ORIGINAL ARTICLE

Traveling Slow Oscillations During Sleep: A Marker of Brain Connectivity in Childhood

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Slow oscillations, a defining characteristic of the nonrapid eye movement sleep electroencephalogram (EEG), proliferate across the scalp in highly reproducible patterns. In adults, the propagation of slow oscillations is a recognized fingerprint of brain connectivity and excitability. In this study, we (1) describe for the first time maturational features of sleep slow oscillation propagation in children (n = 23; 2–13 years) using high-density (hd) EEG and (2) examine associations between sleep slow oscillatory propagation characteristics (ie, distance, traveling speed, cortical involvement) and white matter myelin microstructure as measured with multicomponent Driven Equilibrium Single Pulse Observation of T1 and T2–magnetic resonance imaging (mcDESPOT-MRI). Results showed that with increasing age, slow oscillations propagated across longer distances (average growth of 0.2 cm per year; $R(21) = 0.50$, $p < .05$), while traveling speed and cortical involvement (ie, slow oscillation expanse) remained unchanged across childhood. Cortical involvement ($R(20) = 0.44$) and slow oscillation speed ($R(20) = -0.47$; both $p < .05$, corrected for age) were associated with myelin content in the superior longitudinal fascicle, the largest anterior-posterior, intrahemispheric white matter connectivity tract. Furthermore, slow oscillation distance was moderately associated with whole-brain ($R(21) = 0.46$, $p < .05$) and interhemispheric myelin content, the latter represented by callosal myelin water fraction ($R(21) = 0.54$, $p < .01$, uncorrected). Thus, we demonstrate age-related changes in slow oscillation propagation distance, as well as regional associations between brain activity during sleep and the anatomical connectivity of white matter microstructure. Our findings make an important contribution to knowledge of the brain connectome using a noninvasive and novel analytic approach. These data also have implications for understanding the emergence of neurodevelopmental disorders and the role of sleep in brain maturation trajectories.

Statement of Significance

Sleep is universally recognized as central to a variety of brain and behavioral processes; however, the involvement of sleep in the maturation of neuronal networks still remains unclear. Slow waves during sleep travel across the scalp in fingerprint-like patterns, suggesting that they are a marker of brain connectivity. We obtained high-density electroencephalogram during sleep and white matter myelin microstructure in a cross-sectional sample of 23 healthy children (2–13 years). Sleep slow waves traveled across longer distances with increasing age, and slow wave propagation was linked specifically to intrahemispheric brain myelin content. Thus, slow wave propagation may be a useful marker for normative and impaired brain connectivity.

Keywords: brain maturation, high-density EEG, mcDESPOT, traveling waves, white matter, myelination, neurodevelopment

INTRODUCTION

Understanding development of brain connectivity is increasingly recognized as a global health priority. Initiatives such as the US BRAIN and the Human Brain Project of the European Union have highlighted the critical need to integrate measures of functional brain connectivity to build maps of brain activity.[1] Among the methods for acquiring brain connectivity, high-density electroencephalography (hdEEG) during sleep has excellent time and space resolution and is ideal for noninvasively tracking brain dynamics in vulnerable populations (eg, pediatric).[2] Sleep EEG data also provide an unbiased, electrophysiological perspective on brain connectivity with minimal signal disturbance resulting from activity or motivation. Furthermore, quantification of specific functional components of white matter is now possible.[3] Multicomponent Driven Equilibrium Single Pulse Observation of T1 and T2 (mcDESPOT) overcomes the limitation of artifacts in noninvasive conventional magnetic resonance image (MRI) mapping (eg, image intensity variation),[4] which can degrade the volume segmentation into simple gray and white matter. We integrated these novel methods in preschool and school-age children by means of sleep hdEEG neuronal signatures and brain myelin content.

Slow oscillations are the most prominent feature of deep sleep and a marker of brain connectivity and excitability.[5,6] Mechanistically, deep sleep is characterized by synchronized fluctuations of membrane potentials between hyperpolarized and depolarized states with rhythmic (<1 Hz) alterations between neuronal silence and high neuronal activity displayed by large groups of cortical neurons.[7–9] These slow oscillations emerge from distinct locations on the scalp and propagate across the cortex in specific patterns.[5,6] Although knowledge about how slow oscillations originate and propagate across the cortex is increasing, the anatomical substrates of slow oscillations remain understudied, especially in childhood.

EEG spectral power in the slow wave activity frequency range (1–4.5 Hz) mirrors cortical gray matter,[10–12] and animal data support a link to white matter.[13] Myelin is a central component of the white matter microstructure, and its growth is a principal feature of brain maturation in early life[14] and a cornerstone of cognitive development.[15,16] Further, myelination is considered

a functional component of white matter, as this lipid layer surrounds axons, thus increasing the speed of action potential propagation. The myelin machinery may be associated with neuronal activity specific to sleep.[13,17] This concept is supported by links between conventionally measured white matter macrostructure and slow wave activity in adults (ie, maximal power).[18] Additionally, axial diffusivity measured with diffusion tensor imaging is linked to slow wave morphology (ie, rising slope) and thus, the synchronization of the slow oscillation.[19]

Brain myelin undergoes growth[14] in conjunction with a substantial rewiring of synaptic circuits and changes in behavior that together characterize sensitive developmental periods.[20] Because cognitive functions are linked to the wiring of brain areas, aberrations in connectivity may result in neurodevelopmental disorders with onset in childhood or early adolescence. For example, individuals with schizophrenia exhibit decreased connectivity in sensorimotor and cognitive networks,[21] attention disorders are associated with lagged or shallow connectivity maturation trajectories,[22] and alterations in functional connectivity of the amygdala are observed in early-childhood-onset depression.[23] Throughout childhood and early adolescence, the dynamics of the sleep EEG also exhibit rapid maturation[2,11] and mirror changes in brain function and anatomy.[10,12,24,25] Although the sleep EEG is increasingly acknowledged as a reliable, sensitive, as well as a noninvasive tool for monitoring brain maturation across time, detecting neuronal impairments,[26] and assessing connectivity,[27] its utility in childhood remains relatively limited.

