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► To cite this version:

Nicolas Carpentier, Christian O'reilly, Julie Carrier, Gaétan Poirier, Jean Paquet, et al.. Spindles insufficiency in sleepwalkers' deep sleep. *Neurophysiologie Clinique = Clinical Neurophysiology*, 2020, 50, pp.339 - 343. <10.1016/j.neucli.2020.08.003>. <hal-03493458>

HAL Id: hal-03493458

<https://hal.science/hal-03493458v1>

Submitted on 21 Nov 2022

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ORIGINAL ARTICLE

Spindles insufficiency in sleepwalkers' deep sleep

Nicolas Carpentier^{1,2}, Christian O'Reilly¹, Julie Carrier^{1,3,4}, Gaétan Poirier¹, Jean Paquet¹, Steve A. Gibbs^{1,5}, Antonio Zadra^{1,4}, Alex Desautels^{1,5}

¹*Center for Advanced Research in Sleep Medicine, Hôpital du Sacré-Cœur, Montréal, Canada*

²*Center for Medicine and Research in Sleep, Department of Neurology, Centre Hospitalier Universitaire de Nancy, Nancy, France*

³*Research Center, Institut Universitaire de Gériatrie de Montréal, Montréal, Canada*

⁴*Department of Psychology, Université de Montréal, Montréal, Canada*

⁵*Department of Neurosciences, Université de Montréal, Montréal, Canada*

Running title: Spindles insufficiency in sleepwalkers

Corresponding author:

Dr. Nicolas Carpentier

Centre de Médecine et de Recherche sur le Sommeil (CMRS)

Service de Neurologie

Centre Hospitalier Régional et Universitaire de Nancy

29 avenue du Maréchal de Lattre de Tassigny

54035 Nancy, France

E-mail address: n.carpentier@chru-nancy.fr

Tel.: +33383852377

ABSTRACT

Objectives. Sleepwalkers have consistently shown N3 sleep discontinuity, especially after sleep deprivation. In healthy subjects, sleep spindles activity has been positively correlated to sleep stability. We aimed to compare spindles density during N3 sleep between sleepwalkers and healthy controls.

Methods. Two cohorts of 10 and 21 adult sleepwalkers respectively controlled with 10 and 18 healthy volunteers underwent one baseline and one recovery sleep recording after 38 hours (cohort 1) and 25 hours (cohort 2) of sleep deprivation. For the two recordings, we performed an automatic detection of spindles (11-16 Hz) from EEG signal during N3 sleep, restricted to the first sleep cycle and repeated for all cycles. For better interpretation of results, we extended the analysis to N2 sleep and we also measured the density of slow waves oscillation (SWO) (0.5-4Hz) during the same periods.

Results. Compared to controls, sleepwalkers showed significantly lower spindle densities during N3 sleep considering the first sleep cycle (both cohorts) or all cycles (cohort 1). SWO densities did not differ (cohort 1) or were lower (cohort 2) for sleepwalkers. The effect of sleep deprivation did not interact with the effect of group on spindles and SWO densities.

Conclusion. This work suggests that the instability of N3 sleep inherent to sleepwalkers may be underpinned by a specific alteration of spindles activity.

Keywords: sleep, slow-wave sleep, N3, spindles, sleepwalking, somnambulism, parasomnia

INTRODUCTION

Sleepwalking is currently conceptualized as the clinical manifestation of partial arousals mostly emerging from stage 3 sleep (N3) [17]. Sleepwalkers' N3 sleep is characterized by instability: more awakenings and higher awakening index during N3, lower slow-wave activity (SWA), as well as an increased Cyclic Alternating Pattern (CAP) rate [6]. Moreover, sleep deprivation usually increases the frequency of sleepwalking episodes [14].

In mice, the manipulation of SK2 channels enhanced spindles activity and improved sleep stability under noisy conditions [16]. In humans, spindles density during both N2 and N3 stages is correlated to sleep stability against noise exposure [4]. An impaired upkeep of sufficient spindles activity during the deepening of non-rapid-eye-movement (NREM) sleep may thus underlie the reported N3 discontinuity in sleepwalkers.

