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

Angelo Gemignani, Marco Laurino, Federica Provin, Andrea Piarulli, Giorgio Barletta, Paola d’Ascanio, Remo Bedini, Raffaele Lodi, David Neil Manners, Paolo Allegrini, Danilo Menicucci, Pietro Cortelli

Department of Physiological Sciences, University of Pisa, Pisa, Italy
Extreme Centre, Scuola Superiore Sant’Anna, Pisa, Italy
Institute of Clinical Physiology, National Research Council, Pisa, Italy
Department of Neurological Sciences, University of Bologna, Bologna, Italy
Functional MR Unit, Department of Internal Medicine, Aging and Nephrology, University of Bologna, Bologna, Italy

Article history:
Received 8 December 2011
Received in revised form 9 March 2012
Accepted 13 March 2012
Available online 19 May 2012

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?
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 to 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 onoinic 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 homoyzosity 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 cm² 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 cm² 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/mm², 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 gyrus of the frontal cortex, the cingulate gyrus (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
night being an adaptation night, so that only the second night recording was considered for the analysis.

The case of this study has been compared with a group of eight middle-aged, healthy males. Control subjects were selected according to these criteria: age between 45 and 55 years, no personal or family history of sleep disorders or other medical, psychiatric, or neurological disorders, and drug free for at least six months. Volunteers were not sleep deprived and after an adaptation night they were allowed to sleep at the usual bedtime. All experimental procedures were performed according to the ethical guidelines of the Ethical Committees of the University of Bologna, Italy.

2.5. Sleep EEG recording and preprocessing

EEG recordings were collected by Nihon Kohden Neurofax EEG–1200 64–channels Electroencephalograph (NIHON KOHDEN CORPORATION1–31–4 Nishiochiai, Shinjuku-ku, Tokyo 161–8560, Japan). The EEG was acquired from 21 electrodes positioned according to the 10–20 International Electrodes Placement System; each electrode was referred to a reference electrode in the midline position between Fz and Cz. All signals were sampled at a frequency of 500 Hz, 16 bit resolution, and 0.016–120 Hz band pass filtered. Polysomnographic recording included two electrooculographic (EOG) channels, submental EMG, tibialis anterior bilateral EMG, abdominal effort, and EKG. Signal treatment (from pre-processing to SSO wave analyses) was implemented using Matlab (MathWorks, Natick, MA, USA). All maps were obtained using the EEGLAB Toolbox [22]. EEG raw data were offline re-referenced to mastoid electrodes average potential in order to obtain monopolar-like potentials [3].

2.6. Data analysis

Sleep stages (wake, N1, N2, N3, and REM sleep) were scored offline according to AASM scoring criteria [23] by visual and spectral inspection of 30 s EEG epochs. For the comparison of sleep EEGs between the FFI case and the controls, we also matched the sleep time duration of the FFI case with a portion of the control’s sleep recordings; to this aim, we used only the first sleep cycle data of control subjects.

Epochs belonging to the N2 and N3 stages and free from artifacts (i.e., epochs without movements or arousals) were selected for two independent analyses: (1) Estimation of power spectral distribution of the sleep EEG signals and (2) Detection and analysis of SSOs.

In order to identify the differences between the FFI case and the control group, we compared the patient value to the control sample distribution for each parameter, calculating its t-score.

2.7. Power spectral distribution of the sleep EEG signals

EEG power spectra related to the N2 and N3 sleep stages of each subject were calculated via periodogram (Hamming windowed Fast Fourier Transform with a window length of 30 s), estimated on the corresponding EEG epochs. Spectral power of the EEG signal was calculated for all EEG electrodes in frequency bands, defined as delta (Δ: 0.3–4 Hz), theta (θ: 4–8 Hz), alpha (α: 8–12 Hz), and sigma (σ: 12–15 Hz, spindle activity).

2.8. Detection and characterization of the SSOs

SSOs were detected using the Likeness Method proposed by our group in previous works [24,5]. In summary, we adopt as a definition of full-fledged SSO a wave consisting of (a) two zero crossings separated by 0.3–1.0 s, the first one having a negative slope; (b) a negative peak between the two zero crossings with a voltage less than −55 µV; (c) a negative-to-positive peak amplitude of at least 100 µV. Then our method detects complete events by clustering full-fledged SSOs with concurrent similar waves, even if sub-threshold. These detection criteria are also satisfied by K-complexes.

