Sleep oscillations in the human thalamus and cortex (final report)

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The precise timing and state-dependent dynamics of specific neuronal oscillations play a pivotal role in the regulation of vigilance, consciousness and cognition of human subjects. As the thalamus and the thalamocortical connections are of crucial importance in the generation and organization of these rhythmic neurodynamical phenomena, we aimed to unravel the basic properties of the wake-sleep-dependent brain oscillatory activity by studying invasive records derived from epilepsy patients undergoing presurgical evaluation or Deep Brain Stimulation (DBS) treatment. Given the fact that the anterior thalamic nucleus (ANT) is an approved target for DBS in medically refractory and surgically non-treatable epilepsy, our thalamic focus will mainly relate to this group of thalamic neurons, with the additional consideration of the adjacent mediodorsal (MD) and ventral anterior (VA) nuclei in some cases. The main issues we followed were related to the overall characterization of state-dependent human thalamograms, the involvement of specific thalamic and cortical subsystems (nuclei and cortical layers, respectively) in the generation and regulation of specific wake-sleep dependent neural oscillatory phenomena, as well as the unravelling of assumed thalamofugal and thalamopetal mechanisms underlying the characteristic electrical field potentials.

1. The issue of the proper localization of individual cortical and thalamic leads

The localization of non-invasive, scalp EEG electrodes, as well as of the invasive electrocorticography (ECoG) contacts is well manageable by using classical electrode placement rules or well-known anatomical references visualized by neuroimaging tools. Moreover, transcortical thumb-electrodes provide us with cortical layer-specific information due to post-operative histological reconstruction (Ujma et al., 2021). In contrast to the cortical recordings, the localization of the stereotaxically inserted thalamic leads is a significant issue because of the lack of visually striking boundaries between thalamic (sub)nuclei. Moreover, in contrast to the human cortical structures, the anatomical size of thalamic (sub)nuclei is much closer to the interelectrode distance of standard DBS leads, resulting in additional difficulties in the attempts to provide precise anatomical boundaries for these contacts. In order to overcome the issue of the false localization of thalamic leads, we used a multistep procedure as follows (Simor et al., 2021a; Ujma et al., 2022). Preoperative magnetic resonance imaging (MRI) and postoperative computed tomography (CT) images were co-registered using tools available in the FMRIB Software Library (FSL, Oxford, FLIRT, linear registration, 6 df) to ensure the individualized localization of thalamic contacts. Threshold has been applied on the co-registered CT scans to achieve the desired level of density for proper identification of the lead, thus removing the surrounding brain tissue. Coordinates of the most distal point of the lead has been identified and a more proximal point has been selected along the line of the contacts to mathematically reconstruct the coordinates of the center point of each contact using Euclidean distance in three-dimensional space. These points superimposed over the T1 MRI image provided a guideline for contact localization by examining their location to the anatomic boundaries of the ANT (Figure 1). Anatomical positions according to standard coordinates of the contacts were double-checked by using previously established anatomical guides (e.g. the mamillothalamic tract for the

ANT). With this procedure, we identified thalamic contacts recording from three different thalamic nuclei or regions, the ANT, the MD or the VA on either the left or the right side.

