Number of Tables: 4

Number of Figures: 2

Abstract word count: 228

Manuscript word count: 4070 (excluding abstract, tables, figures and references)

References: 31

Sleep spindles are altered in early- but not late-onset nightmare recallers

Claudia Picard-Deland,[1,2] Michelle Carr,[1,3] Tyna Paquette,[1] and Tore Nielsen[1,4]

[1]Center for Advanced Research in Sleep Medicine, CIUSSS-NÎM – Hôpital du Sacré-Coeur de Montréal

[2]Department of Neuroscience, Université de Montréal, Montréal, Québec, Canada

[3]Department of Psychology, Swansea University

[4]Department of Psychiatry, Université de Montréal, Montréal, Québec, Canada

Paper submitted to: Sleep Medicine

Correspondence and where work was performed:

Tore Nielsen

Dream & Nightmare Laboratory; Center for Advanced Research in Sleep Medicine

CIUSSS-NÎM – Hôpital du Sacré-Coeur de Montréal

5400 Gouin Blvd West,

Montreal, Quebec, Canada H4J 1C5

514-338-2222x3350

tore.nielsen@umontreal.ca

Abstract

Nightmares are a common sleep disorder, defined as highly disturbing mentation which usually awakens the individual from rapid eye movement (REM) sleep. While nightmares are mainly a REM sleep phenomenon, Picard-Deland et al. (in press) recently showed an association between nightmare recall and sleep spindles, which are a non-rapid eye movement (NREM) oscillatory feature; results pointed to fewer slow spindles and a higher oscillatory frequency for fast spindles among frequent nightmare recallers compared with controls. To test the suggestion that nightmares stem from changes to emotional neural circuits arising in early childhood (Nielsen, 2017), including early changes in sleep spindles (Scholle et al., 2007), we investigated if the spindle features of early-onset nightmare recallers, i.e., recalling nightmares since childhood (N=22), differed from those of late-onset nightmare recallers, i.e. since adolescence or adulthood (N=11), or from those of controls (N=23). A retrospective analysis of the sleep spindles of 56 participants who had undergone a polysomnographically-recorded morning nap revealed that Early starters uniquely exhibited lower slow spindle densities in 5 of 6 derivations (all $p<.045$) and higher fast spindle frequencies in all 6 derivations (all $p<.015$). These results add precision to previously reported findings for Nightmare recallers: spindle differences are shown to hold only for Early starters. The lifelong occurrence of nightmares may be closely tied to disruptions in the normal development of spindle generation processes occurring early in development.

Keywords: nightmares; sleep spindles; dreaming; brain maturation

Introduction

Nightmares often emerge during early childhood but in some cases persist through to adulthood. Such persistent, or lifelong, nightmare occurrence has been linked with relatively high levels of psychopathology and with a unique set of personality characteristics.[1-3] One study found that major life events preceded the onset of nightmare disorder in 60% of subjects and that nightmare recallers had more family discord than control subjects and relatively high levels of psychopathology.[1] While it remains unclear how childhood nightmares are triggered and evolve as a chronic condition, their frequent appearance during periods of growth and high brain plasticity suggests that neurophysiological changes related to the maturing brain may contribute to their chronicity.

Several studies converge in demonstrating that fear retention and fear extinction processes mature in a precocious fashion after adversity is experienced in the preschool years.[4,5] These early changes are associated with the development of mental illness in later adolescence and adulthood,[6] including with the development of nightmares.[7] The accelerated development and pathological consequences of these changes are well-documented for the waking state[8] but are still in the early phases of research for sleep stages.[9]

According to the Stress Acceleration Hypothesis of nightmares,[7] a key mechanism that increases risk for future nightmares is that adversity (e.g. neglect, separation, bullying, trauma) interferes with a critical period of brain plasticity that normally occurs around 3.5 years of age—a transition widely referred to as the *infantile amnesia boundary*. Adversity temporally advances this boundary leading, in the waking state, to earlier maturation of fear retention and extinction processes and to an unusually good memory for events that had occurred prior to age 4.[7] With respect to sleep, adversity may accelerate or alter the development of oscillatory brain mechanisms such as sleep spindles that normally show plastic changes near the infant amnesia boundary and are related to the consolidation of emotional memory. One large (n=120) cross-sectional study has shown rapid persistent increases in both %stage 2 (N2) sleep—when spindles most frequently occur—and N2 spindle density between ages 3 and 4.[10] Another has shown increased region- and frequency-specific coherence in the spindle

frequency range through ages 2 to 5, which is suggested to reflect the developmental change in sleep spindle length or density during that period.[11] On the other hand, a longitudinal study of 8 children showed a decrease in spindle frequency and no change in spindle density between ages 2-3 and 5.[12] This study also showed that spindle duration, amplitude and sigma power selective to the slow spindle range (11.25-13.00 Hz) all increased with age. Similarly, a small cross-sectional study of children aged 0-4 years revealed an increase in slow spindle density with age and a negative correlation between mean spindle frequency and age.[13] That these developmental changes were observed primarily for contrasts between subjects older vs. younger than 3.5 years[13] of age indicates that they did, in fact, emerge across the sensitive infantile amnesia boundary period. In sum, early acceleration or alteration of the maturation of either N2 sleep or N2 sleep spindles may lead to changes in characteristics that continue to be visible in adulthood. The precise direction and nature of these early changes still remains unclear and they have not yet been linked to nightmare pathology.

Nonetheless, we found some support for a connection between spindle characteristics and nightmare pathology among nightmare-prone adults.[14] Frequent nightmare recallers possessed fewer slow sleep spindles, higher oscillatory frequencies of fast spindles and marginally higher %N2 than did matched control subjects. Higher slow spindle densities were also associated with higher psychopathology symptoms and less positive emotion in the nightmare recallers' laboratory dreams.