In this study, we examined functional-anatomical brain connectivity by means of slow oscillation propagation and brain myelin content in children. One night of at-home sleep hdEEG was monitored in 23 healthy participants (2–13 years) who followed a stable sleep-wake schedule for at least 5 days before the overnight recording. Quantitative myelin content was obtained using mcDESPOT-MRI.[14] Based upon adult and animal data suggesting a corticocortical mediation of slow oscillations (as opposed to thalamic),[5,28,29] we hypothesized age-related changes in slow oscillation propagation characteristics and associations with intrahemispheric myelin content.

METHODS

Participants

Data from 23 healthy children were included in this study (2–13 years, 5.5 ± 2.6 years, M ± standard deviation [SD]; 14 males; for subsamples see the study by Kurth et al.[30] and Doucette et al.[31]). Screening involved a parent-completed telephone interview and questionnaires to ensure that participants were in excellent health and did not have any personal or family history of sleep disorders, psychosis, bipolar disorder, narcolepsy, chronic diseases or were currently using medications. Children were excluded for travel beyond two time zones within 2 months before the assessments, as well as for caffeine use, daily/nightly cosleeping, physical or developmental disabilities, chronic medical conditions, head injury, preterm or post-term delivery, or low birth weight. After explanation of the study procedures, written parental consent and child assent (when appropriate) were obtained.

Study Protocol

Sleep was stabilized according to habitual bedtimes and wake times during ≥ 5 days before assessments. Schedule adherence was ensured with wrist actigraphy and sleep diaries. One night of sleep was assessed at home using hdEEG, and mcDESPOT-MRI[14] was obtained in all participants within 2 weeks of the sleep assessment. The institutional review boards (Brown University; University of Colorado Boulder) approved study procedures, and the study protocol was in accordance with the declaration of Helsinki.

Sleep EEG

Scheduled at habitual bedtimes, one night of sleep was monitored in all participants using a 128-channel EEG amplifier (Electrical Geodesics Inc., Eugene, Oregon, United States). Signals were referenced to the vertex for direct visualization (NetStation, version 4.5.1). Electrode nets of different sizes were available and selected for each child based on individual head circumference. Nets were adjusted to mastoids and vertex, and electrodes were filled with gel electrolyte. Recordings were obtained with a 500 Hz (0.01–200 Hz) sampling rate and with impedances below 50 kΩ.

To perform sleep stage scoring, the signal was bandpass filtered (0.5–50 Hz) and down sampled to 128 Hz. Artifacts were semiautomatically rejected for 20-second segments if power in the 0.75–4.5 Hz or 20–30 Hz bands exceeded a threshold based on a moving average.[32] Poor quality channels were excluded from further processing. Sleep stages were scored for 20-second epochs according to standard criteria.[33] Visually scored sleep variables indicated that children's sleep quality was good (relatively short sleep latency, 24.4 ± 16.9 minutes; high sleep efficiency, 88.8 ± 4.7%), which is consistent with our previously published data of home-based hdEEG in preschool children.[2] For data quality assurance, slow wave activity analysis was performed (0.5–4.5 Hz, nonrapid eye movement, NREM, sleep). We found a posterior-to-anterior maturational shift in slow wave activity topography and a linear increase of slow wave activity across age (eg, $R(21) = 0.46$, $p < .05$ for Fz, Supplemental Figure S1), confirming previous reports on slow wave activity maturation.[2]

Slow Oscillation Detection and Propagation

Preprocessing for slow oscillation propagation parameters entailed the application of a 0.5–40.0 Hz bandpass filter, the rejection of artifact-containing channels (same detection criteria as described above) and the rereferencing to mastoids (NetStation). A previously published algorithm was used for slow oscillation detection[34] and adapted for pediatric and 128 channel use (previous studies were based on 256 EEG channels). In short, the third most negative sample at each time point (ie, 2.5% of the total channels) was selected to create a single negative reference envelope for detecting local and global slow waves. After bandpass filtering the reference channel as above (ie, 0.5–40 Hz) to center it on zero, negative half waves between 0.25 and 1 second were detected as reference slow waves. Only 20% of waves with the largest amplitudes (most negative) were selected for traveling analysis (Figure 1). We then determined for each electrode the timing of any local maxima that occurred within ±200 ms of the reference peak, that had an amplitude greater than 25% of the peak, and that were within 10 ms of at least one other detected channel peak for that slow wave to ensure that all detections were related to the same underlying slow oscillation. This somewhat strict criterion was chosen to target stereotypical waves, thus allowing the comparison across different ages.