The spindles activity during N3 sleep has already been investigated in a controlled cohort of eleven individuals suffering from a NREM parasomnia (five from sleepwalking and six from night terrors) [5]. The spindles density during N3 sleep was lower in parasomniacs but without a reliably statistical significance across the sleep cycles. Authors explained these results by the increase of slow waves, correlating spindles and slow waves inversely. However, only the percentage of time occupied by the delta band during N3 sleep tended to be slightly increased in parasomniacs, whereas EEG power density during NREM sleep did not differ significantly.

We hypothesized that sleepwalkers have a N3 sleep instability linked to a spindles insufficiency. We compared spindles density during N3 sleep between sleepwalkers and healthy volunteers. To rightly interpret the results, we also analyzed N2 sleep and compared slow wave oscillation (SWO) densities between sleepwalkers and controls.

METHODS

Subjects

Sleepwalkers come from two cohorts that have been already studied by our group [8, 9]. The first cohort comprised 10 adult sleepwalkers (male = 3; median age = 23.5 years; min-max = 20-34 years) and 10 healthy volunteers (male = 3; median age = 25.5 years; min-max = 21-32 years). The second

cohort comprised 21 adult sleepwalkers (male = 10; median age = 27 years; min-max = 18-44 years) and 18 healthy volunteers (male = 8, median age = 26 years; min-max = 20-45 years). All participants were recruited from 1998 to 2000 (cohort 1) and from 1999 to 2007 (cohort 2) through the Sleep Clinic of the Center for Advanced Research in Sleep Medicine (Montréal, Canada). Diagnosis of sleepwalking was based on the International Classification of Sleep Disorders [1]. Subjects did not exhibit any comorbid sleep disorders, or psychiatric, nor neurological disease. The hospital's ethical committee approved the study protocol and all participants provided written consent prior to study.

Material

As previously detailed [8, 9], participants underwent two distinct PSG recordings: during a baseline night and during recovery sleep after 38 hours (cohort 1) or 25 hours (cohort 2) of sleep deprivation. Recordings were acquired using a 32-channel Grass© polygraph (digitized sampling rate: 128 Hz, Harmonie, Stellate Systems, Canada). PSG included nineteen EEG leads based on the 10/20 system (linked-ear reference), left and right electrooculograms, two submental electromyograms (EMG), left and right anterior tibialis EMG, one oro-nasal thermistor, one transcutaneous oximetry and a thoracic strain gauge. Sleep scoring was updated according to the AASM criteria revised in 2018. Mini-epoch containing artefacts due to EMG activity were automatically detected using Fast Fourier Transform (FFT) analysis and then rejected from further analysis. Signal processing was carried out on F3, C3, P3 and T3 derivations. Because most sleep abnormalities found in sleepwalkers are restricted to the first sleep cycle [14], we processed data during all cycles but also during the first sleep cycle alone.

Spindles detection

The spindles detector is an open-access software [11] proceeding as follows: we first applied a bandpass filtering from 11.0 to 16.0Hz using a linear phase Finite Impulse Response (FIR) filter (attenuation = -3.0dB, rectangular window, order = 511). A first forward and a second reverse filtering were performed to obtain a zero phase distortion and double the filter order. We calculated the root mean square (RMS) of the filtered signal using a contiguous 0.25-s time window. A spindle was identified when at least two consecutive RMS time-points (i.e. lasting 0.5s) exceeded the 95th

percentile of the all night-filtered signal RMS values. N2 and N3 spindles densities were defined as the number of spindles per minute of N2 and N3 respectively.

Detection of SWO

For SWO detection, we first applied a bandpass filtering from 0.5 to 4.0 Hz using a linear phase FIR filter (Hamming window; order = 1023; attenuation at cut-off frequencies = -3.0 dB). SWO were detected according to same previously published criteria [12] as follows: (1) negative peak < -40 μ V, (2) peak-to-peak amplitude > 75 μ V, (3) duration of negative deflection > 125 ms and < 1500 ms, and (4) duration of positive deflection < 1000 ms. The N2 and N3 SWO densities were defined as the number of SWO per minute of N2 and N3 stages respectively.

Statistical analyses

The standard polysomnographic variables were analysed using 2-way ANOVA with one independent factor (group) and one repeated measure (recording). To assess group effect on spindles and SWO densities, we performed mixed-models with one independent factor (group) and three repeated measures (stage, derivation, recording). Fixed effects for the group, the stage, the derivation and the recording and full factorial interactions were studied. The global significance of the different effects and interactions was tested for a 0.025 alpha cut-off, according to Bonferroni correction, because data were analysed twice: for all cycles, and for the first cycle alone. Statistical analyses were performed with IBM SPSS Statistics version 20 © software.