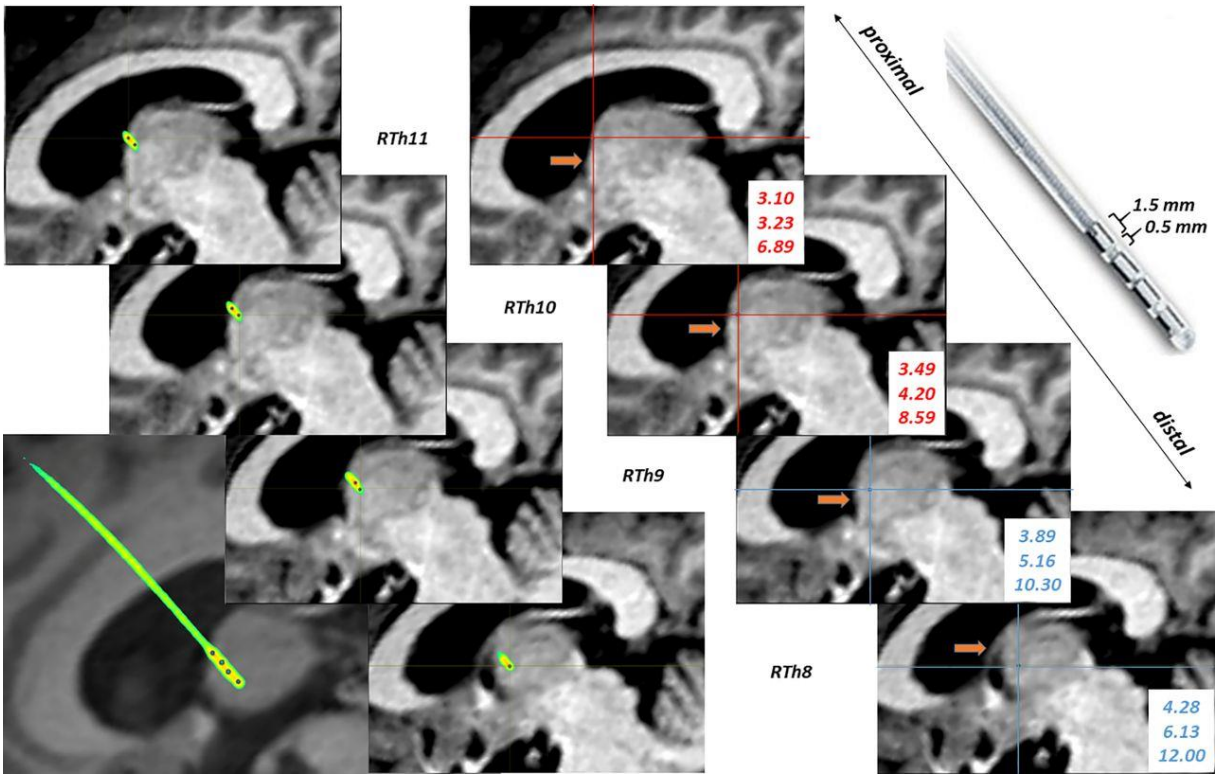

Figure 1. Saggital view of right-hemispheric thalamic contacts in patient #6. Parallel series of images are preoperative MRI-postoperative CT fusions showing the locations of the Medtronic electrode in the brain (left) and successive electrode contact locations based on standard coordinates (measured position of electrode contacts with respect to Mid Commissural Point in mm, left). Red cross-hairs indicate ANT-contacts, whereas blue ones are outside of the ANT (in the mediodorsal nucleus of the thalamus). Brown arrow: tractus mamillothalamicus. Left bottom image is a preoperative MRI-postoperative CT fusion in a skewed plane highlighting all right-side contacts in a single view. Right upper corner: enlarged image of the electrode with contact and intercontact lengths indicated in mm (Simor et al., 2021a).

2. Thalamic field potentials in different sleep-wake states

In contrast to the early reports on featureless thalamic activity, which was considered as largely independent from ongoing cortical field potential fluctuations, we found characteristic time-domain, frequency-domain, as well as time-frequency-based profiles of thalamic activities derived from anatomically verified locations (Szabó et al., 2022).

2.1. Overall time-domain features of the human thalamograms as compared to cortical records

Thalamograms were of lower amplitude as compared to cortical scalp records, except the cases in which one contact was extrathalamic. In this latter cases the records primarily reflected ongoing and phase-reversed cortical activity. In the following we only present data derived from bipolar thalamic channels with both contacts within the same thalamic nucleus or one contact located in the subependymal region. Visible oscillatory activities were detected in the slow wave and the sleep

spindle bands in NREM sleep in some, but not all derivations (including ANT, MD, and VA records). The slow, frontal type of sleep spindles were prevailing in the ANT. Interictal epileptic discharges (IEDs) and occasional ictal patterns seem to spread to the ANT, but evidently do not start in this anatomical structure (Jordán et al., 2017).