In light of these findings, we retrospectively investigated if these spindle alterations would be more apparent among participants for whom nightmare pathology emerged early, as opposed to late, in development. We predicted that participants with early-onset nightmares (since childhood) would be more likely to exhibit the observed pattern of lower slow spindle densities, faster fast spindle frequencies and higher %N2 than would participants with relatively late-onset nightmares (since adolescence or adulthood).

Methods

Participants

This retrospective study is based on a sample of 63 participants (17 M; 46 F; mean age: 23.8±3.68 yrs) who were included in our previous study.[14] The sample consisted of two cohorts who completed very similar experimental protocols but differed in preferred language (see[14] for cohort details and comparison). Participants consisted of 38 who reported recalling at least 2 nightmares or bad dreams per week (Nightmare group: 29 F, 9 M, M=23.89±3.65 yrs) and 23 who recalled at most 1 nightmare or bad dream per month for the past five years (Control group: 16 F, 7 M; M=23.57±3.92 yrs); 2 participants had an intermediate frequency of nightmare recalls and were excluded from analysis. Participants were recruited using ads and posters placed at local universities, on the Laboratory's website and by word of mouth. A standard telephone interview confirmed inclusion criteria and screened for major sleep dysfunction, medical or psychiatric conditions (except for depression and anxiety which were assessed and controlled statistically); excessive intake of alcohol, recreational drugs, nicotine or caffeine; intake of medication affecting sleep, trauma or death in family or friends in the last 6 months and night shift or time-change in the last 3 months. Candidates were required to be 18-50 years of age, to declare themselves to be mentally and physically healthy, to report possessing a good ability to sleep during daytime naps and to remember 2 or more dreams per week on average (to reduce as much as possible group differences in basic dream recall). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Review Board of the CIUSSS-NIM – Hôpital du Sacré-Coeur de Montréal. Participants gave written informed consent and received $100 plus compensation for transport and breakfast expenses.

Within the Nightmare group, participants were separated into two subgroups depending on whether their nightmares started early in childhood (Early Starters) or later in adolescence or adulthood (Late Starters). As the precise age of nightmare onset was not initially

queried during screening, other available questions were used to infer whether participants were Early or Late Starters. Participants were considered Early Starters if they reported having frequent nightmares since childhood or since "always" (a common spontaneous response during screening), OR if they reported having had more than 4 nightmares/wk as a child (Nightmare History Questionnaire (NHQ)) AND if their first nightmare was before the age of 10 (NHQ). They were considered Late Starters if they reported having nightmares only since adolescence or later AND if their worst nightmares occurred after the age of 10 AND if they had less than 2.5 nightmares/week as a child. Following these criteria, 22 participants were considered Early starters (18 F, 4 M; M=23.27±3.27 yrs; 4 had <2.5 NM/wk), 11 were considered Late starters (8 F, 3 M; M=24.00±3.87 yrs) and 5 were excluded from these two groups; thus, in total 56 (42 F, 14 M; M=23.54±3.61) participants were included for group comparison analyses. All 38 participants included in the original Nightmare group were included for the correlational analyses.

Procedures

Participants completed one week of home sleep/dream logs before sleeping in the laboratory. Participants arrived at the lab at 8:00 am, completed the consent form and a series of questionnaires requiring approximately 30 minutes. At 9:00 am participants completed either an Associational Breadth Task (Cohort 1[15]) or a Verbal Fluency Task (Cohort 2[16-18]). A technician then attached a polysomnography montage and participants were given a 2-hour opportunity to nap between 10:00 am and 12:00 pm. They were awakened after 10-15 minutes of REM sleep, but before a maximum of 2 hours of sleep, had elapsed. Upon awakening, they immediately completed a dream report and responded to several questions about dream content. The post-sleep task was then administered—either the Associational Breadth Task or the Verbal Fluency Task—before removal of the electrodes by a technician. Participants then completed a second week of home sleep/dream logs.

Questionnaires

A questionnaire booklet was administered to assess participant demographics and characteristics, including frequency of recalling dreams, bad dreams (without awakening), and nightmares (with awakening), anxiety levels (State Trait Anxiety Inventory – STAI[19]), depression (Beck Depression Inventory-II – BDI-II[20]), nightmare distress (Nightmare Distress Questionnaire – NDQ[21]), nightmare history (Nightmare History Questionnaire: in-house questionnaire). See[14] for an exhaustive list of all the questionnaires that were administered.

Polysomnography (PSG)

Participants slept in bedrooms with continuous audio-visual surveillance and a 2-way intercom. They were recorded with an electrode montage of 6 standard 10-20 EEG channels (F3, F4, C3, C4, O1, O2) and 4 EOG channels (2 vertical, 2 horizontal) referenced to A1 (including A2 for re-referencing offline to A1+A2), 4 bipolar EMG channels (chin, corrugator, dominant arm, dominant leg) and 3 bipolar EKG channels. Biosignals were recorded using a Grass M15 Neurodata Acquisition Systems (-6dB filters with cut-offs at 0.30 and 100 Hz) and archived under the control of Harmonie 5.4 software (Natus Medical Inc., Montreal, Canada). PSG tracings were visually monitored during each nap and were later scored according to current American Academy of Sleep Medicine standards[22]; standard sleep variables (e.g. REM min, %REM, NREM min, %NREM, TST) were calculated by in-house software.