RESULTS

Standard sleep measures

For cohort 1, basic PSG measures have been previously reported [9]. In brief, sleepwalkers exhibited a significant higher number of awakenings from N3 (baseline: 3.7 ± 0.6 vs 1.0 ± 0.6 ; recovery sleep: 5.0 ± 1.1 vs 0.7 ± 1.2 , $p < 0.001$) and a significant increased awakening index from N3 (baseline: $2.8/h \pm 0.5$ vs $0.8/h \pm 0.5$, recovery sleep: $1.9/h \pm 0.4$ vs $0.2/h \pm 0.5$, $p < 0.001$) compared to controls. For cohort 2, basic PSG measures are reported in the table. Compared to controls, sleepwalkers showed a higher

number of awakenings from N2 (21.3 ± 1.7 vs 13.1 ± 1.9 , $p=0.003$) and higher awakening index in N2 sleep ($4.9/h \pm 0.4$ vs $3.1/h \pm 0.5$, $p=0.007$), only during baseline sleep. Fragmentation during N3 sleep was also higher for sleepwalkers, but not statistically significant.

Spindles density

In cohort 1, only the interaction between the effect of group and the effect of stage on spindles density was significant (Group x Stage interaction, all cycles: $p<0.001$; cycle 1: $p=0.001$). Sleepwalkers from cohort 1 exhibited significantly lower spindles density in N3 stage than controls did (all cycles: $1.4/min \pm 0.1$ vs $2.1/min \pm 0.1$, $p<0.001$; cycle 1: $1.6/min \pm 0.2$ vs $2.8/min \pm 0.2$, $p=0.001$) (Figure). Spindles density in N2 stage did not differ between sleepwalkers and controls (all cycles: $p=0.033$; cycle 1: $p=0.350$). In cohort 2, there was no significant factorial interaction with the effect of group. Sleepwalkers from cohort 2 showed lower spindles density during N2 and N3 stages than controls did, reaching statistical significance only for the first cycle (aggregated means: all cycles, $2.5/min \pm 0.1$ vs $2.6/min \pm 0.1$, $p=0.128$; cycle 1: $2.9/min \pm 0.1$ vs 3.4 ± 0.1 , $p=0.003$).

SWO density

Results have already been reported for subjects from cohort 1 [12]. SWO density in cohort 1 did not differ significantly between sleepwalkers and controls. In cohort 2, the effect of group interacted with the effect of the stage, but only significantly for all cycles ($p<0.001$) and not for the first cycle alone ($p=0.023$). Considering all cycles, sleepwalkers exhibited significant lower SWO density in N2 stages ($4.1/min \pm 0.1$ vs $5.9/min \pm 0.1$, $p<0.001$) and in N3 stages ($20.6/min \pm 0.6$ vs $26.8/min \pm 0.7$, $p<0.001$). Focusing on the first cycle alone, sleepwalkers also showed a significant lower SWO density in both N2 and N3 stages (aggregated means: $22.7/min \pm 0.8$ vs $29.3/min \pm 0.8$, $p<0.001$).

DISCUSSION

This work reveals that sleepwalkers exhibit a lower N3 spindles density than healthy controls. The same trend was replicated in the second cohort, reaching the statistical significance only for the first sleep cycle.

The working hypothesis was that sleep spindles might promote sleep stability by disengaging the cortex from sensorial inputs during NREM sleep, in particular from auditory stimuli [3, 16]. Especially since sleepwalkers exhibited an abnormal vulnerability to noise during N3 sleep as a higher mean percentage of auditory stimulations induces arousal responses in sleepwalkers when compared to healthy controls [13]. Environmental auditory stimuli insufficiently filtered by a decreased spindles activity in sleepwalkers may thus heighten N3 fragmentation, or even trigger somnambulistic episodes. However, Sela et al. demonstrated in rats the lack of significant difference in the electrical responses of the auditory cortex to noise between sleep epochs with spindles compared to those without spindles [15]. Spindles insufficiency alone appears to be unsatisfying to support the hypothesis of auditory filtering deficiency in sleepwalkers.

