Introduction
Recent studies brought us a lot of information about slow wave sleep physiological mechanisms and disclosed several oscillating elements integrated in networks whose functional properties are greatly modified by comparison with waking state. We used topographical quantified EEG analysis in order to study slow waves and spindles activities during sleep in the presence of thalamic lesions compared with control data.

Slow waves
Since RECHTSCHAFFEN and KALES definitions [27], unicellular electrophysiological investigations lead to dissociate delta activities between a slow rhythm (below 1 Hz) and truly intrinsic delta oscillations (between 1 and 4 Hz) generated in cortical neurons or as a clock-like rhythm in thalamo-cortical neurons [5]. A slow oscillation (<1Hz) described in intracellular recordings from cortical and thalamic neurons [35,41,42] is able to synchronise and group other sleep rhythms like spindles and delta into complex sequences [32]. The interplay between such oscillations reflects at the cortical level and yields to patterns that take the shape of polymorphic waves [5]. The slow rhythm is essentially induced by alternative sequences of long-lasting depolarisation and hyperpolarisation phases [11,42]. It was initially observed in cats during anaesthesia and has been more recently demonstrated during natural sleep in animals.
[33,34] and humans [1,4,6,42]. A lot of experiments point the cortex as the site of genesis of this slow oscillation where it appears over large areas in a synchronous manner [2,3,5,41,43]. Combined unicellular intracortical recordings and frequency analysis have established the relation between K-complexes and this slow oscillation [4,6].

Intrinsic cortical and thalamo-cortical neurons properties are responsible for delta activities distributed in the 1 to 4 Hz frequency range. The basic mechanism relies on the interplay between two currents ($I_h$ and $I_t$) which are activated at hyperpolarized membrane potentials [5,23,30,31,40].

**Spindles**

Since 1950, visual EEG analysis separated two distinct spindles activities on the basis of frequency and topography [13]. The slower spindles (11.5 — 14.0 Hz) are distributed in the frontal region whereas posterior ones are more focalised in the parietal region and are of higher frequency (14.0 — 16.0 Hz) [16-18,25,29,44]. On the counterpart, intracellular recordings led to a homogenous view of a spindling phenomenon largely distributed in a wide frequency range from 7 to 14 Hz [11,32,36-38,40]. The EEG spindles are the epitome of brain synchronisation at the onset of sleep, mainly due to the pacing role of the rostral part of the thalamic reticular nucleus [37,38,40]. GABAergic reticular neurons inhibit large numbers of thalamo-cortical cells through IPSPs that are able to trigger low threshold calcium spikes (LTS) and associated bursts of action potentials. Integrated in a large thalamo-cortico-thalamic network, these action potentials are transferred to the cortex where they generate spindles waves [12,20,21,32,36,39,40].

**Patients and methods**

Seven patients with vascular thalamic lesions (six patients with unilateral lesions and one patient with a bilateral anterior lesion, 62.86 ± 6.96 (S.D.) years old) were compared to six age-matched control subjects (64.50 ± 6.80 (S.D.) years old). 32 polygraphic whole night recordings were acquired (28 EEG channels) with a NICOLET PATHFINDER I system. Earlobe controlateral to the studied hemisphere was used as reference in order to avoid false lateralisations or temporal region signal contamination due to the reference. We used FFT analyses (0.147 Hz resolution) with spectrum averaging (80 epochs of 6819 msec. duration each) in order to obtain a representative picture of the frequency domain for stages 2 and 4. Spatial normalisation allowed intrinsic topographical comparisons (Z scores with significant threshold established at a p<0.05 level). We applied generalised linear models [19] for classical frequency bands [15] statistical analysis. These methods allowed us to evaluate patient, electrode and sleep stage interactions using a statistical arbitrary left frontal reference point.
Comparison of slow wave sleep EEG results in case of thalamic lesions

Top: MRI or CT-scan data of seven cases (6 patients with unilateral lesions and 1 patient with a bilateral dorso-median lesion)

Middle: topographic maps of EEG rhythms during slow wave sleep. 0.5 to 7.5 Hz signals were acquired during stage 4 and 7.5 to 17.9 Hz activities were analysed during stage 2.

- N: no significant power difference between patient data compared to normal controls
- ↑ or P↑: increased power
- ↓: power at a lower level than for control subjects
- N.P.: no significant difference between patient power level compared with control subjects
- n.s.: no significant

Results

Slow wave activities
Slow delta rhythms (0.5 — 2.0 Hz) are distributed in the frontal anterior and frontal lateral regions during stage 2 or 4. The absolute power level is greatly
higher during stage 4 than during stage 2. Whereas topographical distribution is exactly the same throughout whole slow wave sleep period, statistical focalisation is proportional to the power level, and is significant only during stage 4. Delta rhythms between 2.0 to 3.5 Hz reveal a topographical focalisation in the medial central region that is significantly different than for the frontal slower delta activities. Those frequency range rhythms are also focalised in proportion with their power level. Patient’s data disclosed no significant change in relation with a thalamic unilateral or bilateral lesion. Only minor increased delta power was observed in a case with voluminous haemorrhagic thalamic infarction with probably extra-thalamic involvement (Figure case 1). It was specially interesting to note that a patient with a bilateral dorso-median thalamic infarct responsible for important clinical symptoms and frontal glucose hypometabolism during waking state ($^{118\text{F}}$FDG PET scan), had strictly normal delta activities during slow wave sleep (Figure case 7).