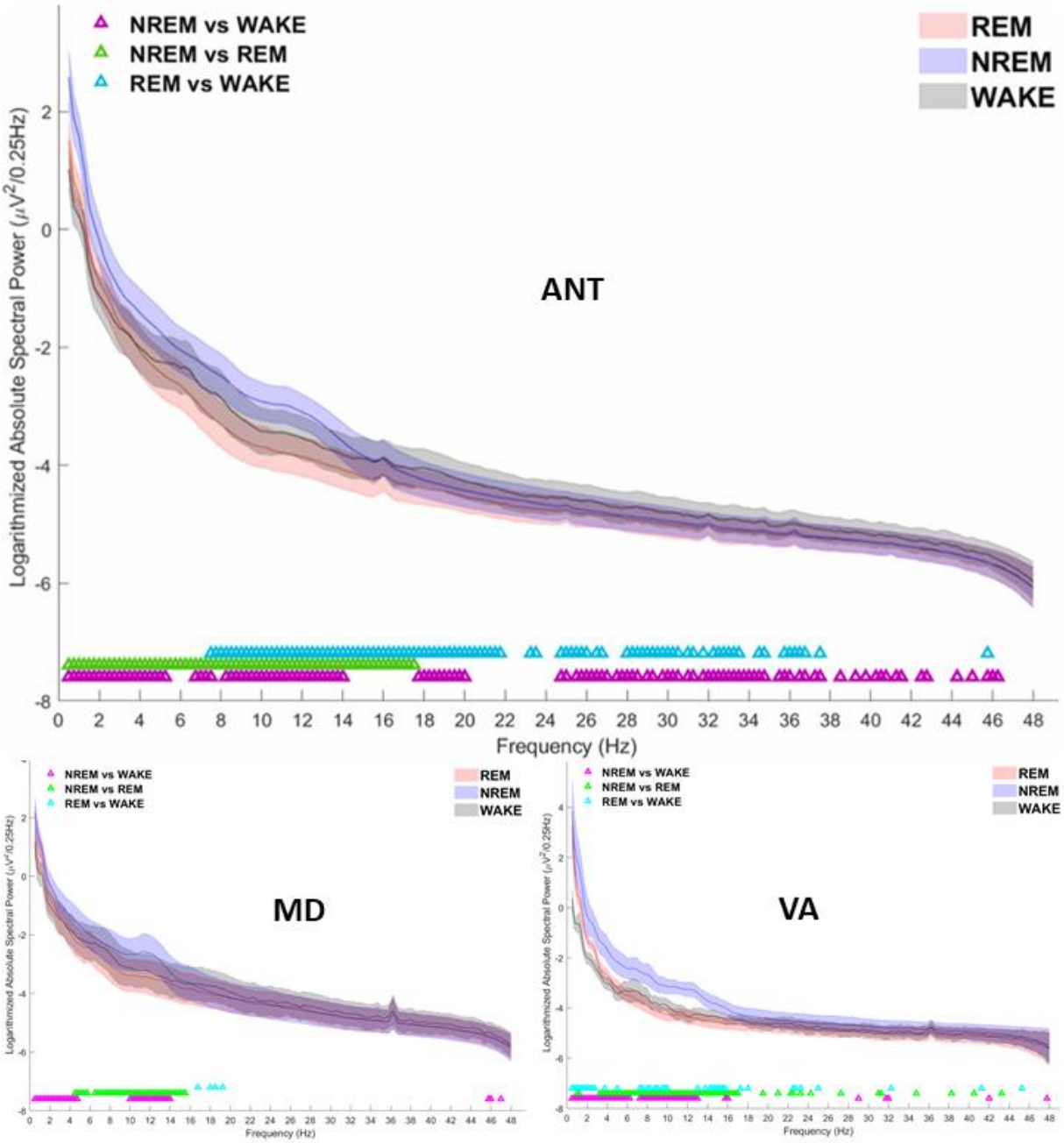

Figure 2. Behavioural state-related spectral features of thalamic records in human epilepsy patients undergoing ANT-DBS treatment. Thalamic leads were externalized and LFPs co-registered with scalp EEG/polygraphy during an undisturbed night of sleep. Continuous lines represent group means, whereas shaded areas 95 % confidence intervals, ANT: anterior nucleus of thalamic; MD: mediodorsal nucleus; VA: ventral anterior nucleus; NREM/REM: non-rapid eye movement/rapid eye movement sleep (based on Szabó et al., 2022).