The SSO behavior of each subject was characterized through the study of (i) the mean rate of SSOs occurrence; (ii) the scalp distributions of the origin sites, and of waves detection; (iii) a set of morphological features that specify the waves shape; and (iv) the SSO positive half-wave ability to group the spindle activity (spindle grouping).

Within each SSO event the earliest negative peak indicated the origin site of the event [4]. The wave shape analysis was based on seven morphological features [5] (Supplementary Fig. 1 in supplementary materials): three amplitude features (N [negative peak] amplitude; P [positive peak] amplitude; NP [negative-to-positive peak] amplitude), two time features (the interval between the negative peak and positive peak – NT time; the first zero crossing to negative peak time – ZN time), and two steepness features (the slope of the signal between the first zero crossing and the negative peak – slope 1; the slope between the negative peak and the second zero crossing – slope 2).

The spindle grouping estimates the change of σ activity (12–15 Hz) passing from the down-state to the up-state. Power estimates were calculated by using a Hamming windowed FFT with a window length of 500 ms: down-state power estimate was derived by centering the FFT window on the negative peak, while the up-state window was centered on the positive peak of each SSO (T1 and T2 time windows in Fig. 3), respectively. We defined the spindle grouping as the difference between the positive peak σ power and the negative peak σ power.

3. Results

3.1. Neuroimaging study

In two out of 14 selected regions of interest the patient demonstrated a mean diffusivity value significantly outside the distribution of the controls: in the thalamus (0.819 × 10⁻³ mm²/s against controls mean ± SD 0.779 ± 0.015 × 10⁻³ mm²/s: p = 0.03) and in the cingulate (0.825 × 10⁻³ mm²/s against controls 0.794 ± 0.009 × 10⁻³ mm²/s; p = 0.013), mean diffusivity was elevated in the patient (Fig. 1). The volume of these and all others structures selected was normal compared to the healthy controls (p > 0.05; data not shown).

3.2. Changes of macrostructure and power spectrum in the NREM sleep of the FFI patient

In the FFI patient, the polysomnographic analysis shows a marked reduction of total sleep time and a severe alteration of the cyclic sleep organization. Typical NREM sleep macrostructural elements (K-complexes, delta waves, and sleep spindles) were markedly reduced, with a predominance of stage 1 sleep intermixed with REM sleep with and without atonia. Thus, no physiological sleep cycles were identifiable in the FFI patient and 40.8 min of N2 sleep stage and 39 min of N3 sleep stage were derived from the whole night recording. Supplementary Fig. 2, bottom panel, shows the FFI patient’s sleep structure during the night compared to that of a representative healthy control (upper panel).

All controls showed a physiological sleep EEG pattern, reaching the deepest stages of NREM sleep (stage N3, or SWS), with K-complexes, spindles, and delta waves. The sleep staging allows the recognition of the first cycle for each individual (Supplementary Fig. 2). In healthy controls NREM stage durations of the first sleep cycle were on average: 32 (SD 16) min for the N2 stage and 32 (SD 11) min for the N3 stage.
As far as the power spectral distribution of the sleep EEG signals is concerned, delta and sigma activity during both the N2 stage and the N3 stage were significantly lower in the FFI patient with respect to controls (Supplementary Fig. 3); this considerable reduction was detected in all cortical areas \((p < 0.05\) for all electrodes). The difference in power spectra was mainly due to the lower amplitude and number of delta waves. It is worth noting that the physiological increase of delta activity from shallow to deep sleep observed in controls is also present in the FFI individual. No significant changes have been observed for theta and alpha activities, which seem to be spared by thalamic neurodegeneration (Supplementary Fig. 3).

### 3.3. Sleep Slow Oscillation changes in the FFI patient

During both the N2 and N3 stages, the rate of SSO events, measured in events per hour \((\text{evs/h})\), was significantly lower in the FFI patient. The regions of interest for which the patient's mean diffusivity was significantly altered with respect to controls are shown, displayed as \(p\)-values (see color scale at right), back projected onto regions of interest selected by FreeSurfer, superimposed on T1 coronal images of the patient. The figure highlights a bilateral involvement of the thalamus and the cingulate cortex.