Whereas spindles densities were found to be lower, sleepwalkers also showed an unimpaired (cohort 1) or lower (cohort 2) SWO densities compared to controls. Slow oscillations and spindles are typically known to be inversely correlated along the sleep, meaning that during the deepening of sleep, SWO increase whereas spindles decrease [5]. These paradoxical results in appearance might be due to different timescales of analysis. While rhythms are studied in a time window of the second, Moelle and colleagues highlighted a different bi-directional relationship between spindles and slow waves. Thus, spindles occurrence increases on either side of the downstate of slow oscillations, and reciprocally the likelihood of subsequent slow oscillations increases with spindle activity [10]. The observed spindle insufficiency in sleepwalkers could reflect a decreased reciprocal drive between spindles and slow waves and participate in the inability for sleepwalkers to generate sustained slow waves. Additional studies focusing on temporal relationships between spindles and slow waves in sleepwalkers may shed light on this issue.

Spindles densities in sleepwalkers and controls were not influenced by sleep deprivation. Thus, spindles activity alone cannot account for why sleepwalkers experienced more clinical events after 38 hours of sleep deprivation as compared to baseline [9].

Our results support the hypothesis that spindles insufficiency during N3 sleep may have a critical role in N3 instability inherent to sleepwalkers. Further studies are needed to explore the link between spindles and slow waves in the emergence of partial arousals.

DISCLOSURE OF CONFLICTS OF INTEREST

AD received research grants from GSK, Novartis pharma, Jazz Pharma and Flamel Ireland Inc, as well as honoraria from speaking engagements from UCB and Paladin labs. The other authors have no conflict of interest.

FINANCIAL SUPPORT

This research was supported by the CIHR (grant # MOP 49515) to AZ and by the FRQ-S to AD. NC received graduate fellowship support from a partnership between Association des Chefs de Service Hospitaliers de Nancy and Groupe Pasteur Mutualité.

REFERENCES

- [1] American Academy of Sleep Medicine. The international classification of sleep disorders: diagnostic and coding manual. Chicago, Illinois: American Academy of Sleep Medicine; 2005.
- [2] Castelnovo A, Riedner BA, Smith RF, Tononi G, Boly M, Benca RM. Scalp and Source Power Topography in Sleepwalking and Sleep Terrors: A High-Density EEG Study. *Sleep* 2016;39:1815–25.
- [3] Dang-Vu TT, Bonjean M, Schabus M, Boly M, Darsaud A, Desseilles M, et al. Interplay between spontaneous and induced brain activity during human non-rapid eye movement sleep. *Proc Natl Acad Sci U S A* 2011;108:15438–43.
- [4] Dang-Vu TT, McKinney SM, Buxton OM, Solet JM, Ellenbogen JM. Spontaneous brain rhythms predict sleep stability in the face of noise. *Curr Biol* 2010;20:626–7.
- [5] Espa F, Ondze B, Deglise P, Billiard M, Besset A. Sleep architecture, slow wave activity, and sleep spindles in adult patients with sleepwalking and sleep terrors. *Clin Neurophysiol* 2000;111:929–39.
- [6] Guilleminault C, Kirisoglu C, da Rosa AC, Lopes C, Chan A. Sleepwalking, a disorder of NREM sleep instability. *Sleep Med* 2006;7:163–70.
- [7] Guilleminault C, Poyares D, Aftab FA, Palombini L, Abat F. Sleep and wakefulness in somnambulism: a spectral analysis study. *J Psychosom Res* 2001;51:411–6.
- [8] Jaar O, Pilon M, Carrier J, Montplaisir J, Zadra A. Analysis of slow-wave activity and slow-wave oscillations prior to somnambulism. *Sleep* 2010;33:1511–6.
- [9] Joncas S, Zadra A, Paquet J, Montplaisir J. The value of sleep deprivation as a diagnostic tool in adult sleepwalkers. *Neurology* 2002;58:936–40.
- [10] Mölle M, Bergmann TO, Marshall L, Born J. Fast and slow spindles during the sleep slow oscillation: disparate coalescence and engagement in memory processing. *Sleep* 2011;34:1411–21.
- [11] O'Reilly C. Spyndle: Un paquetage Python à code ouvert pour l'analyse des transitoires EEG, https://bitbucket.org/christian_oreilly/spyndle/; 2013.
- [12] Perrault R, Carrier J, Desautels A, Montplaisir J, Zadra A. Slow wave activity and slow oscillations in sleepwalkers and controls: effects of 38 h of sleep deprivation. *J Sleep Res* 2013;22:430–3.
- [13] Pilon M, Desautels A, Montplaisir J, Zadra A. Auditory arousal responses and thresholds during REM and NREM sleep of sleepwalkers and controls. *Sleep Med* 2012;13:490–5.