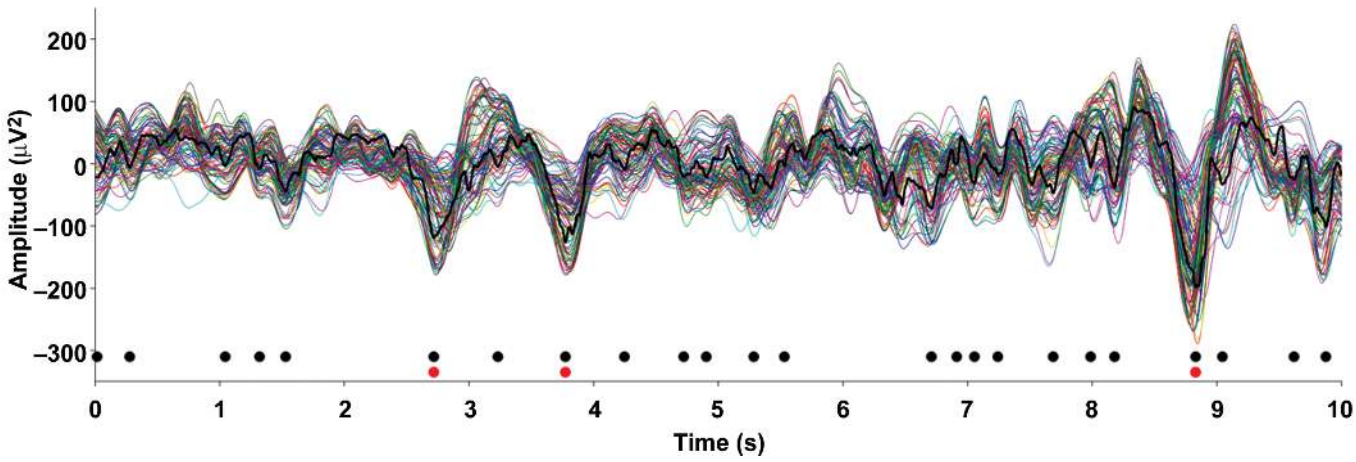

Figure 1—Wave detection. The EEG signal of all channels overlaid for a representative 10-second time segment in NREM sleep stage 3; reference wave is plotted in black. The detection algorithm identified the waves indicated with black dots. Waves surviving the criteria targeting stereotyped large-amplitude waves are indicated with red dots (see Methods).

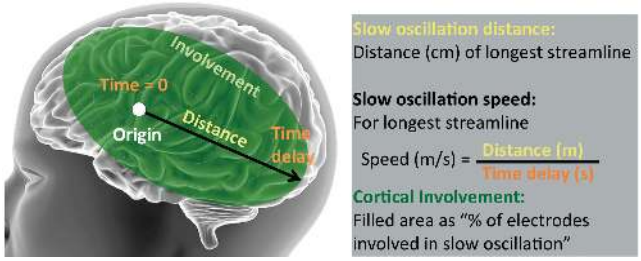

Figure 2—Slow oscillation propagation metrics. Slow oscillation parameters (see also Methods section and Figure 1).

The maxima that occurred most closely to the voltage peak were identified for each electrode. If two equidistant maxima were identified, the earliest maximum was chosen. Maxima were then sorted by time of occurrence to spatially track slow oscillation propagation (Figure 2). A three-dimensional gradient (two for direction, one for timing) was used to calculate streamlines for the propagation of each slow oscillation from every electrode. From the streamlines, we quantified the following measures: (1) slow oscillation distance of each slow oscillation as the length on the scalp of the longest streamline in cm; (2) slow oscillation speed by incorporating scalp distance in cm and the delay for the longest streamline, through which speed for each wave was assessed as the estimated distance between the start and end of longest streamline divided by time; and (3) cortical involvement as the percentage of electrodes in which the slow oscillation was detected relative to the total number of electrodes.

Myelin Water Fraction

White matter myelin content increases rapidly during childhood[14,35] and is recognized as an elementary feature of anatomical brain connectivity.[15] Myelin water fraction (MWF) is a quantitative imaging marker for myelin content, which has been used previously to track neurodevelopmental trajectories related to maturing cognition, language, and behavior.[35–37] We used mcDESPOT-MRI[3] to obtain individual MWF maps in all participants. mcDESPOT is a quantitative multicomponent relaxometry technique that is sensitive to the water trapped between the bilayers of the myelin sheath.[38] A comparison of different MRI parameters for quantitative white matter microstructure confirms good sensitivity of MWF to regional myelin content.[39] Two 3.0 Tesla Siemens Trio scanners (Brown University, University of Colorado Boulder), equipped with a 12-channel head radiofrequency (RF) array, were used during natural sleep[40] or while children were watching a movie. Assessments included age-adjusted scanning protocols with the application of a range of flip angles when acquiring spoiled gradient recalled echo (SPGR) and fully balanced steady-state free precession (bSSFP) images.[14] To correct for transmit magnetic field (B_1) inhomogeneities, inversion-prepared (IR-) SPGR data were acquired, while main magnetic field (B_0) inhomogeneities were corrected by acquiring two diverse phase-cycling patterns of bSSFP data.[41] Voxel volume ($1.8 \times 1.8 \times 1.8$ mm^3) was kept constant, and field of view and imaging matrix were adjusted for head size and age. To perform imaging during natural, nonsedated sleep, maximum imaging gradient slew rates and peak values were lowered to reduce acoustic noise. In addition, passive arrangements included a sound-insulating bore liner, MiniMuff ear pads, and sound-attenuating ear protectors.[40] Image processing included linear coregistration of each participant's raw SPGR, IR-SPGR, and bSSFP images to correct for intrascan motion and to eliminate nonbrain signal. B_0 and B_1 field maps were calibrated, and MWF maps were computed through the application of a three-pool tissue model using constrained fitting delivering stable estimates.[42] MWF maps were nonlinearly coregistered to a common standardized space for group analysis using symmetric diffeomorphic registration available with Advanced Normalization Tools (ANTs[43]). For this alignment, high flip angle T1-weighted SPGR images were used, which were acquired as part of mcDESPOT, and the transformation matrix was applied to individual MWF maps.[14] An initial rigid registration was performed between the participant's high flip angle SPGR images[35] and a template previously created from

