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Original Article

Thalamic contribution to Sleep Slow Oscillation features in humans: A single case cross sectional EEG study in Fatal Familial Insomnia

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ABSTRACT

Objective: Studying the thalamic role in the cortical expression of the Sleep Slow Oscillation (SSO) in humans by comparing SSO features in a case of Fatal Familial Insomnia (FFI) and a group of controls.
Methods: We characterize SSOs in a 51-year-old male with FFI carrying the D178N mutation and the methionine/methionine homozygosity at the polymorphic 129 codon of the PRNP gene and in eight gender and age-matched healthy controls. Polysomnographic (21 EEG electrodes, two consecutive nights) and volumetric- (Diffusion tensor imaging Magnetic Resonance Imaging DTI MRI) evaluations were carried out for the patient in the middle course of the disease (five months after the onset of insomnia; disease duration: 10 months).
We measured a set of features describing each SSO event: the wave shape, the event-origin location, the number and the location of all waves belonging to the event, and the grouping of spindle activity as a function of the SSO phase.
Results: We found that the FFI individual showed a marked reduction of SSO event rate and wave morphological alterations as well as a significant reduction in grouping spindle activity, especially in frontal areas. These alterations paralleled DTI changes in the thalamus and the cingulate cortex.
Conclusions: This work gives a quantitative picture of spontaneous SSO activity during the NREM sleep of a FFI individual. The results suggest that a thalamic neurodegeneration specifically alters the cortical expression of the SSO. This characterization also provides indications about cortico-thalamic interplays in SSO activity in humans.

1. Introduction

Electrophysiological studies in animal models have revealed that, during Slow Wave Sleep (SWS), cortical neurons show slow (<1 Hz) rhythms characterized by a coordinated switching behavior of the membrane potential: they synchronously alternate between a state of hyperpolarization (down state) and a state of wake-like depolarization (up state) [1,2]. This behavior, which represents the fundamental cellular phenomenon underlying different slow neural activities in SWS, such as K complexes and delta waves [3], has also been described in humans and referred to as Sleep Slow Oscillation (SSO) [4,5]. From an EEG stand point SSO (i) corresponds to a sharp negative peak (related to the down-state) followed by a shallow positive half wave (related to the up-state), (ii) originates mainly in frontal regions [4,5], and (iii) propagates across variable cortical territories [4,5]. It has also been observed in animal models and in humans that up-states group spindle and faster activities, which reflects the influence of the neural mechanism underlying SSO on thalamo-cortical cells [6,7].

Despite a deep electrophysiological and EEG characterization of SSOs, an issue is still under debate: is the human SSO generated in the neocortex and then imposed on thalamic territories or is it generated by a mutual interplay between the thalamus and the cerebral cortex?

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The hypothesis of SSO as a purely cortical phenomenon is supported by the following: (i) transections of the cortico-thalamic afferents abolish SSO in thalamo-cortical cells and nucleus reticularis thalami (NRT) neurons [8]; (ii) athalamic animals continue expressing SSO [9]; and (iii) the discovery of intrinsically oscillating neurons in layers V and IV [10].

On the contrary, other works have indicated that: (i) SSO is detectable in thalamocortical neurons of various thalamic nuclei and in neurons belonging to the NRT [11] and (ii) intact thalamocortical circuits have substantial influence on the generation and synchronization of the cortical SSO [12].

Experimental models of selective thalamic lesions in humans can help in shedding light into this physiological controversy. Two models appear to be particularly suited for selectively studying the thalamic role in the physiology of SSO: (i) the bilateral or unilateral thalamic strokes, with limitations related to the inter-subjects variability, and (ii) an autosomal dominant hereditary disease, clinically characterized by loss of sleep, dysautonomia, and motor signs, and pathologically characterized by selective thalamic degeneration [13,14], named Fatal Familial Insomnia (FFI).

This work deals with the study of the thalamic role in the physiology of SSO by examining the latter clinical condition.

FFI is linked to a missense mutation at codon 178 of the prion protein gene PRNP [15] and to the presence of the methionine codon at position 129 in the mutated allele of the PRNP [16]. Methionine/methionine homozygous at codon 129 have shorter disease duration (9–10 months) compared with the methionine/valine heterozygous patients (>24 months) [17]. Longitudinal, serial 24-h polygraphic recordings demonstrate that spindles and delta sleep progressively disappear in the course of the disease [18,19]. In FFI, computed tomography (CT) and magnetic resonance imaging (MRI) scans are unremarkable, but longitudinal PET (18FDG-PET) scans disclosed a hypometabolism confined to the thalamus in the earlier stages of the disease. These studies demonstrate that the hallmark of FFI, particularly in the early stage of the disease, is a thalamic dysfunction.