- [14] Pilon M, Montplaisir J, Zadra A. Precipitating factors of somnambulism: impact of sleep deprivation and forced arousals. *Neurology* 2008;70:2284–90.
- [15] Sela Y, Vyazovskiy VV, Cirelli C, Tononi G, Nir Y. Responses in Rat Core Auditory Cortex are Preserved during Sleep Spindle Oscillations. *Sleep* 2016;39:1069-82.
- [16] Wimmer RD, Astori S, Bond CT, Rovó Z, Chatton JY, Adelman JP, et al. Sustaining Sleep Spindles through Enhanced SK2-Channel Activity Consolidates Sleep and Elevates Arousal Threshold. *J Neurosci* 2012;32:13917.
- [17] Zadra A, Desautels A, Petit D, Montplaisir J. Somnambulism: clinical aspects and pathophysiological hypotheses. *Lancet Neurol* 2013;12:285–94.

FIGURE LEGEND. N2 and N3 spindles densities during all cycles (left column) and the first cycle alone (right column), in cohort 1 (upper row) and cohort 2 (lower row). Considering only the pertinent interactions with the effect of group, values are aggregated means from baseline and recovery sleep and from the four derivations. The effect of stage showed a significant interaction with the effect of group in cohort 1 but not in cohort 2. Estimated marginal means are presented with their respective standard error (bars). The asterisk indicates a significant effect of group on spindles densities. Nb/min: Number/minutes.

TABLE. Sleep variables from baseline and recovery sleep in sleepwalkers and controls of cohort 2.

	Baseline			Recovery sleep			p-values of F-tests		
	SW	CTRL	p	SW	CTRL	p	Recording	Group	Interactions
Sleep latency, min	13.3 (1.5)	8.2 (1.6)	-	4.8 (1.1)	2.4 (1.1)	-	<0.001	0.008	NS
Sleep period, min	486.4 (8.9)	463.6 (9.6)	NS	395.2 (16.5)	443.6 (17.8)	NS	<0.001	NS	0.005
Sleep efficacy, %	89.5 (1.8)	94.2 (1.9)	NS	88.5 (2.2)	88.3 (2.4)	NS	0.006	NS	0.046
Total sleep time, min	436.4 (12.5)	436.4 (13.5)	NS	349.7 (17.1)	391.8 (18.5)	NS	<0.001	NS	0.041
Stage N1, min	35.0 (2.2)	24.9 (2.4)	0.004	23.2 (2.4)	21.9 (2.6)	NS	<0.001	NS	0.027
Stage N2, min	272.1 (9.1)	253.0 (9.9)	-	206.0 (13.0)	214.0 (14.0)	-	<0.001	NS	NS
Stage N3, min	41.7 (5.4)	51.9 (5.8)	-	60.2 (6.4)	76.4 (7.0)	-	<0.001	NS	NS
REM, min	87.7 (6.0)	106.6 (6.5)	-	60.3 (6.3)	79.5 (6.8)	-	<0.001	0.017	NS
Awakenings in N2	21.3 (1.7)	13.1 (1.9)	0.003	11.2 (1.4)	16.2 (1.5)	0.023	0.026	NS	<0.001
Awakenings in N3	1.7 (0.5)	1.1 (0.5)	-	2.7 (0.6)	1.7 (0.6)	-	0.013	NS	NS
AI in N2, /h	4.9 (0.4)	3.1 (0.5)	0.007	3.6 (0.5)	4.7 (0.5)	NS	NS	NS	<0.001
AI in N3, /h	2.9 (0.7)	1.6 (0.7)	-	3.2 (0.6)	1.5 (0.7)	-	NS	NS	NS

AI: Awakening index. NS: Non significant. REM: Rapid-eye-movement stage. Estimations are presented with their respective standard error in parentheses. P-values for baseline and recovery sleep are related to post-hoc t-tests and presented in case of significant interactions between the effects of group and recording.