T1-weighted data of children of equal age and approximately in the space of the Montreal Neurological Institute (MNI) template.[14] A participant-specific template was then created from these roughly aligned SPGR images (buildtemplateparallel.sh, ANTs package). Because the study-specific template was created from children of a similar age range, effects of brain size on the normalization are reduced. Such effects could be an issue when registering imaging data from a child to an adult template; yet, the population template in our sample minimized this limitation. 3D Gaussian kernel smoothing (4 mm full-width-at-half maximum) was applied within a white and gray matter mask. Mean MWF values were calculated for a restricted number of brain regions to reduce the likelihood of a type-I-error that may result from multiple comparisons in cross-sectional, modest-size samples. MWF tracts were identified based upon our previously published approach,[14] including the thresholding of the MNI white matter probability image provided within FSL at 180, registration of the transformation between the MNI template and a pediatric study template, and the transformation of masks to the study space. The John Hopkins University DT-MRI white matter atlas was used for referencing.[44] Brain regions included were whole brain and two core fiber tracts as defined in the study by Deoni et al.[14]: the corpus callosum, the primary interhemispheric connectional pathway and largest white matter structure in the brain and the superior longitudinal fascicle, representing the largest anterior-posterior, intrahemispheric white matter connection. MWF within the anatomical masks for fiber tracts was calculated as the average of left and right hemispheres. Individual MWF values measured from standard space have previously been shown to strongly agree with native space MWF values.[45]

Statistical Analyses

Kolmogorov-Smirnov tests were applied to examine whether data were normally distributed. Pearson correlations were performed between slow oscillation propagation measures, age, and MWF. Partial correlations were performed to control for effects of age, head size, or a combination of both. Head size was calculated as head circumference measured from the structural MR images. All results are reported at the significance threshold of $\alpha = 0.05$. To minimize the number of tests, across-night measures of slow oscillation parameters were incorporated. Outliers were statistically classified using Grubb's criteria (5% level), with slow oscillation measures (speed, distances, and cortical involvement) considered at the individual level (contrasting each data point relative to all slow oscillations in each participant). Signal analysis and statistics were performed with the software package MATLAB (Mathworks, Natick, Massachusetts, United States, version R2012a) and the statistics toolbox (Mathworks).

RESULTS

Sleep Slow Oscillations Propagate Across Longer Distances With Increasing Age

Across our sample, we detected 813–2697 of the defined large-amplitude slow oscillations during nighttime hdEEG sleep recordings (Figure 3), which corresponds to an average of 2.2–7.0 waves/minute NREM sleep in each participant. Medians of wave characteristics were calculated for each child. Average group slow oscillation speed was 3.0 ± 0.3 m/s (M ± SD), distance was 8.3 ± 1.0 cm, and cortical involvement was 12.9 ± 2.5%. Slow oscillation distance increased significantly with age, showing a growth of 0.2 cm per year [$R(21) = 0.50$, $p = .02$], which persisted after correcting for "head size" [$R(20) = 0.44$, $p = .04$; Figure 3, Table 1]. In contrast, slow oscillation speed and cortical involvement did not show an age-related change. Importantly, head size was not linearly associated with any of the three slow oscillation propagation parameters, even after controlling for age. As expected, however, age was associated with head size (Table 1).

Long-Distance Are Faster Than Short-Distance Slow Oscillations

We then examined the relationship among slow oscillation measures. Slow oscillation distance was correlated with cortical involvement [$R(21) = 0.55$, $p = .006$], which survived correction for age [partial correlation factor "age": $R(20) = 0.55$, $p = .008$] and head size [factor "head size" $R(20) = 0.53$, $p = .01$; partial correlation "age:" + "head size" $R(19) = 0.55$, $p = .009$]. Interestingly, a similar relationship was found between slow oscillation distance and speed, demonstrating that the longer the traveling path the faster the speed [$R(21) = 0.63$, $p = .001$; partial correlation, factor "age": $R(20) = 0.61$, $p = .003$; partial correlation, factor "head size": $R(20) = 0.62$, $p = .002$; partial correlation "age" + "head size": $R(19) = 0.61$, $p = .003$]. Because this relationship survived corrections (Table 1), we reject the possibility that in larger brains propagation speed is generally faster. In contrast, no correlation was found between speed and cortical involvement [$R(21) = 0.06$, $p = .80$; partial correlation, factor "age": $R(20) = 0.02$, $p = .90$; partial correlation, factor "head size": $R(20) = 0.04$, $p = .90$; partial correlation "age" + "head size": $R(19) = 0.02$, $p = .90$]. These results demonstrate that slow oscillation propagation matures primarily in a directional manner and that longer waves not only travel across wider brain regions but are also faster than shorter waves.

Weak Association Between Global Myelin Content and Slow Oscillation Propagation

We found a moderate positive association between whole-brain MWF and slow oscillation distance [$R(21) = 0.46$, $p = .03$]. After correcting for head size, this relationship showed a nonsignificant trend but disappeared after age correction (Table 2). In other words, age remained a stronger predictor of slow oscillation propagation distance over and above global myelin content. Further, neither slow oscillation speed nor cortical involvement was associated with whole-brain MWF (p = n.s.).

Associations Between Slow Oscillation Propagation and Myelin Content in the Superior Longitudinal Fascicle

We then examined the relationship between slow oscillations and myelin content by concentrating on two core interhemispheric and intrahemispheric fiber tracts—the corpus callosum and the superior longitudinal fascicle (Figures 4 and 5). With older age, myelin content in the corpus callosum increased [$R(21) = 0.85$, $p < .0001$], which was also the case in whole-brain myelin showing a similarly strong relationship [$R(21) = 0.71$, $p = .0002$]. Yet, no age-related change was observed for the superior