Spindle detection

Each spindle was detected automatically on 6 artifact-free derivations (F3, F4, C3, C4, O1, O2; re-referenced to A1+A2 offline) for N2 sleep (as in [14]). The C3, C4, F4 and O2 derivations were excluded once each from spindle detection due to the presence of artifacts for more than 80% of the nap in those channels (resulting N=55). Raw digitized signals were bandpass-filtered from 11 to 16 Hz using a linear phase finite impulse response (FIR) filter (-3 dB at 11.1 and 15.9 Hz). Forward and reverse filtering was performed to obtain zero phase distortion and double the filter order. The root mean square (RMS) of the filtered signal was then calculated with a 0.25-s time window and thresholded at the 95th percentile.[23] A spindle was identified when at

least two consecutive RMS time-points exceeded this threshold and the spindle duration met the criterion of 0.5 s. Spindle frequency was calculated as the number of zero-crossings divided by time in seconds. Spindle amplitude was measured as the maximum RMS peak-to-peak difference in voltage expressed in µV, and spindle duration was measured in seconds.

A cut-off of 12.8 Hz was used to distinguish slow (10.0-12.79 Hz) from fast (12.8-16.0 Hz) spindles (see[14] for spindle frequency distributions). Spindle densities were computed for each channel as the count of total (10.0-16.0 Hz), slow or fast spindles detected in N2, divided by the number of minutes of time passed in artifact-free N2 in the corresponding channel.

Statistical analyses

Demographics, psychopathology measures and nightmare onset measures were compared between Control and Early starter groups, between Control and Late starter groups and between Early and Late starter groups using Chi-square tests, Student T-tests or Welch T-tests when variances were not equal according to Levene's test. Mann-Whitney non-parametric tests were used when variables were not normally distributed according to the Shapiro-Wilk test of normality. Sleep measures and spindle characteristics were compared between Early Starters, Late Starters and Control groups using non-parametric Kruskal-Wallis tests since variables did not meet the assumption of normal distribution for ANOVAs. Two-tailed Spearman correlations were used to measure associations between spindle characteristics and nightmare onset measures. All analyses were completed using SPSS 24 for Windows. Topographical scalp maps were designed with the EEGLAB[24] toolbox in MATLAB 2017a. The maps are based on the 6 derivations recorded in this study (F3, F4, C3, C4, O1, O2) and color-coded values outside of these derivations are solely the result of 2-D interpolation and are thus displayed for illustrative purposes only. Our principal hypotheses were that Early Starters would differ from Late Starters and Controls by exhibiting lower slow spindle densities, higher fast spindle frequencies and higher %N2. Secondary hypotheses were that nightmare onset measures (age) would correlate positively with slow spindle densities and negatively with fast spindle frequencies. Although these were directional a priori hypotheses, two- rather than one-tailed Bonferroni corrected p-

values thresholded at α=0.05 were used to indicate statistical significance. For secondary, exploratory analyses a more conservative p-value of α=.01 was used.

Results

Demographics, psychopathology measures and nightmare onset

Late starters had both higher dream and nightmare recall frequencies than did the Early starters at the moment of the study (*U*(33)=63.5, p=.025 and *U*(33)=69.5, p=.044, respectively) (see Table 1). Late starters were higher on Nightmare Distress (*t*(31)=-2.490, p=.018) and marginally higher on state anxiety (p=.099). The two groups had their first nightmare at a similar age (p=0.328), but Early starters had their worst nightmares notably younger than did Late starters (10.61 vs 19.95 yrs; *U*(32)=24.5, p<.001) and had over four times more nightmares or bad dreams weekly during childhood (*U*(31)=22.0, p<.001). The two groups differed in reporting that a specific event triggered their nightmares: 70% (7 out of 10 who responded to this question) of Late starters reported that a specific event triggered the appearance of their frequent nightmares, while only 27.3% (6 out of 22) of Early starters identified such an event ($\square^2$=5.203, p=.023). Moreover, those events occurred at a significantly older age for Late starters (19.86±5.11 yrs) than for Early starters (6.75±2.09 yrs) (*t*(11)=-5.85, p<.001).

Table 1. *Demographic, psychopathology and nightmare onset measures for Control subjects, Early starters and Late starters.*

	Control (N=23)	**Early (N=22)**	**Late (N=11)**	**Early vs Ctl**		**Late vs Ctl**		**Early vs Late**	
	M±SD	M±SD	M±SD	p-value	test	p-value	test	p-value	test
Age	23.57±3.92	23.27±3.27	24.00±3.87	*.873*	*U*	*.763*	*T*	*.758*	*U*
Dreams/wk	4.41±2.33	4.93±2.66	6.46±2.12	*.476*	*U*	***.022***	*U*	***.025***	*U*
Bad dreams/wk	0.29±0.35	2.52±1.43	2.77±1.49	***<.0001***	*U*	***<.0001***	*U*	*.593*	*U*
Nightmares/wk	0±0	0.92±1.17	1.55±1.10	***<.0001***	*U*	***<.0001***	*U*	***.044***	*U*
STAI: state	30.13±6.59	30.45±5.92	37.18±11.82	*.863*	*T*	*.088*	*T-c*	*.099*	*T*
STAI: trait	36.14±10.44	38.50±10.10	42.64±12.80	*.449*	*T*	*.119*	*T*	*.307*	*T*
BDI	4.43±4.02	9.23±9.17	15.27±12.25	*.075*	*U*	***.002***	*U*	*.104*	*U*
Nightmare distress	25.57±5.58	31.91±7.95	39.27±8.14	***.004***	*T-c*	***<.0001***	*T*	***.018***	*T*
Age First Nightmare	6.64±3.63	5.43±2.04	7.9±5.38	*.212*	*U*	*.805*	*U*	*.328*	*U*

Age Worst Nightmares	10.20±4.31	10.61±5.84	19.95±4.11	*.733*	*U*	***<.001***	*U*	***<.001***	*U*
NM-BD/wk: Child	2.84±3.39	6.27±4.36	1.28±0.75	***.002***	*U*	*.105*	*U*	***<.001***	*U*
NM triggered by event	na	6/22 (27.3%)	7/10 (70%)	*na*		*na*		***.023***	$\square^2$
Age when event	na	6.75±2.09	19.86±5.11	*na*		*na*		***<.001***	*T*

STAI: State-Trait Anxiety Scale; BDI: Beck Depression Inventory-II; M: Mean; SD: Standard Deviation; NM: Nightmare; BD: Bad dream; Ctl: Control; Child: <12 yrs; NM triggered by event: proportion of participants who reported that a precise event triggered their nightmares. P-values of Mann-Whitney test (*U*), T test (*T*) and Chi-squared test ($\square^2$) are shown in bold when significant at p<.05. Welch adjustment of degrees of freedom is applied when variances are not equal according to Levene's test (T-c).