We evaluated the polysomnographic recording obtained in a FFI subject (D178N–129M) at a middle stage of the disease, when the pathological process is mainly bounded in the thalamus and NREM sleep is still detectable, and compared the FFI patient with a set of age/sex matched healthy controls. The purpose of this study is determine the influence of a thalamic dysfunction on the SSO physiology.

After a general evaluation of the changes in the sleep macrostructure, as well as of the power spectra, we focused the analysis on SSO activity. We found that, in the FFI individual, the SSO rate is dramatically reduced, the SSO segment related to the transition from down-state to up-state has a greater duration, and the SSO ability to group spindle activity is greatly impaired. These findings parallel a selective thalamic degeneration identified through MRI evaluation.

These results indicate that thalamo-cortical interplays are crucial for the SSO in humans.

2. Material and methods

2.1. Case report

A Caucasian 51-year-old male patient, born in North East Italy, was admitted due to a five month history of sub-acute onset of "inability to sleep." His wife reported additional peculiar oneiric episodes during the night, characterized by gestures mimicking daily-life activities, such as pointing to something, eating, or drinking. Since the beginning of these symptoms, he had also developed hypertension, erectile dysfunction, fluctuating episodic diplopia, and a weight loss of about 7 kg. The neurological examination showed short-term memory deficit; impaired horizontal and vertical saccadic eye movements, and spontaneous and evoked myoclonus. He was a member of an FFI family that had already been published – the V-59 subject of the genealogical tree described in literature [15]. Analyses of DNA extracted from peripheral leukocytes revealed both the D178N mutation and the methionine/methionine homozygosity at the polymorphic 129 codon of the PRNP gene. He died of a sudden, generalized autonomic failure, complicated with infections, 10 months after the onset of sleep problems.

2.2. MRI study

The FFI patient was studied in a 1.5 Tesla GE system. A T1-weighted axial volumetric image was acquired using the fast spoiled gradient echo (FSPGR) sequence (TI = 600 ms; TE = 5.1 ms; TR = 12.5 ms; 25.6 cm^2 FOV, 1 mm slice thickness; in-plane resolution = 256 × 256), while axial DTI images were obtained (5 mm slice thickness without inter-slice gap) using a single-shot spin-echo planar imaging (SE-EPI) sequence with echotime (TE) = 89.2 ms, repetition time (TR) = 10 s, 32 cm^2 field of view (FOV), in-plane resolution = 256 × 256. Five T2-weighted scans without diffusion gradients and 25 with direction-encoding gradients at strengths corresponding to *b*-value 900 s/mm^2, were acquired. Ten healthy individuals of similar ages, who had previously undergone the same MRI exams, were selected from our database of studies for comparison purposes.

2.3. Data analysis of the FFI individual and healthy controls

DTI processing was performed using the FMRIB software library (http://www.fmrib.ox.ac.uk/fsl). We acquired DTI-EPI images to compensate for the effect of eddy current distortions using the image registration software FLIRT. Parameter maps for mean diffusivity were determined voxel-wise using the program DTIFIT.

The volumetric image was segmented into multiple cortical, subcortical, and white matter regions using the software tool FreeSurfer (http://surfer.nmr.mgh.harvard.edu/). Segmentation labels were transferred to the DTI image volumes by aligning the unweighted EPI images to the T1-weighted volume, first by an affine registration, then by a non-linear one (FLIRT and FNIRT from the FMRIB software library). Regions of interest were selected from a sulcal- and gyral-based cortical parcellation atlas provided by FreeSurfer [20] corresponding to regions reportedly involved in SWS [21]. The regions of interest comprised the thalamus, the superior, middle, and the opercular, orbital, and triangular parts of the inferior gyri of the frontal cortex, the cingulate gyri (divided into the main part and isthmus), the frontal middle and inferior, pericallosal and cingulate sulci, and the precuneus. The median bilateral mean diffusivity was calculated for these areas and the structure volume was estimated using FreeSurfer. A *t*-statistic was calculated for the control group assuming a normal distribution and a probability that the patient observation derived from the same group was estimated, using the formula of Geissen, taking $p < 0.05$ as significant.

2.4. Sleep study of the FFI individual and the healthy controls

The FFI patient was hospitalized for two consecutive days. He was allowed to sleep ad libitum, living in a temperature (24 ± 1 °C) and humidity (40–50%) controlled room, lying in bed except when eating, in a light–dark schedule (dark period: 11 p.m.–7 a.m.). The patient was placed on a 1.800 kcal/day diet divided into three meals (8 a.m., 12 a.m., 6 p.m.) and three snacks (10 a.m., 4 p.m., 11 p.m.). The EEG activity of the FFI patient was recorded during the dark period for two consecutive days, the first