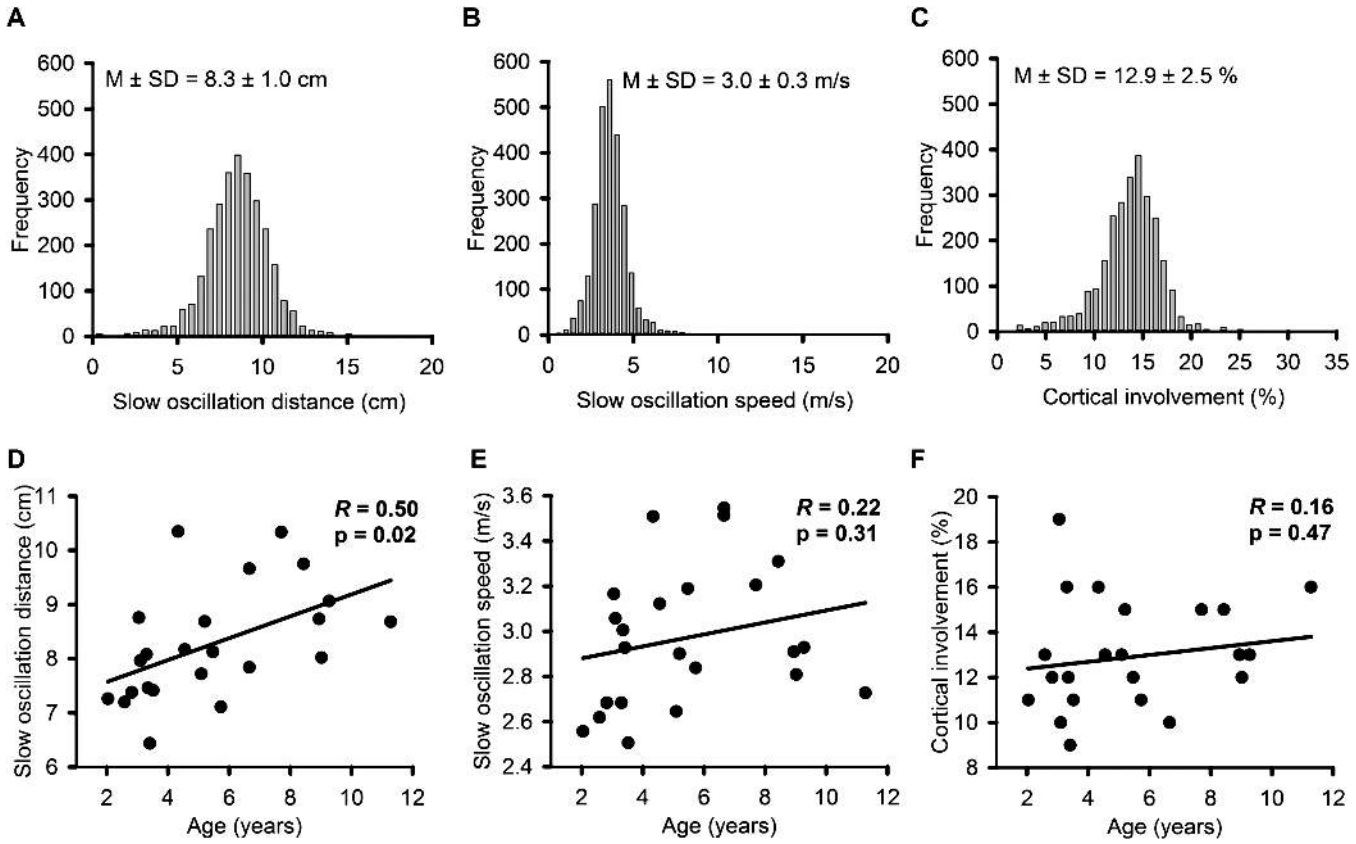

Figure 3—Slow oscillation propagation distance but not speed or cortical involvement increases with age. Histograms based on data distribution for each participant and then averaged across participants for (A) slow oscillation distance (skewness 0.2–0.5, kurtosis 2.3–2.5), (B) slow oscillation speed (skewness 1.4–2.2, kurtosis 4.8–8.8), and (C) cortical involvement (skewness 0.3–0.7, kurtosis 2.2–2.7). M ± SD indicate mean and standard deviation. Pearson correlations between age and (D) slow oscillation distance, (E) slow oscillation speed, and (F) cortical involvement; *df* = 21. Partial correlations reveal $R(20) = 0.44$, $p = .04$ for age versus slow oscillation distance, factor "head size", $R(20) = 0.19$, $p = .40$ for age versus slow oscillation speed, factor "head size", and $R(20) = 0.09$, $p = .71$ for age versus cortical involvement, factor "head size".

Table 1—Pearson Correlation Parameters for Traveling Slow Oscillations With Age or Head Size (*df* = 21); Partial Correlations Control for "Head Size" or "Age" (*df* = 20).

Correlation	Age (years)		Age (years), corrected for head size		Head size (cm)		Head size (cm), corrected for age	
	R	*p*	*R*	*p*	*R*	*p*	*R*	*p*
Head size	**0.52**	**.01**						
Slow oscillation distance	**0.50**	**.02**	**0.44**	**.04**	0.27	.21	0.01	.96
Slow oscillation speed	0.22	.31	0.19	.40	0.12	.60	<0.01	.99
Cortical involvement	0.16	.47	0.09	.71	0.17	.44	0.10	.65

Significant associations are given in bold. Associations of slow oscillation propagation with age and head size.

longitudinal fascicle (p = n.s.). Consistent with this observation, MWF in corpus callosum and whole brain significantly increased with head size [$R(21) = 0.44$, $p = .04$; $R(21) = 0.57$, $p = .006$], while again no such association was found for the superior longitudinal fascicle (p = n.s.).

When correcting for age, cortical involvement showed a positive association with intrahemispheric MWF in the superior longitudinal fascicle (Figure 4, Table 2). Further, slow oscillation speed showed a moderate negative association with MWF in the superior longitudinal fascicle (Figure 4, Table 2). This negative relationship between slow oscillation speed and the superior longitudinal fascicle was stable (ie, existing above and beyond effects of age and head size). We also found a moderate-to-large positive correlation between slow oscillation distance and interhemispheric MWF in the corpus callosum [$R(21) = 0.54$, $p = .009$], although subjection to first-order partial correlations

Table 2—Pearson Correlations (*df* = 21) Between Slow Oscillation Propagation Parameters and Myelin Water Fraction (MWF), Corrected for "Age" or "Head Size" With Partial Correlations (*df* = 20).