Table 2. *Sleep characteristics for Control subjects and Early and Late nightmare starters.*

	Control (N=23)	**Early (N=22)**	**Late (N=11)**	**Kruskal-Wallis test**	
	m±IQR	*m*±IQR	*m*±IQR	$\chi^2(2)$	p
Sleep latency	5.00±8.00	6.00±9.00	12.00±15.00	1.017	*0.601*
Latency to persistent sleep	5.50±21.50	10.25±19.38	18.00±28.00	1.413	*0.493*
N1 Latency	5.00±6.50	6.00±8.88	11.50±14.50	2.122	*0.346*
N2 Latency	10.00±11.00	13.75±16.00	20.50±17.00	5.883	*0.053*
N3 Latency	25.00±24.88	31.75±7.63	31.00±19.50	2.085	*0.353*
REM Latency	42.50±26.75	48.00±40.75	58.50±85.25	1.554	*0.460*
Sleep duration	72.50±35.50	65.25±24.88	85.00±33.50	4.075	*0.130*
Wake duration	11.00±25.00	17.25±22.75	22.50±25.50	1.725	*0.422*
Number of awakenings	6±8	5±4.5	6±7	1.106	*0.575*
Sleep efficiency (%)	87.58±18.72	80.09±23.89	74.25±21.70	1.897	*0.387*
N1 duration	14.00±10.50	13.00±10.75	12.00±12.50	0.305	*0.859*
N2 duration	29.50±24.00	32.50±10.38	29.50±14.50	0.515	*0.773*
N3 duration	15.00±20.50	2.50±11.75	10.00±27.00	3.357	*0.187*
NREM duration	61.00±38.00	53.00±13.88	63.00±30.00	4.046	*0.132*
REM duration	15.00±10.50	13.75±16.00	13.50±15.00	1.185	*0.553*
%Wake	12.41±18.72	19.91±23.89	25.74±21.70	1.856	*0.395*
%N1	13.55±20.77	18.92±17.10	26.35±23.34	0.456	*0.796*
%N2	43.69±22.36	51.59±11.77	44.53±32.14	3.646	*0.162*
%N3	15.67±22.76	5.67±18.27	13.33±18.96	2.084	*0.353*
%NREM	81.72±13.60	78.74±21.19	82.94±19.10	0.885	*0.642*
%REM	18.28±13.60	21.26±21.19	17.06±19.10	0.885	*0.642*

N1, N2, N3: Stages 1, 2, 3; *m*: Median; IQR: Interquartile range. Latencies and durations are in minutes. Bonferroni corrected p-values of Kruskal-Wallis tests and pairwise comparisons tests are shown in bold when p<.05.

Group differences in sleep and spindle measures

A priori hypotheses. Counter to our expectation, %N2 sleep was not different between groups (p=.162). Other sleep architecture measures also did not differentiate the groups (see Table 2). However, as predicted, slow spindle density was generally lower for Early than for Late starters, reaching significance in O2 (p=.015) and marginally so in C4 (p=.084; Figure 1A), and fast spindle frequency was greater for Early starters in C3, C4 and O2 (all p<.05) and tended to be greater in frontal regions (p<.1; Figure 1B). As shown in Figure 1 and Table 3, the

differences in slow spindle density and fast spindle frequency between Early and Late starters were not present between Late starters and the Control group (all p>.539).

