Clinical Neurophysiology 125 (2014) 306–312

Contents lists available at SciVerse ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Loss of sleep spindle frequency deceleration in Obstructive Sleep Apnea

Diego Z. Carvalho [a,*], Günther J.L. Gerhardt [b], Guilherme Dellagustin [a], Emerson L. de Santa-Helena [c], Ney Lemke [d], Alan Z. Segal [e], Suzana V. Schönwald [a]

[a] Sleep Laboratory, Pulmonary Medicine Division, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brazil
[b] Department of Physics and Chemistry, Universidade de Caxias do Sul, Brazil
[c] Department of Physics, Universidade Federal de Sergipe, Brazil
[d] Department of Physics and Biophysics, Institute of Biosciences, Universidade Estadual Paulista Julio de Mesquita Filho, Brazil
[e] Department of Neurology and Neurosciences, Weill Cornell Medical College, NY, USA

ARTICLE INFO

Article history:
Accepted 5 July 2013
Available online 27 July 2013

Keywords:
Spindle
EEG
Chirp
OSA
Sleep
Matching pursuit

HIGHLIGHTS

- This study makes use of a novel approach to systematically address non-stationarity in sleep spindle oscillatory frequency: quantification of internal frequency modulation or chirp rate.
- Study suggests that Obstructive Sleep Apnea (OSA) not only slows down sleep spindle frequency, but also disrupts spindle internal frequency modulation.
- Loss of physiological sleep spindle deceleration may signal disruption of the thalamo-cortical loops involved in learning and memory.

ABSTRACT

Objective: Sleep spindles have been suggested as surrogates of thalamo-cortical activity. Internal frequency modulation within a spindle's time frame has been demonstrated in healthy subjects, showing that spindles tend to decelerate their frequency before termination. We investigated internal frequency modulation of slow and fast spindles according to Obstructive Sleep Apnea (OSA) severity and brain topography.
Methods: Seven non-OSA subjects and 21 patients with OSA contributed with 30 min of Non-REM sleep stage 2, subjected to a Matching pursuit procedure with Gabor chirplet functions for automatic detection of sleep spindles and quantification of sleep spindle internal frequency modulation (chirp rate).
Results: Moderate OSA patients showed an inferior percentage of slow spindles with deceleration when compared to Mild and Non-OSA groups in frontal and parietal regions. In parietal regions, the percentage of slow spindles with deceleration was negatively correlated with global apnea-hypopnea index ($r_s = -0.519$, $p = 0.005$).
Discussion: Loss of physiological sleep spindle deceleration may either represent a disruption of thalamo-cortical loops generating spindle oscillations or some compensatory mechanism, an interesting venue for future research in the context of cognitive dysfunction in OSA.
Significance: Quantification of internal frequency modulation (chirp rate) is proposed as a promising approach to advance description of sleep spindle dynamics in brain pathology.

1. Introduction

Sleep spindles have been suggested as neurophysiological markers of sleep homeostasis (Aeschbach et al., 1997; Wei et al., 1999; Himanen et al., 2002). They were found to play a role in important brain functions, such as memory consolidation and learning processes, with significant implications also in brain pathology (Schabus et al., 2004; Born et al., 2006; Ktonas et al., 2009; Urakami, 2009; Barakat et al., 2011; Fogel and Smith, 2011). Traditionally, they have been described through three parameters: voltage, duration and central frequency. Central frequency is usually considered stationary within a spindle's short time frame. Human sleep spindles are often divided into slow

* Corresponding author. Address: Sleep Laboratory, Pulmonary Medicine Division, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos 2350/sala 2050, Porto Alegre, RS 90035-003, Brazil. Tel.: +55 5191079669.
E-mail address: diego.carvalho@ufrgs.br (D.Z. Carvalho).

1388-2457/$36.00
http://dx.doi.org/10.1016/j.clinph.2013.07.005

and fast types. Slow spindles are more prevalent in frontal regions, whereas fast spindles occur more often in parietal locations (Jobert et al., 1992; Broughton and Hasan, 1995; Aeschbach et al., 1997; Werth et al., 1997; Zeitlhofer et al., 1997; Huupponen et al., 2008; Barakat et al., 2011).

Recently, however, internal (within-spindle) frequency variation (chirp) has been demonstrated in rats (Sitnikova et al., 2009) as well as in humans (Andrillon et al., 2011), and systematically measured in humans (Ktonas et al., 2009; Schönwald et al., 2011). The train of discharges that generates the sleep spindle can increase (“accelerate”), decrease (“decelerate”) or maintain a stable frequency over time. In a previous study, we have found that sleep spindles, as measured over central scalp regions of healthy volunteers, preferentially decelerate (Schönwald et al., 2011). In other words, negative chirping (deceleration) is more prevalent than positive chirping (acceleration). This possibly represents physiological modulatory mechanisms related to termination of spindle oscillations at the thalamic reticular level (Destexhe et al., 1994; Steriade, 2000; Destexhe and Sejnowski, 2009) and to its interplay with cortical projections (Bonjean et al., 2011; Caporro et al., 2012).