**Spindles**

Multiple peaks are observed in the normal mean spectra within the frequency range of spindle activities (7.5 — 15.2 Hz). Two main groups are distinguished on the basis of power level and topographical distribution. Anterior spindle rhythms are observed in the medial frontal and central regions within 10.0 to 12.5 Hz frequency range. They are statistically different from the posterior spindles that are disclosed in the medial central and parietal areas within the 12.5 to 15.2 Hz ranges. Differential absolute power statistical maps clearly define opposite topographical distributions between these two rhythms. The same results are obtained with normalised power spectra that show slower activities on Fz than faster ones on Pz. Statistical focalisation is only seen during stage 4 when power level is lower and topographic extension more restricted than during stage 2. This aspect is completely different that what happens for delta activities. Patients with voluminous unilateral thalamic lesions involving the rostral part of the lateral portion of the thalamus had a dramatic modification of the spindle activities (Figure cases 1 and 5). Absolute power was increased on the controlateral side of the lesion and the topographical distribution of either frontal or parietal spindles was largely extended. One patient with a smaller lesion restricted to the posterior and lateral part of the thalamus had lateralised spindle activities on the safe side without significant power level or topographic extension modification (Figure case 2). Patients with unilateral dorsal thalamic or anterior bilateral small lesions had normal spindle activities parameters (Figure cases 3, 4 and 7).
Conclusions
Our results indicate that slowest delta activities during slow wave sleep are distributed over frontal regions without any significant change in the presence of a unilateral thalamic lesion. These rhythms are preserved even if there is a lesion in the thalamic nuclei for which frontal cortex is the projection area. We hypothesise that the slow rhythm described at the unicellular level is the basis of these slowest delta activities and that they have a frontal cortex substrate. This relation leads us to evoke a direct link between frontal slow activities and fronto-basal combined with frontal cingular regions cerebral blood flow preferential decrease described with PET studies [9,14,22] during slow wave sleep. Delta activities in the 2.0 to 3.5 Hz frequency range probably reflect the whole network interplay of dorsal thalamic and cortical neurons which share intrinsic oscillating properties at a hyperpolarized membrane voltage level, reflecting preferentially in the central cortical region. Spindles activities are distributed over a wide frequency window segmented into two compartments in regard with their frontal or parietal median distribution.
Our results obtained with patients are in good accordance with a pacemaker role devoted to the rostral part of the reticular thalamic nucleus. Moreover, we observed power increase in the spindle frequency range on the controlateral side of a thalamic lesion if the anterior and lateral portion of the thalamus was involved in the pathologic process. Those data raise the hypothesis of a bithalamic functional counterbalance in the regulation of the cortical expression of spindling activities. Anatomical animal data demonstrated direct bithalamic relationships involving reticulo-recticular or reticulo-dorso-thalamic pathways [7,8,10,24,26,28] that could be the substrate of such control. Quantified EEG topographical studies during sleep give data that can be integrated in the whole field of functional evaluation of the brain during a state that is characterised by important electrophysiological and metabolic modifications by comparison with wake. They allow human global cortical functional measurements even in the presence of cerebral lesions. Our studies have to be developed in the future with coregistration with other functional techniques like PET scan or MRI. REM-sleep study is mandatory. Other mathematical signal analyses, like time-frequency methods, would be of a great interest in order to avoid FFT temporal resolution compression. EEG signal analysis remains thus one interesting way of functional investigation in closed relationship with neuronal firing greatly modified during sleep that is characterised by a brain environmental disconnection.
Bibliography

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Inter-individual phase differences in circadian rhythms and sleep

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Morning-type (M-type) individuals reach an earlier phase position of their circadian rhythms than evening-type (E-type) individuals. This has not only been observed under natural conditions (e.g. for body temperature, subjective alertness and mood), where masking influences may have been involved, but also under constant conditions, where direct masking influences were eliminated or kept constant. Thus, evidence exists for the endogenous nature of the circadian phase difference between M-types and E-types. When allowed to choose their preferred sleep times, E-types generally have their sleep onset at an earlier phase of their temperature rhythm than M-types. Given the well-documented relationship between the phase of the temperature rhythm and REM-sleep propensity, a M-type vs E-type difference would be expected with respect to the time-course of REM-sleep. Contrary to expectation, E-types appear to have a higher REM-sleep propensity in the first part of their sleep than M-types. As a likely result of the interactive inhibition between REM-sleep and slow wave sleep, E-types also show a relative curtailment of slow wave sleep during their first NREM-REM cycle. The impact of a relatively small difference in the phase relationship between sleep and body temperature was investigated by systematically shifting the timing of the sleep period of M-types and E-types, while keeping constant the length of their prior wakefulness. Rectal temperature recordings confirmed that the sleep shifts had not affected the phase of the body temperature rhythm. The results showed that: 1. the sleep shifts had a similar influence upon the sleep structure of the two groups of subjects; a relative advance of the sleep period was associated with an increased REM latency, an increased percentage of slow wave energy during the first nonREM period, and a compensatory reduction of the percentage of slow wave energy during the later half of sleep; and 2. the E-types had a higher overall REM propensity than the M-types. The latter difference may be associated with a difference in personality and behavioral characteristics of the two groups of subjects.