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Significant thalamocortical coherence of sleep spindle, theta, delta, and slow oscillations in NREM sleep: Recordings from the human thalamus

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ABSTRACT

The electrophysiological studies of thalamocortical oscillations were mostly done in animal models. Placement of stimulation electrodes at the anterior nucleus of the thalamus (ANT) for seizure reduction enables the study of the thalamocortical interplay in human subjects. Nocturnal sleep electroencephalograms (EEGs) and local field potentials (LFPs) of the left and right thalamus (LT, RT) were recorded in three subjects receiving ANT stimulation. Sleep stages were scored according to American Academy of Sleep Medicine criteria. The whole-night time–frequency coherence maps between EEG (C3, C4) and LFP (LT, RT) showed specific coherence patterns during non-rapid eye movement (NREM) sleep. Pooled coherence in the NREM stage was significant in slow, delta, theta and spindle frequency ranges. The spindle oscillations had the highest coherence (0.17–0.58) in the homolateral hemisphere. Together, these observations indicate that the oscillations were related to thalamocortical circuitry.

Sleep oscillations are highly regulated brain activities. Studies in cats [33] have shown that thalamic-reticular cells generate sleep spindles (7–14 Hz oscillation). Cortical neurons, through cortico-thalamic feedback projections, help trigger and synchronize spindle oscillations in the thalamus [7,9]. Clinically, sleep spindle activities are associated with mnemonic retention [5,35]. Cortical and thalamic neurons might "work" together to generate epilepsy [4,28,36]. The recording of thalamic neuronal activities has shown that slow oscillations (<1 Hz) can group together periods of sleep spindles and delta oscillations (1–4 Hz) during depolarization or hyperpolarization [27–29]. In addition to theta oscillations in the hippocampus, synchronized theta (4–7 Hz) activity has been observed between the visual cortex and lateral geniculate nucleus in cat models [12,13,15].

Electric stimulation in the anterior nucleus of the thalamus (ANT) via quadripolar electrodes has been used to reduce seizures in patients with refractory epilepsy [16,17,37]. This provides a unique opportunity to study the electrophysiology of the thalamus in humans. However, controversial results have been reported regarding whether the activities of normal or abnormal sleep spindles are regulated by the centromedian nucleus of the thalamus [39,40]. In the present study, we investigated the coherence spectra during whole-night sleep between electroencephalogram (EEG) and thalamic local field potential (LFP) in patients receiving ANT stimulation for the treatment of epileptic seizures.

Three patients (age 30–33 years) receiving ANT stimulation to treat epileptic seizure served as study participants. Demographic data and clinical findings are summarized in Table 1. Under local anesthesia, single unit activity was recorded extracellularly with an intraoperative platinum iridium microelectrode (FHC, Bowdoinham, ME; impedance 0.3–0.5 MΩ) amplified by the Leadpoint system (Medtronic, Minneapolis, MN) to identify neuronal signals from the ANT. Medtronic 3387 DBS quadripolar platinum-iridium cylindrical electrodes (diameter: 1.27 mm, contact length: 1.5 mm, spacing: 1.5 mm) were implanted bilaterally at the ANT. The location of the stimulation leads was confirmed by postoperative brain magnetic resonance imaging (MRI). The surgery and microelectrode recording procedures are described elsewhere [17].

All subjects underwent a three-day long-term monitoring of scalp EEG and bilateral thalamic LFP with the Nicolet BMSI 6000 and/or NicoletOne systems (Nicolet Biomedical, Madison, WI) within one week after implantation of the stimulation electrodes. A 19-channel EEG, 2-channel electrooculogram (EOG), and a chin electromyogram (EMG) were acquired at a sampling rate of 400 Hz (Nicolet BMSI 6000) or 2000 Hz (NicoletOne) according to the international 10–20 system and standard polysomnographic settings

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Table 1
Demographic and clinical data of study subjects.

Subject	Gender	Age (years)	Age (years) at seizure onset	EEG background	MRI findings
1	F	30	1	Diffuse slow waves with left hemisphere emphasis	Left cerebral hemiatrophy and post-pallidotomy lesion
2	F	33	9	Intermittent right fronto-central theta waves. Paroxysmal sharp waves over bilateral central area with the right hemisphere emphasis	Right frontal cortical and subcortical gliosis
3	F	30	16	Slow waves over bilateral fronto-centro-parietal area	Normal

[6]. Thalamic LFP were parallel-recorded from bilateral quadripolar electrodes (LT0, LT1, LT2, LT3, RT0, RT1, RT2 and RT3). The recordings were referred to the left mastoid (subjects 1 and 2) or the linked mastoid (subject 3). Sleep stages were scored manually as W (wake), N1 (stage I), N2 (stage II), N3 (stages III and IV), or R (rapid eye movement, REM) by 30-s epochs according to American Academy of Sleep Medicine (AASM) scoring criteria [6]. Electrophysiological signals were retrieved from an exported data file using functions included in the Biosig toolbox [25] and were analyzed using customized software in Matlab (The Mathworks, Natick, MA). Epochs related to major body movements or artifacts were excluded from analysis.