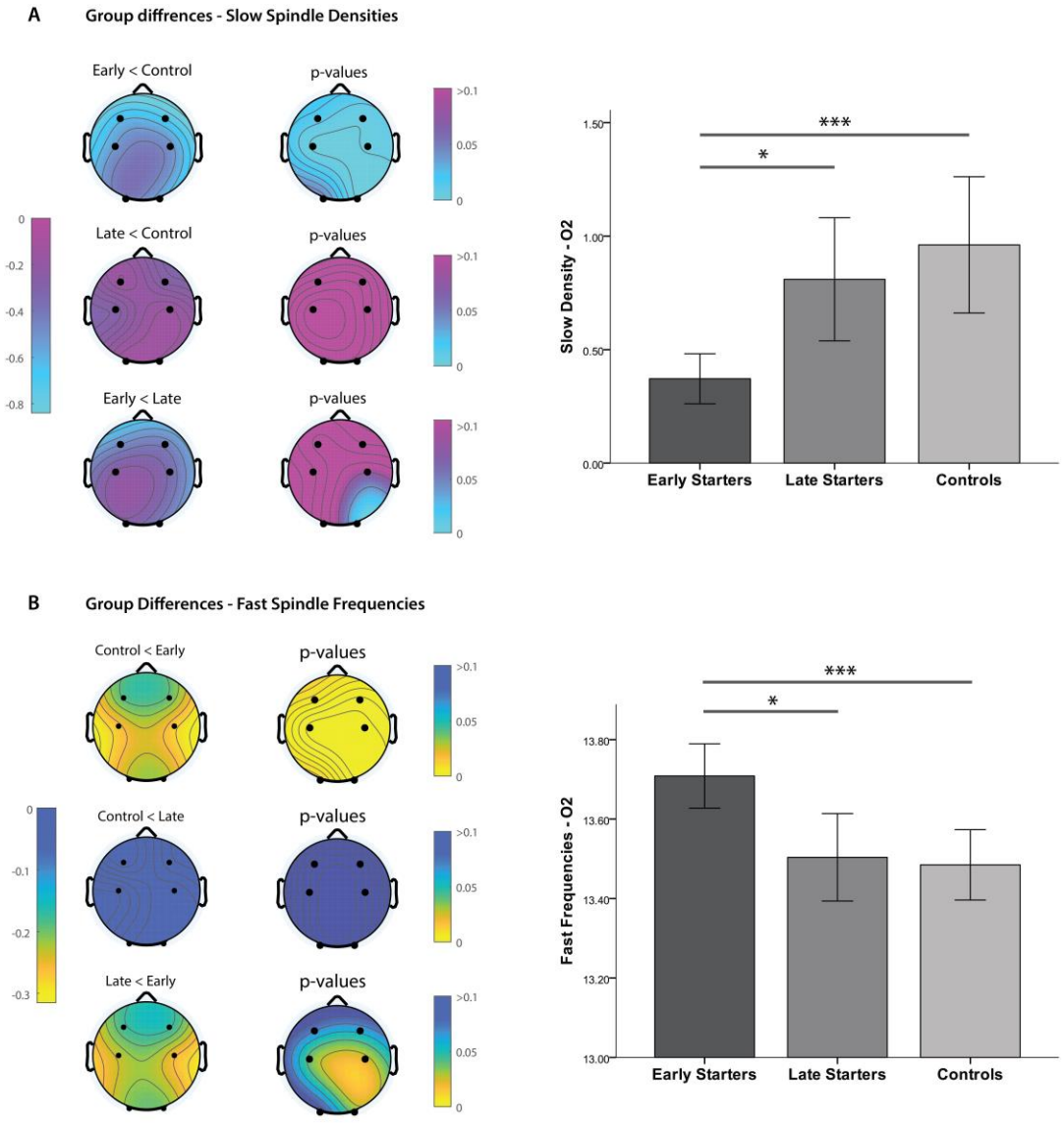

Figure 1. Interpolated scalp maps (left) to illustrate mean group differences and corresponding p-values for Kruskal-Wallis post-hoc tests on N2 slow spindle density (A) and fast spindle frequency (B) on six electrodes derivations (F3, F4, C3, C4, O1, O2). Bar graphs (right) show group differences on spindle measures in O2. Kruskal-Wallis post-hoc tests (see Table 3 for corresponding medians, IQR and statistical test results) compare distributions between Early and Late starters, between Early starters and Controls, and between Late starters and Controls. Bonferroni correction for multiple comparisons is applied to p-values. *p<.05, ***p<.001; two-tailed tests.

Secondary analyses. Fast spindle density did not differentiate groups (all p>.189; see Table 3), nor did total spindle density (slow+fast: 10-16 Hz). Total spindle (slow+fast) oscillatory frequency did differentiate groups in C3, C4, O1, O2 (all p<.007) and F3, F4 (all p<.05), being higher for Early than for Late starters in C4 (p=.01) and marginally higher in C3 and O2 (p<.05) (individual values not shown). Slow spindle oscillatory frequency was similar for both groups (all p>.322; see Table 3).

Table 3. *Median slow and fast spindle densities and frequencies for Control subjects, Early starters and Late starters.*

	Control (N=23)	**Early (N=22)**	**Late (N=11)**	**Kruskal-Wallis test**		**Early vs Ctl**	**Late vs Ctl**	**Early vs Late**
	m±IQR	*m*±IQR	*m*±IQR	$\chi^2(2)$	p	p	p	p
Slow spindle (<12.8 Hz)								
Density								
F3	1.232±1.221	0.901±0.761	1.301±0.883	8.74	***0.013***	***0.014***	*1.000*	*0.155*
F4	1.367±1.166	0.812±0.569	1.220±1.150	10.42	***0.005***	***0.004***	*1.000*	*0.203*
C3	0.657±0.616	0.296±0.223	0.657±0.715	14.91	***0.001***	***<.001***	*0.539*	*0.213*
C4	0.712±0.913	0.349±0.396	0.867±0.896	11.30	***0.004***	***0.004***	*1.000*	*0.084*
O1	0.556±0.499	0.294±0.333	0.657±0.859	6.94	***0.031***	***0.047***	*1.000*	*0.155*
O2	0.740±0.653	0.318±0.325	0.743±0.710	15.48	***<.001***	***0.001***	*1.000*	***0.015***
Oscillatory Frequency								
F3	12.290±0.145	12.307±0.190	12.323±0.091	0.17	*0.920*	-	-	-
F4	12.300±0.124	12.269±0.158	12.319±0.091	0.79	*0.672*	-	-	-
C3	12.320±0.260	12.316±0.229	12.356±0.247	1.65	*0.438*	-	-	-
C4	12.314±0.204	12.262±0.149	12.285±0.194	2.27	*0.322*	-	-	-
O1	12.243±0.255	12.230±0.157	12.242±0.413	0.43	*0.805*	-	-	-
O2	12.232±0.208	12.240±0.139	12.217±0.238	0.26	*0.879*	-	-	-
Fast spindle (≥12.8 Hz)								
Density								
F3	2.048±1.051	2.473±1.045	2.038±1.025	3.34	*0.189*	-	-	-
F4	2.004±0.912	2.427±0.914	2.416±1.310	3.17	*0.205*	-	-	-
C3	2.622±0.532	2.862±0.524	2.821±1.346	2.32	*0.314*	-	-	-
C4	2.499±0.621	2.671±0.817	2.742±1.736	0.27	*0.876*	-	-	-
O1	2.226±0.798	2.347±0.715	2.552±1.659	0.67	*0.717*	-	-	-
O2	2.032±0.772	2.323±0.836	2.486±1.831	2.01	*0.367*	-	-	-
Oscillatory Frequency								