---

**Fig. 1.** The regions of interest for which the patient’s mean diffusivity was significantly altered with respect to controls are shown, displayed as \(p\)-values (see color scale at right), back projected onto regions of interest selected by FreeSurfer, superimposed on T1 coronal images of the patient. The figure highlights a bilateral involvement of the thalamus and the cingulate cortex.

**Fig. 2.** SSO origin and detection maps for the controls (Ctrls) and the FFI patient (Pt). For Ctrl, the figure shows the grand mean of the maps over individuals. Each map represents the frequency (reported as percentage) of SSO event origins or SSO detections for each electrode.
individual (N2: 55 evs/h; N3: 153 evs/h) with respect to controls (N2: 445 ± 139 evs/h; N3: 943 ± 180 evs/h). The SSO detection rate showed, like for delta activity, a relative increase from the N2 to the N3 stage both for the FFI individual and for the controls.

The reduction of SSO detection rate observed in the FFI individual uniformly encompassed all cortical areas. As a result the scalp distribution of SSO origins and detections in the FFI individual remained unaltered with respect to healthy controls: the origins were mainly detectable in frontal areas, while detections were maximal over medio-frontal and parietal areas (Fig. 2).

The analysis of wave shape highlighted two distinct morphological changes: (i) the FFI individual had a grand mean NP time increase (p-value <0.001) and (ii) the FFI individual had a grand mean slope 2 reduction (p-value <0.01) (Table 1).

### Table 1

<table>
<thead>
<tr>
<th>Features</th>
<th>Ctrls mean (SE)</th>
<th>Pt mean</th>
<th>p-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP amplitude (µV)</td>
<td>96.3 (5.5)</td>
<td>84.2</td>
<td>NS</td>
</tr>
<tr>
<td>N amplitude (µV)</td>
<td>–65.5 (4.7)</td>
<td>–56.6</td>
<td>NS</td>
</tr>
<tr>
<td>P amplitude (µV)</td>
<td>34.9 (3.1)</td>
<td>29.1</td>
<td>NS</td>
</tr>
<tr>
<td>NP time (ms)</td>
<td>490.2 (18.5)</td>
<td>612.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ZN time (ms)</td>
<td>268.6 (8.2)</td>
<td>280.6</td>
<td>NS</td>
</tr>
<tr>
<td>Slope 1 (µV/ms)</td>
<td>–0.241 (0.01)</td>
<td>–0.224</td>
<td>NS</td>
</tr>
<tr>
<td>Slope 2 (µV/ms)</td>
<td>0.218(0.014)</td>
<td>0.147</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Fig. 3 illustrates the pathognomonic feature occurring in the SSO, i.e., the spindle grouping. In healthy controls the superimposition of raw data (Fz electrode) to the same EEG epoch filtered in delta and sigma bands highlights a specific temporal link between the SSO positive peak and the crowning spindle (Fig. 3, panel A). In the FFI individual this association was undetectable (Fig. 3, panel B).

Spindle grouping reduction in the FFI individual had the specific scalp distribution depicted in Fig. 4: the reduction of sigma activity encompassed all electrodes with a greater impairment in frontal leads.

### 4. Discussion

In order to identify, in humans, a thalamic role in SSO behavior, we herein statistically characterized the spontaneous SSO activity in one D178N–129M FFI individual compared with eight age and gender-matched healthy controls.

The comparison of EEGs, corroborated by DTI and Spectroscopy MRI, highlights both conserved and modified behaviors that we can therefore respectively associate to cortical and thalamic roles on SSO generation and sustaining. Conservations consist of (i) the same relative topologies of SSO events and origins and (ii) the same sizes, or spreads, of SSO events. Changes in the FFI patient consist of (i) a dramatically lower global event rate, (ii) a slower...
oscillation, i.e., a longer duration around the negative peak and a shallower return to positive potential, and (iii) a strong reduction of spindle grouping, mainly on the frontal areas. We shall discuss these findings in detail.