2.2. Frequency domain characteristics of human thalamograms

Spectral analysis revealed wake-sleep-dependent differences in the power spectral density of thalamograms at distinct frequency ranges (Figure 2). Individual averages of local field potential (LFP) power values at which NREM sleep ANT activity (blue) exceeds WAKE (black) and REM (red) activity are the 0.25–14 Hz and 0.25–18 Hz ranges, respectively. An opposite trend of increased WAKE as compared to NREM spectral power emerges in several bins above 18 Hz. Furthermore, WAKE exceeds REM in frequencies above 7.5 Hz. Note the significance of all comparisons in the 7.5–14 Hz range covering the alpha and the sleep spindle ranges, which suggests the potential relevance of these ANT oscillations in characterizing behavioural state-specific thalamic activity (Szabó et al., 2022). We found similar state-dependent features in other thalamic nuclei, including both MD and VA, with the exception of lower statistical power (due to a lower number of available subjects), a somewhat higher spindle frequency peak power in MD and larger NREM sleep 0.25–14 Hz power values in VA LFP (bottom part of Figure 2).

Due to the increasingly recognized relevance of the scale free nature of cortical LFP captured by 1/f-type spectra, we developed a method and a theoretical framework of parametrizing scalp EEG by a set of non-redundant measures: measures of the 1/f-type scaling and peak power parameters; Bódizs et al., 2021). In spite of the excellent fit of these indexes with empirically measured power spectral density of cortical EEG, thalamograms do not seem to conform power law scaling. Consequently, we were not able to describe the thalamic LFP spectra by this set of parameters we identified in our study focusing on cortical activity (Bódizs et al., 2021). The reasons of this divergence in thalamic and cortical activities is not yet clear and need further studies to be deliberately unravelled.

2.3. Time-frequency profiles of thalamic and cortical sleep oscillations

Specific oscillatory activities, which are assumed to play a crucial role in the functionality of the thalamocortical system were analysed by means of time-frequency analyses, namely wavelet type of analyses. The two types of analyses we performed in this regard transcend the state-level analyses and provide a royal road to the understanding of the role of thalamocortical interactions in the regulation of microstates.

2.3.1. Cortical slow oscillation as a thalamopetal driving force

In our first approach we focused on scalp-derived slow oscillatory activity and its thalamic counterparts. Scalp-derived NREM sleep EEG slow waves were detected by means of previously published method, whereas both scalp and thalamic activity were analysed in terms of their temporal association with the specific phases of the down state peaks used as triggers. We found that thalamic activity (ANT, MD, and VA) during scalp slow waves is highly similar to what is observed on the scalp itself. Slow wave downstates, previously shown to be characterized by widespread disfacilitation-induced hyperpolarization are characterized by delta, theta and alpha activity and followed by beta, high sigma and low sigma activity during subsequent upstates. Gamma activity in the thalamus is not significantly grouped by slow waves. Theta and alpha activity appeared first on the scalp, but sigma activity appeared first in the thalamus. These effects were largely independent from the scalp region in which slow waves were detected and the precise identity of thalamic nuclei. Our results suggest that while small thalamocortical neuron assemblies may initiate cortical oscillations, especially in the sleep spindle range, the large-scale neuronal activity in the thalamus which is detected by field potentials is principally driven by global cortical activity, and thus it is highly similar to what is observed on the scalp (Ujma et al., 2022; Figure 3). In sum, our work

provides evidence for a widespread, stereotypical neuronal activity pattern in the human thalamus during scalp slow waves, with little heterogeneity across thalamic nuclei or scalp origins. While slow activity occurs first on the scalp and fast activity first in the thalamus, time lags are modest and the time-frequency composition of local thalamic field potentials is similar to what is observable on the scalp. We hypothesize that slow rhythms in the thalamus are strongly affected by propagating cortical activity through nonspecific corticothalamic projections, but we also find evidence for a reverse pattern in case of spindle-frequency activity.