F3	13.282±0.274	13.487±0.320	13.306±0.157	10.16	***0.006***	***0.008***	*1.000*	*0.083*
F4	13.300±0.247	13.478±0.391	13.309±0.161	11.96	***0.003***	***0.003***	*1.000*	*0.070*
C3	13.436±0.330	13.810±0.368	13.570±0.204	14.28	***0.001***	***0.001***	*1.000*	***0.044***
C4	13.452±0.358	13.760±0.369	13.520±0.287	15.54	***<.001***	***0.001***	*1.000*	***0.026***
O1	13.489±0.469	13.695±0.357	13.548±0.351	9.28	***0.010***	***0.012***	*1.000*	*0.112*
O2	13.438±0.318	13.670±0.285	13.500±0.285	12.67	***0.002***	***0.002***	*1.000*	***0.042***

m: Median; IQR: Interquartile range. Bonferroni corrected p-values of Kruskal-Wallis tests and pairwise comparisons tests) are shown in bold when p<.05.

Spindle associations with nightmare onset and early severity

To examine possible graded relationships between spindle measures and nightmare onset and early severity, we further investigated if total spindle density, total spindle frequency, slow spindle density and fast spindle frequency measures correlated with the age at which participants had their first nightmare (AgeFirstNM) and the age at which they had their worst nightmares (AgeWorstNM). Correlations are shown in Figure 2 (for total spindle density, slow spindle density and fast spindle frequency; 2A: AgeFirstNM, 2B: AgeWorstNM) and Table 4. While correlations with total spindle frequency never surpassed p<.05 (all p>.087), total spindle density correlated positively with AgeFirstNM, surpassing p<.05 for central and occipital derivations, and with AgeWorstNM only in occipital derivations. Slow spindle density also tended to correlate positively with both variables, but no coefficients surpassed p<.05. In contrast, correlations with fast spindle frequency tended to be negative for both age-of-onset measures, although they surpassed p<.05 only with AgeFirstNM in the F4 derivation. In sum, estimates of earlier nightmare onset were associated in a graded fashion with some key spindle measures , i.e., with lower total spindle density (central, occipital), lower slow spindle density (trends), and higher fast spindle frequencies (frontal). However, only correlations between AgeFirstNM and total spindle density at C3 and O1 would survive an error correction of .01.

Table 4. *Spearman coefficients and 2-tailed p-values for correlations between spindle measures and nightmare onset and early severity in Nightmare participants (N=38).*

	Spearman ρ		**p-value (2-sided)**	
Age of	First NM	Worst NM	First NM	Worst NM
Slow-Density				

F3	0.249	0.184	*0.143*	*0.283*
F4	0.298	0.227	*0.082*	*0.190*
C3	0.179	0.199	*0.303*	*0.251*
C4	0.180	0.163	*0.293*	*0.344*
O1	0.019	0.127	*0.915*	*0.461*
O2	0.141	0.317	*0.418*	*0.063*
Fast-Frequency				
F3	-0.232	-0.304	*0.173*	*0.072*
F4	-0.399†	-0.317	*0.018*	*0.064*
C3	-0.318	-0.251	*0.062*	*0.146*
C4	-0.258	-0.328	*0.128*	*0.051*
O1	-0.251	-0.187	*0.140*	*0.275*
O2	-0.219	-0.257	*0.205*	*0.136*
Total Density				
F3	0.318	0.118	*0.059*	*0.493*
F4	0.207	0.168	*0.234*	*0.335*
C3	**0.439***	0.136	***0.008***	*0.435*
C4	0.333†	0.312	*0.047*	*0.064*
O1	**0.453***	0.408†	***0.006***	*0.013*
O2	0.406†	0.421†	*0.015*	*0.012*
Total Frequency				
F3	-0.183	-0.163	*0.285*	*0.341*
F4	-0.205	-0.163	*0.238*	*0.348*
C3	-0.204	-0.247	*0.241*	*0.152*
C4	-0.212	-0.290	*0.216*	*0.087*
O1	-0.38	-0.162	*0.828*	*0.344*
O2	-0.116	-0.288	*0.507*	*0.093*

Spearman coefficients and p-values are shown in bold when p<.01. NM: Nightmare. †p<.05; *p<.01; ; two-tailed tests