The study of both origin and detection scalp distributions indicates that, also in the FFI individual, the frontal area network is more prone to produce SSOs than networks in the posterior and temporal areas. The finding of a similar mean event size in the FFI individual compared to controls also indicates that the SSO’s spreading capability is spared by the thalamic neurodegeneration. This is in line with data showing that the cortical travel is mainly sustained by cortico-cortical mechanisms [25].

The FFI individual showed a dramatically lower rate of SSO events during NREM stages N2 and N3. In the FFI case the wave shape has shown specific morphologic alterations such as NP time increase and slope 2 reduction, which could be related to a reduced thalamic synchronization on the cortical neuronal pool coming out from the downstate of the SSO [26,27].

Finally, our results in the FFI individual show a consistent lack of spindle activity concurrent with the depolarizing phase of SSO, which is in turn consistent with thalamo-cortical cell impairments in oscillating in spindle frequency, and, hence, with reverberating spindle activity on the cortex through thalamo-cortical volleys. Actually, both animal and human data indicate that SSOs have the capability of grouping spindles [6,7]. These studies demonstrate that the depolarization of neocortical pyramidal cells during the up-state drives the generation of spindle oscillations in thalamo-cortical feedback loops. Our data are thus consistent with the observations that (i) in athalamic animals SSO is still present at a cortical level while spindles are suppressed [1] and (ii) in animal models ibotenic acid selective lesions of the dorsomedian thalamic nuclei induce a loss of sleep spindles [28].

As depicted in Fig. 4, we have also identified a topological alteration of sigma activity grouped by the SSO up-state. The more dramatic reduction has been observed in frontal electrodes, which detect neural activity modulated by thalamic volleys starting from anterior and dorsomedian thalamic nuclei. These nuclei are selectively degenerated in FFI [29,30]. Based on studies using in vivo and in vitro techniques, the dorsal thalamus is known to play a key role in the generation of spindles [28,31]. We cannot exclude the possibility that loss of sleep spindles in FFI could also be associated to the neurodegeneration of the nucleus reticularis [30]. It is difficult to precisely ascertain to what extent this nucleus is affected in FFI. Anatomical connections between the reticularis and the dorsomedian thalamic nucleus have been traced: in particular, this nucleus receives afferents from the oral pole of the reticular nucleus [32]. Therefore, degeneration of the dorsomedian thalamic nucleus could be responsible for the loss of spindling activity in FFI, either isolated or crowned on the depolarizing phase of SSO.

In our patient, these SSO changes seem to be related to specific structural and selective thalamic alterations or to its functional effect on the cingulate [33,34], as indicated by DTI and Spectroscopy MRI. These findings reproduced the results obtained with PET (18FDG-PET) in a group of FFI patients and a healthy carrier of the D178N–129M genotype [33,34]. Thus, the results obtained in this single case study, with relative speculations, also suggest that the study of SSO in presymptomatic FFI carriers can represent a useful tool for the early identification of preclinical thalamic dysfunctions.

5. Conclusions

Beyond the SSO changes, we confirmed deficits in delta and spindle activity of the FFI patient. All these results are in line with the well-known assumption that the thalamus plays a critical role in the generation of typical graphoelements of SWS, such as spindles (sigma activity), K complexes, and delta waves (delta activity). Herein we proved that a thalamic role is also fundamental for SSO behavior in humans.
Given the limited research available in humans and the limitation stemming from a single case study we can only speculate about the mechanisms mediating thalamic reticular nucleus and thalamo-cortical nuclei deficits in FFI underlying alterations of cortical SSO behavior. Recently, a review [11], mainly focused on electrophysiological recordings in animals, stated that “slow oscillation originates from the dynamic interplay of three cardinal oscillators: the synthaptically based cortical oscillator and two thalamic oscillators, the thalamocortical and NRT neurons.” Our data support this hypothesis of a bidirectional cortico-thalamic interplay in generating and modulating the SSO features.

Conflict of Interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2012.03.007.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.sleep.2012.03.007.

References

[27] Crunelli V, Cope DW, Hughes SW. Thalamic T-type Ca2+ channels and NREM sleep. Cell Calcium 2006;40:175–90.