Correlation	Slow oscillation distance		Slow oscillation speed		Cortical involvement	
Whole brain	*R*	*p*	*R*	*p*	*R*	*p*
MWF	**0.46**	**.03**	−0.04	.86	0.31	.15
MWF, corrected for age	0.18	.42	−0.25	.28	0.30	.18
MWF, corrected for head size	*0.41*	*.07*	−0.09	.69	0.28	.22
Corpus callosum						
MWF	**0.54**	**.009**	0.25	.27	0.19	.39
MWF, corrected for age	0.29	.20	0.17	.45	0.13	.56
MWF, corrected for head size	**0.50**	**.02**	0.25	.28	0.14	.54
Superior longitudinal fascicle						
MWF	−0.04	.85	**−0.49**	**.02**	*0.40*	*.07*
MWF, corrected for age	0.05	.82	**−0.47**	**.03**	**0.44**	**<.05**
MWF, corrected for head size	−0.07	.77	**−0.50**	**.02**	*0.39*	*.08*

Significant associations are given in bold, relationships at trend level are italicized. The integration of age and head size as combined correction factors revealed similar results [partial correlation factors "age" and "head size": MWF whole brain, all p = n.s.; MWF corpus callosum, all p = n.s.; MWF superior longitudinal fascicle vs. slow oscillation speed $R(19) = -0.48$, $p = .03$; MWF superior longitudinal fascicle vs. cortical involvement $R(19) = 0.43$, $p = .06$].

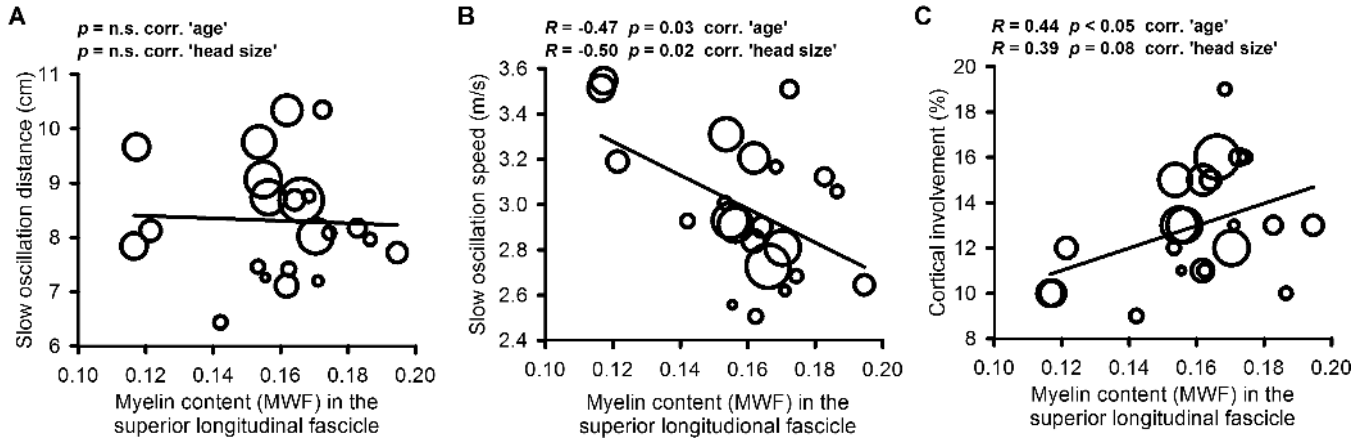

Figure 4—Relationship between slow oscillation propagation and myelin water fraction (MWF) in the superior longitudinal fascicle. (A) Slow oscillation distance, (B) slow oscillation speed, and (C) cortical involvement. Statistics indicate partial correlations with factor "age" and "head size" (*df* = 20). Correlations survive controlling in most cases (MWF in superior longitudinal fascicle vs. slow oscillation speed; MWF in superior longitudinal fascicle vs. cortical involvement). Circle size is age coded with larger circles signifying older participants.

indicated a confounding effect of age-related but not head size–related changes (Table 2).

In summary, we demonstrate three main findings relating slow oscillation parameters with brain myelin anatomy (Figure 5): first, cortical involvement is a positive indicator of intrahemispheric myelin as represented by MWF in the superior longitudinal fascicle; second, slow oscillation speed is a negative reflector of intrahemispheric myelin defined as MWF in the superior longitudinal fascicle; and third, slow oscillation distance is a positive reflector of whole-brain and inter-hemispheric myelin, the latter represented by callosal MWF.

DISCUSSION

This study examined age-related changes in traveling slow oscillation characteristics and their associations with the anatomical connectivity of white matter microstructure. Maturational changes of slow oscillation parameters and associations with intrahemispheric myelin content demonstrate that slow oscillation distance, speed, and cortical involvement reflect unique aspects of neuronal connectivity. Past knowledge on neuronal activity in children's sleep has been largely based on sleep architecture,[46] EEG power derived from a few electrodes[11,47,48] or topographical maps,[2] coherence,[27,49] and wave morphology.[24,50]

