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Original Article

Sleep spindle density in narcolepsy☆

Julie Anja Engelhard Christensen [a, *], Miki Nikolic [a], Mathias Hvidtfelt [a], Birgitte Rahbek Kornum [a, b], Poul Jennum [a]

[a] Danish Center for Sleep Medicine, Department of Clinical Neurophysiology, Rigshospitalet, Nordre Ringvej 57, DK-2600 Glostrup, Denmark
[b] Molecular Sleep Laboratory, Department of Clinical Biochemistry, Rigshospitalet, Nordre Ringvej 69, DK-2600 Glostrup, Denmark

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ABSTRACT

Background: Patients with narcolepsy type 1 (NT1) show alterations in sleep stage transitions, rapid-eye-movement (REM) and non-REM sleep due to the loss of hypocretinergic signaling. However, the sleep microstructure has not yet been evaluated in these patients. We aimed to evaluate whether the sleep spindle (SS) density is altered in patients with NT1 compared to controls and patients with narcolepsy type 2 (NT2).

Methods: All-night polysomnographic recordings from 28 NT1 patients, 19 NT2 patients, 20 controls (C) with narcolepsy-like symptoms, but with normal cerebrospinal fluid hypocretin levels and multiple sleep latency tests, and 18 healthy controls (HC) were included. Unspecified, slow, and fast SS were automatically detected, and SS densities were defined as number per minute and were computed across sleep stages and sleep cycles. The between-cycle trends of SS densities in N2 and NREM sleep were evaluated within and between groups.

Results: Between-group comparisons in sleep stages revealed no significant differences in any type of SS. Within-group analyses of the SS trends revealed significant decreasing trends for NT1, HC, and C between first and last sleep cycle. Between-group analyses of SS trends between first and last sleep cycle revealed that NT2 differ from NT1 patients in the unspecified SS density in NREM sleep, and from HC in the slow SS density in N2 sleep.

Conclusions: SS activity is preserved in NT1, suggesting that the ascending neurons to thalamic activation of SS are not significantly affected by the hypocretinergic system. NT2 patients show an abnormal pattern of SS distribution.

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1. Introduction

Narcolepsy is categorized by excessive daytime sleepiness (EDS), other clinical symptoms and electrophysiological abnormalities. Clinically, the diagnosis relies on the results of the Multiple Sleep Latency Test (MSLT), typically preceded by a polysomnography (PSG) [1]. Type 1 narcolepsy (NT1) also includes sudden loss of muscle tonus (cataplexy) and, if measured, low cerebrospinal fluid (csf) levels of hypocretin-1 (csf-hcrt-1). Hypocretin deficient narcolepsy (NT1) is due to loss of hypocretinergic neurons in the ventral hypothalamus, likely due to cellular autoimmunity [2–5]. Type 2 narcolepsy (NT2) also presents EDS, but not cataplexy and normal csf-hcrt-1 level. The background for NT2 is not yet fully understood.

Electrophysiological findings include rapid eye movement (REM) sleep abnormalities, instability of daytime and nocturnal sleep-wake and REM-nonREM (NREM) transitions [6–11], altered amount of rapid eye movements (EMs) in REM sleep [12–16] and NREM sleep [12], sleep stage dissociation in N1 sleep [17] and an altered power spectra profile in NREM sleep [15]. Hypocretinergic neurons are involved in wake-sleep regulation via projections to brain stem areas including the reticular activating system (RAS)

Abbreviations: AASM, American Academy of Sleep Medicine; NT1, Narcolepsy type 1; NT2, Narcolepsy type 2; CSF, Cerebrospinal fluid; EEG, electroencephalography; EMG, electromyography; MSLT, multiple sleep latency test; PSG, polysomnography; REM, rapid eye movement; SS, sleep spindles.

☆ Institution at which the work was performed: Danish Center for Sleep Medicine, Department of Clinical Neurophysiology, Rigshospitalet, Glostrup, Denmark.