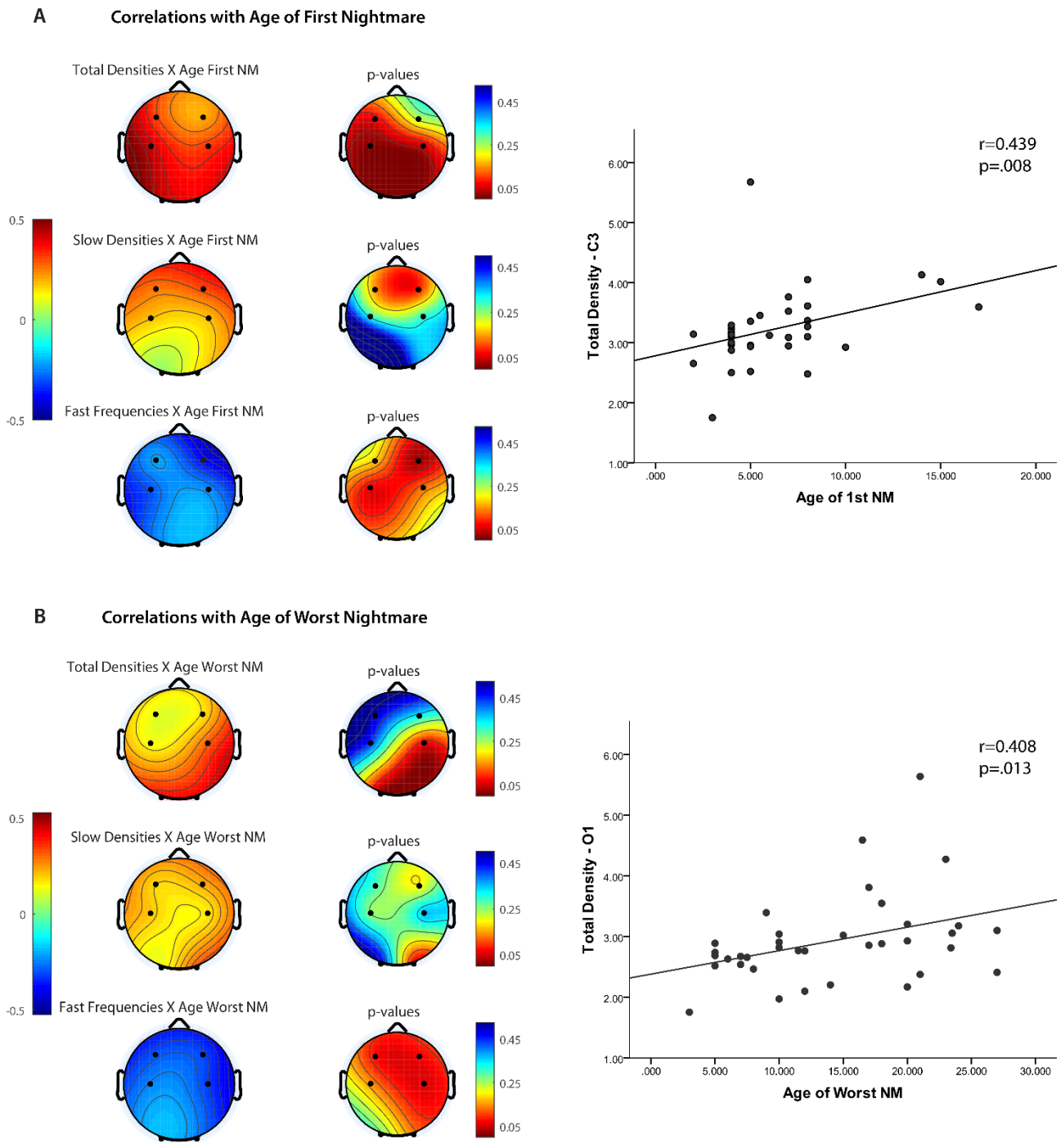

Figure 2. Interpolated scalp maps (left) illustrating Spearman correlations (rho and corresponding p-values) between nightmare onset – age of first nightmare (A) and age of worst nightmares (B) – and total spindle density, slow spindle density and fast spindle averaged frequency in Nightmare participants. Scatterplots (right) show Spearman correlations between

nightmare onset and total spindle density in C3 (A) and O2 (B). NM: Nightmare; two-tailed tests.

Discussion

Results support our expectations that individuals who started recalling nightmares earlier and later in life would differ in both slow spindle densities and fast spindle frequencies. Although expected differences in sleep architecture were absent, group differences in sleep spindle structure were striking. Specifically, Early starters had generally fewer slow spindles and a higher mean frequency of fast spindle oscillations than did Late starters. Comparisons with Control participants indicated that Late starters resembled Controls on these spindle measures, i.e., showed essentially normal spindle characteristics. These findings clarify previously reported findings[14] that NM recallers undifferentiated by age of onset differ from Controls in having fewer slow spindles and higher frequency fast spindles; these differences are here shown to hold only for Early starters.

This pattern of findings may mean that lifelong nightmares are more closely tied to early changes in basic spindle generation processes than are nightmares that start later in development. As reviewed in the Introduction, there is a normal progression of changes in sleep and spindle characteristics throughout development and some relatively abrupt changes occur around the early period of high brain plasticity (infantile amnesia boundary), e.g., increases in spindle density from age 2 to age 4-5.[10,13] Adversity-induced disturbances in sleep and spindle mechanisms at this early age may lead to permanent alterations that are detectable in adult early nightmare recallers. Thus, perturbations in the normal changes in N2 spindles between ages 3 and 4 may lead to the anomalies in spindle density and oscillatory frequency that we saw in early nightmare starters. It remains unclear, however, what the normal progression of spindle development is, with studies of different design and statistical power providing a variety of results[10-13] and the precise nature of the early perturbations (e.g., acceleration vs. other alterations) needs additional study.

That the median age of nightmare onset reported by the Early starters was around 4.5 years of age in this study is consistent with the assumption of the Stress Acceleration

Hypothesis of nightmares that adversity-induced developmental changes in sleep mechanisms contributing to nightmares occurs close to the infantile amnesia boundary at 3.5 years of age.[7] The self-reported earliest nightmares do not exactly correspond to the infantile amnesia boundary, but this may be due to a number of factors. First, as individuals grow older, they tend to postdate the actual ages of their autobiographical memories, particularly when these occurred early in life.[25] Second, there may be delays between the occurrence of early adversity and the first appearance of nightmares; genetic dispositions (e.g. Coolidge et al., 2010)[26], age of first adversity, accumulation in number and types of adversity, and individual resilience factors may all contribute to delays. Third, individuals' retrospective reporting of nightmares from this early age may be inherently unreliable.