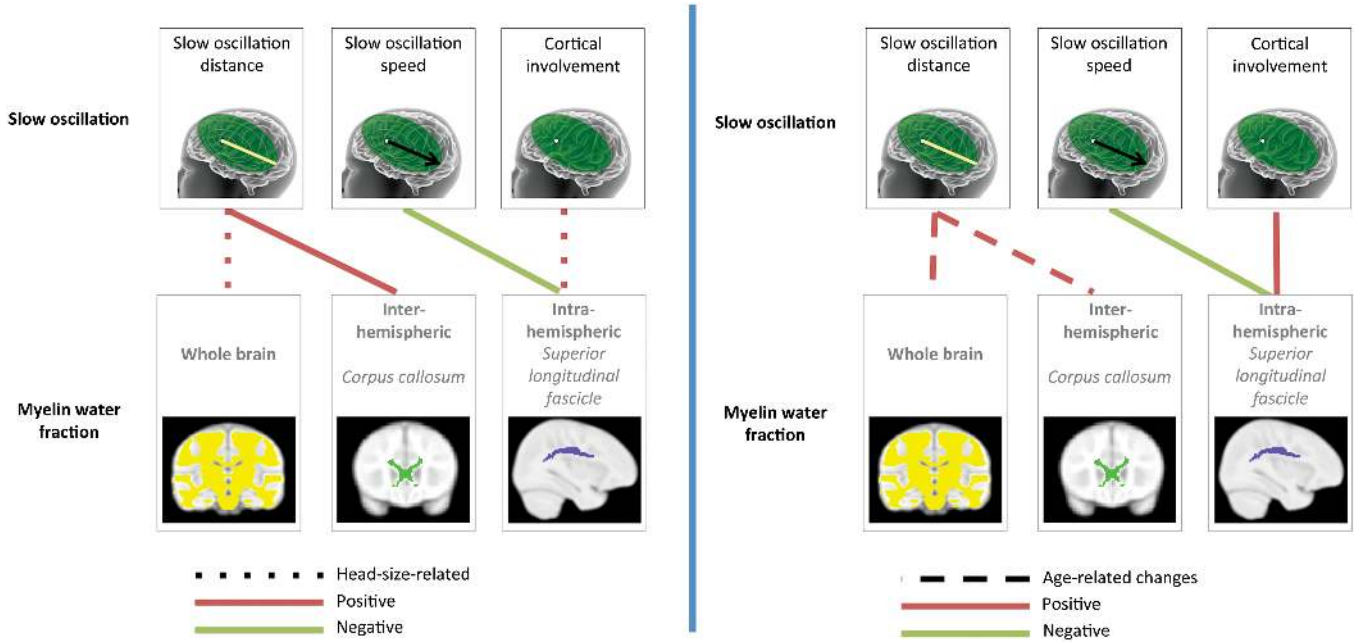

Figure 5—Summarized relationships between slow oscillation propagation and myelin water fraction (MWF). Connections coded for corrections (dotted lines when relationships did not survive controlling for "head size", left side, dashed line when relationships did not survive controlling for "age", right side) represent correlative associations between slow oscillation parameters (distance, speed, cortical involvement) and MWF (data are presented in Figures 3 and 4, and Tables 1 and 2). MWF was included for the whole brain, the superior longitudinal fascicle, which is the primary intrahemispheric fiber tract of anterior-posterior connectivity, and, respectively, the corpus callosum, representative of interhemispheric connectivity.

Our observations are based on a unique spatiotemporal domain by quantifying propagation patterns of sleep slow oscillations across childhood. We discuss our bidirectional findings in the context that sleep slow oscillations are useful to illuminate functional and anatomical underpinnings of brain connectivity. We believe these tools show strong promise for increasing understanding of normative and pathological maturation of neuronal connectivity. Because it has been proposed that slow oscillations may functionally mediate the benefits of sleep at the systems and cellular levels,[51–53] we discuss possible implications of our cross-sectional findings for neurodevelopment.

Sleep slow oscillations quantify spontaneous brain network activity. They travel along the major connectional network[5,6] and are initiated and maintained through cortical intrinsic currents and network interactions, as shown in vivo,[28,29,54] in vitro,[55] and in computo.[56,57] Here, we targeted stereotyped slow oscillations with a detection algorithm. This selection of specific waves together with no a priori restriction of scalp regions minimized potential maturational effects in EEG amplitude and frequency,[24] while allowing for topographical variation within the sample.[2] Numbers of slow oscillations were comparable to previous reports in children and young adolescents.[50] Detection frequency (ie, 2.2–7.0 slow oscillations per minute) and speed (3.0 ± 0.3 m/s) were within the range observed in adults.[5] Adults generally show a larger range in both slow oscillation speed (1.2–7.0 m/s reported by Massimini et al.[5]) and cortical involvement (a gradient from local to global involvement reported by Nir et al.[58]), which may have emerged from strictly targeting stereotyped large-amplitude oscillations. Slow oscillation distance (8.3 ± 1.0 cm) was slightly shorter as reported in adults.[5]

In developmental model systems, many neurophysiological parameters change longitudinally as a process of growth, which is consistent with our cross-sectional finding of an age-related increase in slow oscillation distance. Longer propagation distance indicates increased functional efficiency and/or connectivity possibly originating from the growth of long-range corticocortical structures.[59–61] Because cortical involvement did not depend on age, these findings together suggest a directional rather than a global growth in the spatial domain of cortical connectivity. Slow oscillation speed did not change with age, and importantly, none of the investigated slow oscillation propagation parameters were related to head size. Yet, because associations existed between head size and MWF, "age", as well as "head size" were included as control variables throughout the analysis. The associations among our variables were generally preserved after applying the separate and combined corrections for head size and age.

The second major finding was the association between slow oscillation propagation and myelin content: cortical involvement was positively associated with MWF in the superior longitudinal fascicle, while slow oscillation speed showed a negative association with the same MWF tract. Cortical involvement explained 15%–19% of variability in myelination of the superior longitudinal fascicle and slow oscillation speed explained 22%–25% of variability in this tract. In contrast, the links

between slow oscillation distance and MWF were driven by age or head size.

Regional associations were thus shown between cortical involvement and slow oscillation speed centered on intrahemispheric myelin content. Links have been reported between cortical anatomy with deep sleep EEG traits[10] and regional white matter with slow-wave activity in adults[18,19]—both supporting positive associations between white matter and cortical synchronization. Yet, comparing propagation parameters of slow oscillations and myelin-sensitive MRI with the previously published stationary metrics (ie, those that lack the spatial dimension) requires careful interpretation.