* Corresponding author. Danish Center for Sleep Medicine, Department of Clinical Neurophysiology, Rigshospitalet, Nordre Ringvej 57, Entrance 5, 4th floor, DK-2600 Glostrup, Denmark.
E-mail address: julie.anja.engelhard.christensen@regionh.dk (J.A.E. Christensen).

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thus influencing wakefulness, REM-NREM and autonomic regulation [18,19]. Until now there has, however, been little interest in evaluating sleep microstructure as e.g. sleep spindle (SS) activity in narcolepsy, despite that this may potentially be involved in narcolepsy due to the alterations in sleep structure. We aim to investigate whether SS density (unspecified, slow, and fast) is altered in narcolepsy type 1 and 2 as compared to controls.

2. Materials and methods

2.1. Subjects and recordings

All patients were recruited from the Danish Center for Sleep Medicine, Department of Clinical Neurophysiology at Rigshospitalet in Glostrup, Denmark. A clinical sample of a 67 patients initially referred to the clinic suspected for central hypersomnias were included in this study. All patients were evaluated with PSG followed by a MSLT (PSG-MSLT) and a lumbar puncture determining the csf-hcrt-1 level. The patients were instructed to withdraw their medication (sodium oxybate, tricyclic antidepressants, selective serotonin re-uptake inhibitors (TCAs/SSRIs) and central stimulating medication (methylphenidat and modafinil) two weeks prior to the PSG-MSLT. The PSG-MSLT recordings were evaluated in accordance to the AASM criteria [20]. The quality of each PSG were individually evaluated manually, and low quality PSG were repeated when it could not be used for clinically diagnosing the patients. Recordings were excluded if the analyzed channels were disconnected or contaminated with too much artifacts. The analyzed PSGs are from the PSG-MSLT procedures, that were used to clinically set the diagnosis and were of high enough quality to be used for this study.

Twenty-eight of the 67 patients fulfilled the criteria for NT1 (at least two REM sleep periods and short sleep latency in the MSLT) and had low csf-hcrt-1 levels ($\leq$110 pg/mL), 20 of them fulfilled the criteria for NT2 (at least two REM sleep periods and short sleep latency in the MSLT) and had normal levels of csf-hcrt-1 (>200 pg/mL) and 19 of them did not fulfill the criteria for either type of narcolepsy. These were included as clinical controls (C). Furthermore, 18 healthy control subjects (HC) not formerly diagnosed with any sleep or neurological disorder and not referred to a clinic were included as an additional control group. The demographic and PSG data for the four evaluated groups is seen in Table 1.

2.2. Automatic detection procedure and definition of sleep cycles

SS were detected in the central EEG channel c3-a2 and the frontal EEG channel f3-a2 following a procedure inspired by Latreille et al. [21]. Three different detection routines were performed for each subject: 1) unspecified SS (frequency profile 11–15 Hz) and 2) fast SS (frequency profile 13–15 Hz) were identified in the central EEG channel, and 3) slow SS (frequency profile 11–13 Hz) were identified in the frontal EEG channel. It has previously been reported that SS, both unspecified and the fast ones are most pronounced in the central and parietal sites, whereof the slow SS are most pronounced frontally [22–24]. Prior to all three routines, EEG was filtered forward and reversed with two Butterworth filters – one notch filter for removal of power-line noise (50 Hz) and one band-pass filter (0.3–35 Hz). Additionally, EMG artifacts were automatically detected [25], and epochs with EMG artifacts were rejected. The SS detection procedures are all described by previously published data [21,24,26] and begins with a band-pass filtration (11.1–14.9 Hz for detection of unspecified SS, 11.1–12.9 Hz for detection of slow SS, and 13.1–14.9 Hz for detection of fast SS) of the pre-processed EEG, followed by a calculation of the root-mean-square (RMS) value for each 0.25-s window. Instead of a FIR filter, we used a fourth order Butterworth filter with cut-off (−3 dB) at the cutoff frequencies indicated. We used a threshold for the RMS values at the 95th percentile, and a SS was detected when at least two consecutive 0.25-s windows exceeded the threshold. The SS density was defined as number of SS per minute of sleep and was computed for all stages of NREM sleep (N1, N2, N3) and REM sleep between lights off and on.