To estimate functional coupling between the cortex and thalamus, a power spectrum and coherence analysis was used to analyze the correlation between EEG and LFP signals. The magnitude coherence function reflects the linear association between two signals $x(t)$ and $y(t)$ at each frequency, defined as a normalized cross-spectrum $C_{xy}(f) = |P_{xy}(f)|^2/(P_{xx}(f) \times P_{yy}(f))$, where P_{xy} denotes a cross-spectrum and P_{xx} and P_{yy} refer to auto-spectra. The magnitude of coherence varied from 0 to 1, where a higher coherence is linked to a higher degree of phase synchrony at the specified frequency. The ipsilateral coherence was computed between the central EEG and the bipolar LFP: C3 vs. LT0–LT3 (hereafter LT) and C4 vs. RT0–RT3 (RT). The contralateral coherence was computed based on C3 vs. RT and C4 vs. LT. The central EEG channels (C3 and C4) were selected because of having higher thalamocortical coherence compared with other EEG channels, and the AASM also recommended using C3 and C4 for scoring the sleep stages. The coherence spectra of the epochs in NREM sleep were pooled for further analysis [2].

To test whether the coherence was non-zero, the upper α% confidence limit for coherence estimation from n disjoint segments assuming independence was determined from: $1-(1-\alpha/100)^{1/(n-1)}$ [10,20,24]. The phase difference at the specified frequency was computed by $\phi(f) = \arg\{P_{xy}(f)\}$, with variance given by $\sigma^2(f) = [1/C_{xy}(f) - 1]/2n$. The slope of phase difference in a frequency range was used to calculate time lag of two signals [20,26]. The ipsilateral (C3–LT, C4–RT) and contralateral (C4–LT,

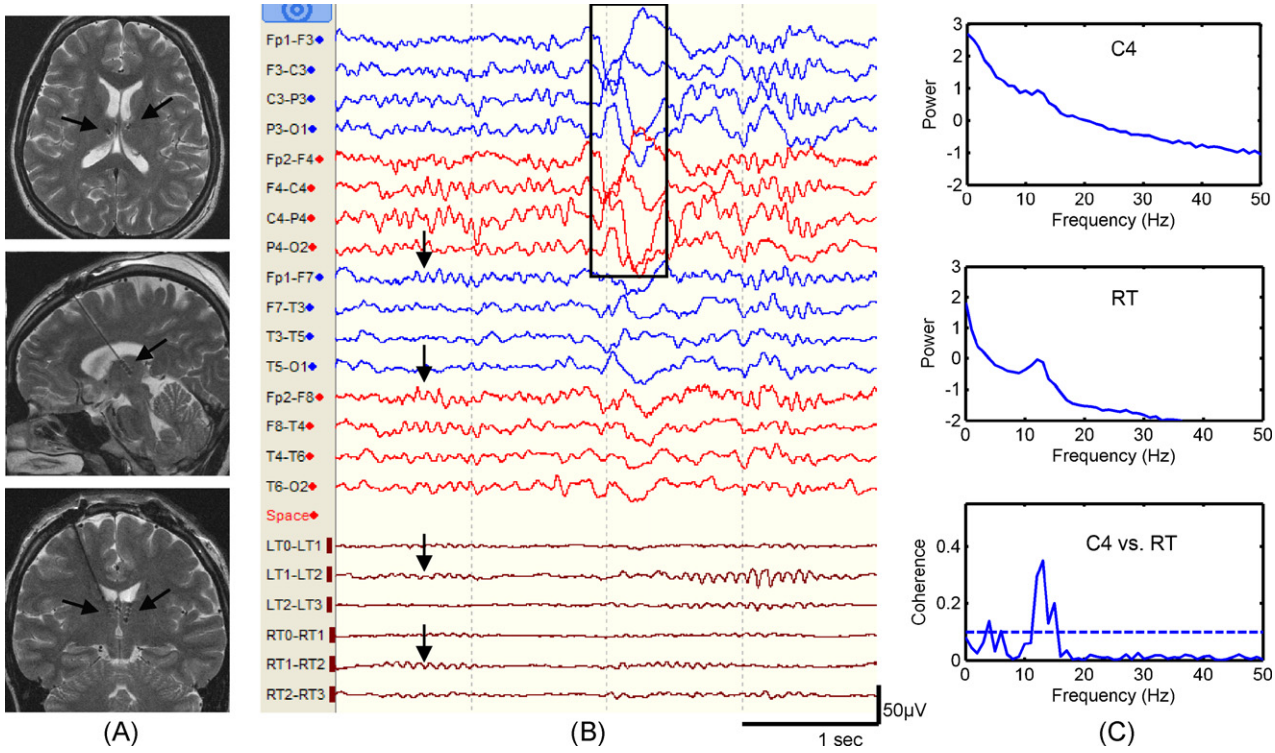

Fig. 1. Representative recording from subject 3. (A) Magnetic resonance images (axial, left sagittal, and coronal views) confirmed that the quadripolar electrodes (arrows) were implanted at the anterior nucleus of the thalamus (ANT). LT0 and RT0: deepest electrode to the left and right, respectively. LT3 and RT3: most superficial electrode to the left and right, respectively. (B) A 4-s sleep stage N2 electroencephalogram (EEG at Fp1, F3, C3, . . ., O2) and local field potentials (LFP at LT0, . . ., 3 and RT0, . . ., 3) with bipolar montages and a passband of 1–70 Hz. Sleep spindles (arrows) were visible in both EEG and LFP, while K complex (box) was visible only in EEG. (C) The power spectral density of EEG at C4 and LFP at RT (RT0–RT3) showed a peak in spindle frequency. Coherence revealed two peaks above the 95% confidence limit (0.1, the dashed line): 0.13 at 13 Hz and 0.14 at 4 Hz. Power spectral density is reported in units of $\log_{10}\mu V^2/Hz$. The estimated spectra and coherence were calculated from 90 disjointed segments of 1 s in length.