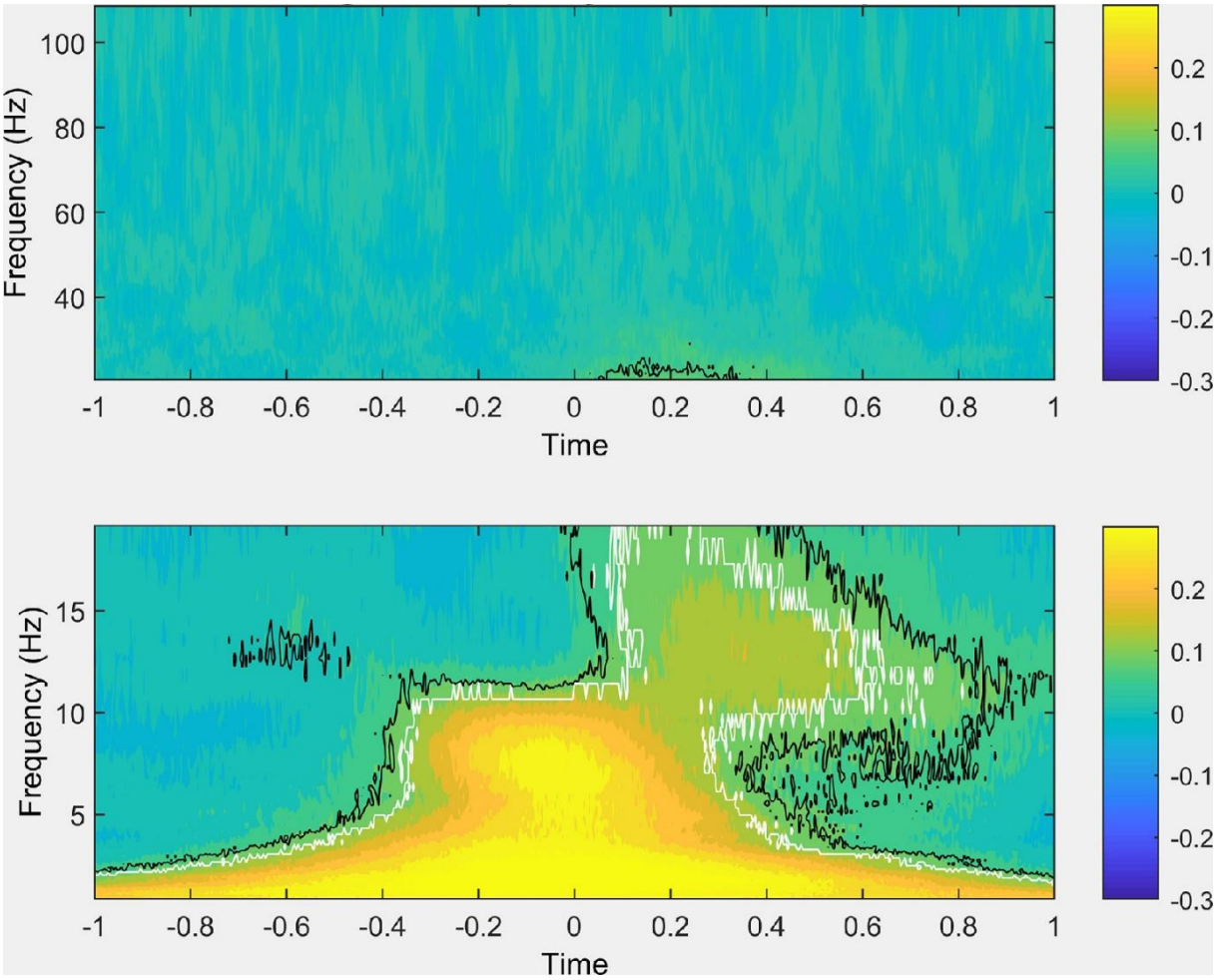

Figure 3. Representative time-frequency plot (data averaged across all patients, representing average LFP in the left anterior thalamus, triggered to the negative peak of slow waves detected on the left frontopolar scalp recording location Fp1). Black lines trace time and frequency values where activity was significantly more extreme than in random segments at uncorrected p<0.05. White lines trace time and frequency values where the effects also survived correction for the false discovery rate. The bottom and top subplots show <20 Hz and >20 Hz activity, respectively, with no data gap but a break in scale for optimal visibility (Ujma et al., 2022).