Slow oscillation speed is assumed to be an important measure for functional connectivity given the trait-like characteristic of the sleep EEG.[62,63] The negative association between slow oscillation speed and MWF in the superior longitudinal fascicle is somewhat surprising, as myelin is generally considered to increase the speed of action potential propagation along axons. A possible explanation is that slow oscillation speed is more closely related to cortical thickness or to cortical myelin content than to myelin content in the deep white matter. Interestingly, transmission speed in cortical gray matter is estimated to be about 1000 times slower compared to white matter, assuming ~0.2 mm/s for action potential across synapse and >25 m/s for electrical impulse propagation along nerve axons.[64] It is now clear that cortical thickness and MWF reflect distinct but complementary neurodevelopmental processes[65] that are reciprocally linked.[66] Indeed, in certain transitional developmental periods, gray and white matter progress in opposite directions: cortical thickness first increases, then declines,[67] while white matter grows[68] across the childhood and adolescence. One may thus speculate that maximal cortical thickness—which is attained in late childhood—is associated with minimal slow oscillation speed, such that propagation is slower in neuronal networks with many/dense synapses compared to networks with fewer/sparse synapses. Across the adolescent years, slow oscillation speed may then again change as a result from the thinning of cortical thickness (ie, reduction of synapses). The wide age range in our study and thus the presence of these processes likely explain the lack of overall age-related changes in slow oscillation speed.

Unlike intrahemispheric MWF, associations with whole-brain and interhemispheric MWF were largely driven by head size or age, demonstrating minimal relationships with slow oscillation propagation. As shown previously with the survival of slow oscillations of thalamectomy,[29] and their interruption with surgical/pharmacological disconnection of intracortical pathways,[28] is the propagation of slow oscillations only determined to a minor degree by interhemispheric myelin. Although driven by age, the relationship between callosal MWF and slow oscillation distance may imply the callosal promotion of slow oscillation travel across hemispheres, which would explain the increased propagation distance. Spatially segmenting MWF into smaller regions and integrating the direction of slow oscillation propagation may address certain discussed phenomena; yet, the analytical approach exceeds statistical possibilities in our cohort. Nevertheless, these data further support the conclusion that primarily intrahemispheric myelin content reflects functional connectivity measured as slow oscillation propagation.

Of note, no age-related MWF increase was found in the superior longitudinal fascicle, as would be expected from large-population data[14] [$R(21) = -0.20$, $p = .37$]. Large community samples show great interindividual variability in MWF, which could explicate the limited age correlations in our rather small but well controlled and healthy subpopulation of good sleepers. The above discussed lack of age-related changes in slow oscillation speed may also relate to this case.

Furthermore, we do not exclude the possibility that a sufficiently powered voxel-wise analysis approach may uncover additional changes with age and additional associations between sleep slow oscillation propagation patterns and brain myelin content. Results should be considered exploratory given the small sample size and low statistical power.

As expected, the slow oscillation measures were not independent, showing correlations between distance and cortical involvement, and between distance and speed. These findings indicate that longer waves not only spread across wider areas, but also propagate faster compared to shorter waves. Interestingly, speed was unrelated to cortical involvement, in contrast to the strong correlation with distance. Considering the possibility of a negative proportional relationship between slow oscillation speed and synaptic number/density, faster waves may generally traverse areas with relatively sparse synapses and propagate longer and wider paths. It remains to be investigated whether long-distance propagation is determined by myelin per se via isolating fiber bundles and allowing for unhindered action potential propagation. Two different types of slow waves have been observed for which two distinct synchronization processes have been hypothesized: a subcorticocortical, arousal system-dependent bottom-up process, and a corticocortical, horizontal synchronization process.[34] The dissociation between wave types in the current data may reveal insight into the maturation of two temporally and locally distinct synchronization networks.

Electrical brain activity alone can effectively induce functional changes, as measured in alterations of synaptic strength,[69,70] fiber architecture,[71–73] and coherent activity across brain networks.[74] Accordingly, it was proposed that slow oscillations promote the self-organization of spontaneously active neuronal networks. This process of modular organization may underlie the learning of novel experiences[75] or maintaining the connectional backbone.[6] Our findings support the concept that EEG features are promising markers for revealing details of underlying global[76] and local[77] sleep-dependent plasticity. Although earlier studies have proposed the possibility that myelin content underlies functional EEG connectivity maturation,[30,49] a consequential step is to examine whether neuronal activity associated with sleep slow oscillations directly or indirectly affects myelin growth. Our data demonstrate sleep-myelin links on a systemic, cross-sectional level with comprehensive neuroimaging tools. This approach may also provide important understanding of neuronal networks inherent to behavior development.

In conclusion, slow oscillations are a multidimensional neurophysiological marker through which maturational refinement processes of neuronal network anatomy can be targeted. Tracking slow oscillation propagation in childhood is a novel

approach for monitoring the maturation of the brain connectome and may facilitate understanding of sleep as a key factor in healthy and pathologic brain maturation trajectories.

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SUPPLEMENTARY MATERIAL

Supplementary Material is available at *SLEEP* online.

FUNDING

This work was supported by the Swiss National Science Foundation (grant numbers PBZHP3-138801, PBZHP3-147180 to SK; PP00A-114923 to RH), the National Institutes of Health (grant number R01-MH086566 to ML), Jacob's Foundation (to SD), the Clinical Research Priority Program Sleep and Health of the University of Zurich (to SK), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (T32 HD007489 to DD and P30 HD003352 to the Waisman Center) and seed funding from the Center for Innovation and Creativity at the University of Colorado Boulder (to ML).

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication April, 2017
Submitted in final revised form June, 2017
Accepted for publication July, 2017
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University of Colorado Boulder, Boulder, CO, USA and Brown University, Providence, RI, USA.

DISCLOSURE STATEMENT

SK, DD, JO, RH, OJ and ML have nothing to disclose. BR reports grants and nonfinancial support from Philips Healthcare, grants from Merck Pharmaceuticals, outside the submitted work. SD reports personal fees from Nestle Research, outside the submitted work.