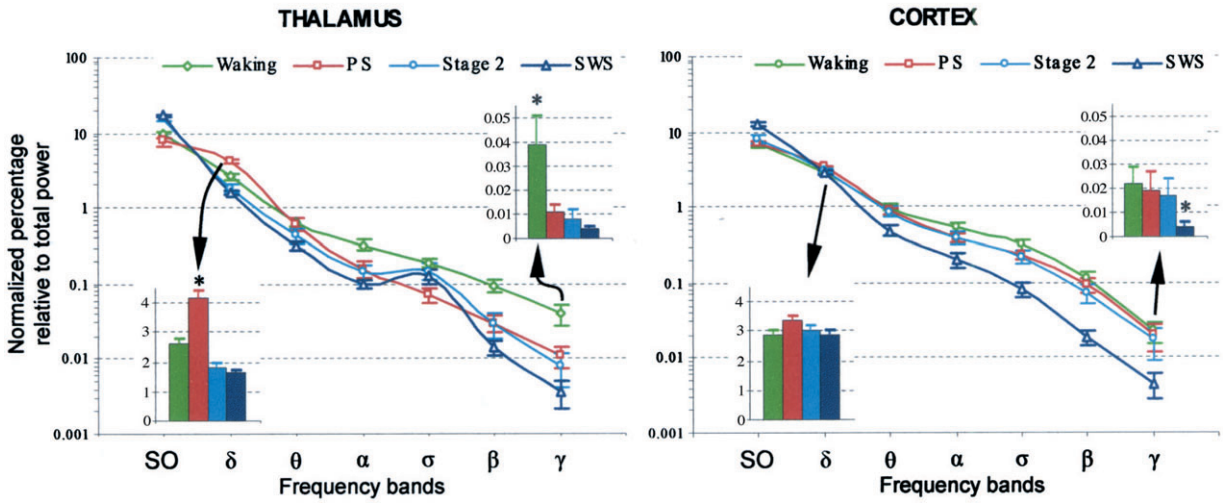

Figure 3. Spectrograms of thalamic PuM and cortical activities during the four vigilance states (average of 11 patients). Note the significant increase of relative power in the delta (δ) frequency band during PS, specifically at the thalamic PuM level (bottom left histograms, $*P < 0.001$). In the beta (β) and gamma (γ) bands, thalamic PuM relative powers during PS are significantly lower than in waking ($*P < 0.01$; top right histograms; β not illustrated) while, at cortical level, beta and gamma relative powers do not differ during these two vigilance states, but are significantly higher than during SWS ($*P < 0.05$).

Discussion

Our data show that thalamic PuM activity during PS departs from cortical activity in the delta, beta and gamma frequency bands. However, one first question arising is whether the above particularities in PuM activity during PS could be related to epilepsy or anti-epileptic medication. This is unlikely, considering that these phenomena were observed in all patients, independently of the localization and extent of their respective epileptogenic focus (temporo-mesial or neocortical) and independently of the type and daily dosage of anti-epileptic treatment. Moreover, while anti-epileptic drugs are well known to modify cortical activity, their impact has not so far been reported as acting selectively during one specific vigilance state (Duncan, 1997). Finally, our results at the cortical level are similar to those obtained in non-epileptic animals (Franken *et al.*, 1994; Maloney *et al.*, 1997) and humans (Llinas and Ribary, 1993) and in epileptic patients (Gross and Gotman, 1999). From these considerations, we are inclined to conclude that our data reflect a true physiological process.

Possible Origin of the Discrepancy between Thalamic PuM and Cortical Activities during PS

The increase of cerebral high-frequency (>30 Hz) activities known to occur during PS is mainly consecutive to the activation of widespread brainstem cholinergic projections terminating at both thalamic and cortical levels (Steriade *et al.*, 1997). In contrast to the other thalamic nuclei, PuM exhibits an extremely weak cholinergic innervation (Hirai and Jones, 1989). Thus, the low power in high-frequency bands we observed in this nucleus during PS could be related to a lack of cholinergic activation during PS. In addition, the thalamic PuM nucleus remaining in a non-activated state would be in a situation favourable to the development of preponderant delta activities.

Putative Functional Consequences with Respect to Dream Contents

The possible functional implications of a discrepant level of activity between PuM and cortical areas can be interpreted with reference to the presumed relationship linking cerebral activity and cognitive experience. During wakefulness, the spatio-temporal binding of high-frequency activities at several locations within the cerebral cortex and in the thalamic nuclei to which they project has been proposed as the underlying mechanism of cognitive events (Singer, 1998; Rodriguez *et al.*, 1999; Jones, 2001). The similarity of cerebral activity between awake and PS states makes plausible the assumption that oneiric cognitive events could arise from a similar mechanism. However, contents of dreams present bizarre features. These features resemble the altered perceptions experienced during waking by brain-damaged patients (Schwartz and Maquet, 2002), in whom the spatio-temporal binding of high-frequency activities could occur only partially between the remaining uninjured cortical areas. One might thus hypothesize that, in normal subjects, altered perceptive experiences reported in dreaming are the result of an imperfect high-frequency spatio-temporal binding.

In this context, our results could find a possible functional counterpart. Connections linking the cerebral cortex and the thalamus make them a unified oscillatory entity in which each constituent influences the other (Steriade, 1997). The preponderant delta and the depleted beta and gamma frequency activities we observed in PuM during PS are thus able to interfere with activation of associated cortical areas connected with this thalamic nucleus. Recent data support this hypothesis by showing that three cortical areas densely connected with PuM (posterior cingulate, dorso-lateral prefrontal and parietal cortices; Baleydier and Mauguière, 1987; Romanski *et al.*, 1997; Gutierrez *et al.*, 2000), exhibit a distinct behaviour during PS. They present a lack of increased blood flow, i.e. a deficient activation, contrasting with the rest of the cerebral cortex (Maquet *et al.*, 1996; Maquet, 2000) in this state. This situation could reflect an incomplete binding in the high-frequency range of different cortical areas, a phenomenon resulting in the vagaries typical of oneiric contents.

Notes

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