2.3.2. Sleep spindles at the crossroads of thalamic and cortical activity

In the second approach of our studies we focused on sleep spindles. Spindle starting points according to the Individual Adjustment Method (IAM) were used as triggers in our time-frequency analyses of thalamic LFPs. Thalamic sleep spindles were grouped on a frequency basis (slow and fast), as well as according to presence or absence of a spindle-associated ripple activity (80–200 Hz). Ripple-

associated thalamic sleep spindles (~10% of all spindles) were characterized by longer duration and exceeded pure spindles in terms of 80–200 Hz thalamic, but not cortical activity as indicated by time-frequency analysis. Furthermore, ripple amplitude was modulated by the phase of sleep spindles within the ANT and the MD. No signs of pathological processes were correlated with measures of ripple and spindle association, furthermore, the density of ripple-associated sleep spindles in the ANT showed a positive correlation with general intelligence. The findings of longer ripple-associated versus non-associated sleep spindles cohere with our report on the lengthening of those sleep spindles associated with hippocampal IEDs (Sákovics et al., 2022). Thus, ongoing enhancement of physiological (80–200 Hz thalamic ripples) or pathological (hippocampal IEDs) neuroplasticity is associated with an increased duration of sleep spindles in humans. The above neurophysiological findings cohere with results of the non-invasive studies indicating the link between the maturation of sleep spindles and stages of developmental plasticity in humans (Gombos et al., 2022).

Layer-specific cortical sleep spindle activity (as detected by the IAM) was analysed in order to test if specific thalamocortical connections contribute to distinct types or subsets of spindles. The idea is based on the known layer-specificity of distinct thalamofugal inputs. We revealed a rather stereotypical sleep spindle generating mechanism. Our results indicate that extremely local spindles may occur in any cortical layer, but co-occurrence at other locations becomes likelier with increasing amplitude and the relatively large spindles detected on ECoG channels have a stereotypical laminar profile. We found no compelling evidence that different spindle types are associated with different laminar profiles, suggesting that they are generated in cortical and thalamic circuits with similar cortical innervation patterns. Local neuronal activity is a stronger candidate mechanism for driving functional differences between spindles subtypes (Ujma et al., 2021).

2.4. The dichotomy of REM sleep: a perspective from human ANT activity

REM sleep is far from being a homogenous behavioural state. Distinct physiological and neurocognitive processes were found to characterize periods of bursting eye movement activity (phasic REM) as compared with time windows best described by ocular immobility (tonic REM). Findings indicate that exteroceptive and interoceptive processing is partially reinstated during tonic REM periods, whereas neural activity during phasic periods seems to be detached from the surroundings, indicating internally driven sensorimotor processing (Simor et al., 2021b). These states were never analysed in terms of human thalamic LFP before. Indeed, we found increased ANT high-α and β frequency power in tonic compared with phasic REM, emerging as an intermediate state between phasic REM and wakefulness. Moreover, we observed increased thalamocortical synchronization in phasic compared with tonic REM sleep, especially in the slow and fast frequency ranges. Wake-like activity in tonic REM sleep may index the regulation of arousal and vigilance facilitating environmental alertness. On the other hand, increased thalamocortical synchronization may reflect the intrinsic activity of frontolimbic networks supporting emotional and memory processes during phasic REM sleep. In sum, our findings highlight that the heterogeneity of phasic and tonic REM sleep is not limited to cortical activity, but is also manifested by anterothalamic LFPs and thalamocortical synchronization (Simor et al., 2021a).

3. Summary

Clinically indicated invasive cortical electrophysiological measurements and thalamic records derived from DBS electrodes convey potentially valuable information on the dynamics of thalamocortical

oscillations peculiar to specific macroscopic behavioural states as well as to instantly changing microstates of sleep. A fine graded and proper anatomical definition of individual recording sites is a significant methodological challenge, but also of utmost importance in depicting neurophysiologically relevant LFPs. Analysis of the human thalamic records indicate the involvement of thalamic nuclei in the differentiation of wake-sleep macro- and microstates. The dominant role of cortical driving forces in shaping overall thalamic activity is of crucial importance in the NREM sleep slow oscillation-related thalamocortical oscillations. IEDs, ictal phenomena and physiological ripples are parts of the thalamic LFPs, whereas sleep spindles seem to reflect the double influence of descending cortical and local thalamic sources, being sensitive to transient increases in neuroplasticity. ANT mechanisms in transient increases of vigilance in the tonic episodes of REM sleep were evidenced. Further research focusing on more refined localization of thalamic contacts (including the specific involvement of different subnuclei) by means of high definition imaging tools is needed.

4. References

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