To investigate the nocturnal distribution of SS activity, we computed the SS density (for the unspecified, slow SS, and fast SS) in N2 sleep and in all NREM sleep in the first four sleep cycles and the last sleep cycle. We investigated if the SS densities differed between the first and the last sleep cycle within each group. Additionally, we investigated if the density trends differed between groups across the first four sleep cycles and between the first and last sleep cycle. Comparing the first and last sleep cycle ensures inclusion of data from the first and last part of the night, and balance out the inter-subject variability in number of sleep cycles. We defined sleep cycles as periods starting from wake or NREM and ending with REM or wake. We defined a sleep cycle to end with a REM epoch when 20 min or more of other stages separated that epoch from the next REM epoch. The first sleep cycle was defined to start at lights off and the last sleep cycle was defined to end at lights on if no REM sleep was present. This definition has been used previously [16]. For subjects exhibiting a sleep onset to REM sleep period of $\leq$15 min (SOREMP) in the PSG, the end of the first sleep cycle was defined based on the second period of REM sleep to ensure N2 sleep, and to avoid a bias due to the presence of SOREMP.

Table 1
Demographic data for the evaluated groups. Statistical comparison of the fraction of men is done using chi-square tests. All other statistic comparisons are made using Kruskal–Wallis tests for testing if any of the four groups differ from the other groups. For CSF hypocretin-1 levels the Kruskal–Wallis test was testing for differences between the three groups where the hypocretin-1 levels were available. BMI: Body mass index; CSF: cerebrospinal fluid; REML: rapid eye movement (REM) sleep latency.

Parameter	Healthy controls	Clinical controls	Narcolepsy type 2	Narcolepsy type 1	P
Total count (Male/Female)	18	20	19	28	
Fraction of men	0.33	0.40	0.53	0.57	0.3704
Age [years, $\mu \pm \sigma$]	36.00 ± 10.51	35.30 ± 13.72	28.95 ± 11.36	34.39 ± 20.27	0.2962
BMI [kg/m^2, $\mu \pm \sigma$]	24.40 ± 5.77	23.65 ± 4.01	23.02 ± 3.50	26.36 ± 4.90	0.0484
CSF hypocretin-1 level	–	401.35 ± 58.81	363.79 ± 66.80	32.00 ± 25.40	1.77×10^{-11}
Sleep efficiency [%, $\mu \pm \sigma$]	91.70 ± 5.61	85.84 ± 14.40	93.77 ± 3.23	85.75 ± 9.99	0.0073
Time in bed [min, $\mu \pm \sigma$]	468.78 ± 42.08	479.53 ± 35.96	512.58 ± 139.43	467.05 ± 55.97	0.5968
REML [min, $\mu \pm \sigma$]	87.17 ± 50.75	90.05 ± 50.47	98.45 ± 114.47	61.54 ± 80.85	0.0280
W [%, $\mu \pm \sigma$]	8.30 ± 5.61	14.15 ± 14.38	6.18 ± 3.22	14.19 ± 10.02	0.0080
REM [%, $\mu \pm \sigma$]	20.34 ± 6.41	18.07 ± 7.10	20.35 ± 6.63	19.06 ± 6.96	0.6709
N1 [%, $\mu \pm \sigma$]	5.34 ± 2.74	5.72 ± 3.19	5.41 ± 3.02	10.78 ± 7.34	0.0080
N2 [%, $\mu \pm \sigma$]	46.73 ± 7.60	44.16 ± 10.75	47.23 ± 10.39	40.22 ± 10.97	0.1475
N3 [%, $\mu \pm \sigma$]	19.29 ± 9.14	17.88 ± 8.22	20.78 ± 7.90	15.69 ± 9.39	0.1516

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