Our present analyses do not allow for further examination of such factors; future testing of this hypothesis will require a more fine-grained breakdown of nightmare onset by age. Nonetheless, the present findings that altered spindle characteristics are specific to early nightmare starters are generally consistent with the hypothesis.

Moreover, the graded relationships between age of nightmare onset and spindle anomalies support the notion that the most serious spindle changes occur among individuals whose nightmares emerged at the youngest ages. Those correlations could also mean that a disruption in the development of sleep spindles in fact occurs more gradually over childhood and even adolescence, rather than exclusively in the infantile amnesia plasticity window. Longitudinal studies of spindle development over childhood and puberty have found increasing spindle frequency,[27,28] increasing high frequency sigma power (fast spindle range),[29] and decreasing frontal spindle power[27,29 13] with age. Much of this evidence is consistent with a maturational shift toward a pattern which resembles the spindle anomalies exhibited by our cohort of early nightmare starters and thus points to the possibility that lifelong nightmare recallers undergo an accelerated or altered spindle development during those years.

A further possibility raised by our results is that, because the mean age of worst nightmare recall was similar for the Early starters and the Control participants—a result in line with the Differential Susceptibility framework[3]— inherent plasticity factors manifesting early in life may render certain individuals more malleable or susceptible than others to environmental

influences. In the present case, while both Early starters and Control participants may similarly experience nightmares in response to early stressors, only the 'differentially-susceptible' Early starters exhibit neuroplastic changes in response to such experiences.

Adaptive mechanism among lifelong nightmare recallers?

Our previous results[14] showed that slow spindles are less numerous for frequent nightmare recallers than for control subjects, but are closely tied to affective symptoms (anxiety, depression, nightmare distress) and linked to some extent with negative dream content (dream fear, reduced dream positive-emotion). Based on these results, we speculated that a shift to higher spindle frequencies may in fact reflect an adaptive emotional regulation among nightmare recallers that could have developed through childhood during periods of high plasticity in thalamocortical networks.

Our current results support this possibility by showing that Late starters, who exhibit higher slow spindle densities than Early starters, also have significantly more distress related to nightmares, a higher nightmare recall frequency and marginally higher state anxiety. Exhibiting lower spindle frequencies or higher slow spindle densities may then indicate an absence of this adaptive change among the nightmare recallers and lead to higher emotional dysregulation. A similar observation was made by Kales et al.[1] who found that, within a cohort of adult nightmare sufferers, those who had an onset of nightmare disorder after age 18 scored higher on almost every clinical MMPI (Minnesota Multiphasic Personality Inventory) scale than did subjects who had an earlier age of nightmare onset.

It might also be that Late starters are generally closer—both in time and in remembrance—to an adversity that triggered the late appearance of their nightmares and may have suffered increased stress due both to the recent life stressor and the associated nightmare. When asked whether their nightmares started after a specific event and at what age, 70% of our Late starter cohort could identify a specific event, occurring on average around the age of 19 (19.86±5.11 yrs), while only 27% of the Early starter cohort could identify such an event, and at a significantly younger age when they did (6.75±2.09 yrs). While these results were expected, they may help explain why Late starters score higher on nightmare distress. Although

speculative, it is possible that Early starters benefit from having had more time to adapt to specific adverse events, allowing their nightmares to become less replicative and more symbolic over time. In a study of dreams and nightmares following trauma, Hartmann[30] observed that with time, as a traumatic experience resolves, dreams evolve from accurate replay of the event to images that deal with the experience's dominant emotions. It has been suggested that for post-traumatic patients, a shift in nightmare content from being recurrent or replicative of the traumatic event to being more symbolic of it is related to an improvement of their conditions.[31] Future research would benefit from a focus on how nightmare content evolves relative to adverse experiences and how it differentiates early- from late-onset nightmare recallers.

Conclusion and limitations

Whereas our previous results demonstrated that nightmare-prone individuals exhibit lower slow spindle densities and higher fast spindle frequencies than do controls, our present findings show that these changes in spindle properties hold only for early onset nightmare recallers. These findings are consistent with the suggestion that the chronicity of nightmares since childhood is tied to aberrations in the normal early development of spindle generation processes. However, it remains unclear if the spindle anomalies observed for lifelong nightmare recallers arise because of adversities occurring close to the infantile amnesia boundary, develop more gradually across childhood and adolescence, or reflect adaptive emotional regulation begun in early development.

A number of limiting factors in the present methods prevent us from investigating these possibilities further and suggest caution in generalizing the results. As the work is a retrospective analysis of responses which did not include a query about the precise age of nightmare onset, the criteria for determining group assignment were based on multiple questions and on individuals' own retrospective reporting of early nightmares. This increases the risk that estimates of nightmare onset were unreliable and limits further interpretation on whether the age of nightmare onset or the frequency of nightmares in childhood is more closely related to spindle changes. Moreover, statistical power is limited by our small sample of

Late starters (N=11). Replication of these findings with larger cohorts of frequent nightmare recallers and more precise questions about nightmare onset are clearly warranted.

Acknowledgments

Canadian Institutes of Health Research (CIHR: MOP-115125; Nielsen), Natural Sciences and Engineering Research Council of Canada grant (NSERC: RGPIN-31227-2012; Nielsen) and Scholarships from the Canada Graduate Scholarships-Master's Program (NSERC; Picard-Deland) and Fonds de Recherche du Québec – Santé Master's Training (FRQS; Picard-Deland).

Disclosure Statement

Financial Disclosure: none.

Non-financial Disclosure: none.

Abbreviations

REM: rapid eye movement

NREM: non-rapid eye movement

N1: stage 1

N2: stage 2

N3: stage 3

STAI: State-Trait Anxiety Scale

BDI: Beck Depression Inventory-II

M: Mean

SD: Standard Deviation

NM: Nightmare

BD: Bad dream

Ctl: Control

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