Sleep spindles have been proposed as sensitive electrophysiological markers of brain dysfunction in Obstructive Sleep Apnea (OSA) Schönwald et al., 2012. In OSA, repetitive episodes of complete or partial upper airway obstruction result in reduced blood oxygenation, sleep fragmentation and numerous consequences to health and quality of life, including memory impairment and increased accident and cardiovascular risk (AASM, 2005). Sleep spindles have been shown to become slower in OSA (Himanen et al., 2003; Ondze et al., 2003; Schönwald et al., 2012), especially in frontal but also in parietal regions. These findings corroborate neuropsychological and imaging studies showing diffuse, predominantly frontal cortical dysfunction in OSA (Naëgelé et al., 1995; Décary et al., 2000; Morrell et al., 2003; Mallat and Zhang, 2002; Alchanatis et al., 2004; O'Donoghue et al., 2005; Thomas et al., 2005).

Considering that sleep spindle oscillations represent thalamocortical activity, a subtle modulation of sleep spindle frequency characteristics, such as chirping, could bear relevant information in the context of neuropathophysiology in OSA. We hereby evaluate, for the first time, slow and fast sleep spindle chirping rate and negative chirp percentage in different brain regions, in patients with and without OSA.

2. Methods

2.1. Subjects and EEG recordings

This study was approved by the institutional review board and ethical committee. All participants provided informed written consent. The present sample has been used in a previous work on general spindle characteristics in OSA (Schönwald et al., 2012), whereby consecutive patients with clinically suspected OSA (AASM, 2005) were prospectively enrolled for polysomnography (PSG) at a university hospital-based sleep clinic between April 2007 and July 2009. On the basis of Apnea-Hypopnea Index (AHI) AASM, 2005, study groups were defined as Non-OSA (AHI < 5), Mild (AHI 5–14) and Moderate (AHI 15–29) OSA. Twenty-one patients with Mild (11) and Moderate (10) OSA and 7 Non-OSA subjects participated in the study. They had no significant inter-group differences in age, gender, body mass index, subjective sleepiness (Johns, 1991; Bertolazi et al., 2009), sleep architecture or mean Non-REM sleep O_2% saturation. Arousal index was higher in moderate OSA when compared to non-OSA subjects. Tricyclic antidepressants were the only medications present in patient regimens well-known to change sleep architecture; however, they were similarly expressed among groups (1 in Non-OSA, 2 in Mild and 2 in Moderate OSA). The other medications were non-psychotropic drugs for non-neurological co-morbidities. For additional details refer to (Schönwald et al., 2012).

Continuous recordings were performed on a 64-channel, 16 bit resolution digital system (Deltamed, Racia-Alvar, France). The recording protocol followed standard guidelines (Iber et al., 2007). Silver electrodes were placed over standard 10–20 IS EEG positions with initial impedances below 10 Kohms. The signal was acquired with 256 Hz sampling rate, filtered at 0.5–35 Hz and analyzed off-line using Coherence 3NT software version 4.4 (Deltamed, France). Sleep stages, arousals and respiratory events were visually scored by a trained rater in accordance with standard recommendations, applying obstructive hypopnea rule 4B (Iber et al., 2007).

2.2. EEG sample

Each subject contributed with 30 min of Non-REM sleep stage 2 (N2) from initial, middle and final (10 min each) portions of the PSG study, to better account for within-night variability. Study epochs were sequential, but not necessarily consecutive, as 30 s epochs containing excessive white noise or any arousals, apnea or hypopnea events were filtered out from the analysis. This measure, which excluded severe OSA subjects from the study, was proposed to minimize potential confounding effect caused by alpha activity in the automatic detection of slow spindles, since respiratory events have been shown to affect EEG frequency even in the absence of visually detected arousals (Dingli et al., 2002), and faster alpha and lower sigma activity (typical of slow spindles) lie in the same frequency range (11–13 Hz). Signal analysis was performed on left and right frontal (F3, F4), central (C3, C4) and parietal (P3, P4) regions. Spindles are known to peak over the midline (Jobert et al., 1992), so that Fz, Cz, and Pz electrodes might be considered better suited to capture spindle frequency behavior. However, the montage used for signal analysis aimed to approximate current AASM guidelines for sleep scoring (Iber et al., 2007) where F3/F4, C3/C4 and O1/O2 electrode positions are the standard recommendation. EEG channels were referenced to (A1 + A2)/2. After a preliminary analysis that did not show significant interhemispheric differences in spindle number, frequency, duration and chirping rate characteristics, results were pooled together for frontal ($F3 \cup F4$), central ($C3 \cup C4$) and parietal ($P3 \cup P4$) regions, allowing a reliable description of sleep spindle behavior over these regions while decreasing family-wise error rate resulting from multiple channel comparisons.

2.3. Automatic spindle detection and chirp quantification

In order to obtain satisfactory time vs. frequency resolution for the automatic detection of sleep spindles and chirp rate quantification, signal analysis was carried out with a Matching pursuit procedure (MP) with Gabor chirplet functions, as described in better detail in Schönwald et al. (2011). Briefly, MP is not a transform, it is an adaptive approximation procedure, whereby the original signal is decomposed into waveforms corresponding to a set of fundamental functions from a large dictionary, which can be represented as atoms in a time–frequency plane. If a signal structure does not correlate well with any particular dictionary function, decomposition will result into a number of non-relevant elements and information will be diluted. MP has been previously described in detail (Mallat and Zhang, 2002; Mallat, 1999) and shown to be suitable for sleep spindle representation (Durka et al., 2001; Durka et al., 2002; Schönwald et al., 2006). To allow chirp quantification, the MP procedure presented in http://eeg.pl (Durka et al., 2001)