

## EEG Sleep Slow-Wave Activity as a Mirror of Cortical Maturation

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**Deep (slow wave) sleep shows extensive maturational changes from childhood through adolescence, which is reflected in a decrease of sleep depth measured as the activity of electroencephalographic (EEG) slow waves. This decrease in sleep depth is paralleled by massive synaptic remodeling during adolescence as observed in anatomical studies, which supports the notion that adolescence represents a sensitive period for cortical maturation. To assess the relationship between slow-wave activity (SWA) and cortical maturation, we acquired sleep EEG and magnetic resonance imaging data in children and adolescents between 8 and 19 years. We observed a tight relationship between sleep SWA and a variety of indexes of cortical maturation derived from magnetic resonance (MR) images. Specifically, gray matter volumes in regions correlating positively with the activity of slow waves largely overlapped with brain areas exhibiting an age-dependent decrease in gray matter. The positive relationship between SWA and cortical gray matter was present also for power in other frequency ranges (theta, alpha, sigma, and beta) and other vigilance states (theta during rapid eye movement sleep). Our findings indicate a strong relationship between sleep EEG activity and cortical maturation. We propose that in particular, sleep SWA represents a good marker for structural changes in neuronal networks reflecting cortical maturation during adolescence.**

**Keywords:** adolescence, cortical maturation, EEG, slow-wave sleep, structural MRI

### Introduction

Sleep is one of the oldest and most tantalizing enigmas of neuroscience. While sleep functions are still largely unknown, its importance is highlighted by its ubiquity in the animal kingdom (Tobler 2005; Allada and Siegel 2008; Cirelli 2009). When we sleep, we go through a characteristic sequence of nonrapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. During the deep part of NREM sleep, also called slow-wave sleep, cortical neurons exhibit slow oscillations (Steriade et al. 1993). They are characterized by an alternation of depolarized upstates and hyperpolarized downstates, which can be measured as slow waves in the electroencephalogram (EEG). The activity of these slow waves (i.e., slow-wave activity, SWA, EEG power between 1 and 4.5 Hz) is a well-established electrophysiological measure for sleep depth (in terms of the difficulty to awaken an individual; Borbély and Achermann 2005). Moreover, we know that sleep slow waves are regulated homeostatically: SWA increases in proportion to the time spent awake and decreases during sleep (Borbély and Achermann 2005). At a mechanistic level, sleep SWA reflects synaptic number and efficacy because more or stronger synapses favor neuronal synchronization (Esser et al. 2007; Vyazovskiy et al. 2009).

Intriguingly, SWA varies strongly with age: in the first years of life, SWA increases with a maximum before puberty and then decreases during adolescence into adulthood, as reported recently using longitudinal data (Campbell and Feinberg 2009) and earlier with cross-sectional data (Jenni and Carskadon 2004). Interestingly, a similar time course has been demonstrated for brain energy consumption (Chugani et al. 1987). Furthermore, synaptic density in the prefrontal cortex exhibits the same pattern of increase during childhood and subsequent decrease across adolescence (Huttenlocher and Dabholkar 1997). Thus, as demonstrated in many species, including man, rhesus monkey, cat, and mice, the maturation of neural circuits in the cerebral cortex is characterized by an initial overproduction of synapses, followed by a net elimination or pruning during the pre-adult years (reviewed in Rakic et al. 1994). The process of elimination or stabilization seems to be steered by a complex interaction between signal molecules and neuronal activity (Innocenti and Price 2005). Interestingly, the maturation of dendritic trees and the sizes of the pyramidal cells in the dorsolateral prefrontal cortex also show an inverted u-shaped curve, in a layer-specific pattern with a later peak in layer III than in layer V (Petjanek et al. 2008). The extent of this pruning process is exemplified by an electron microscopy study in macaque monkeys showing an estimated loss of 5000 synapses per second during the pre-adult years (Bourgeois and Rakic 1993). This massive synaptic remodeling during adolescence supports the notion that adolescence represents a sensitive period for cortical maturation.

While synaptic density can only be studied postmortem in humans, changes in gray matter volume may be tracked in vivo with magnetic resonance imaging (MRI). Studies have reported volume increases and subsequent decreases across wide parts of the cortex, with regionally specific peak times: lower order somatosensory or visual cortices peak earlier than higher order association cortices (Giedd et al. 1999; Gogtay et al. 2004; Elston et al. 2009; Tamnes et al. 2010). In summary, the age-related changes in sleep SWA show the same pattern as the metabolic and synaptic changes seen during adolescence. Thus, this observation may imply that SWA is a marker of cortical maturation during the sensitive period of adolescence, as already pointed out by Campbell and Feinberg (2009).

We therefore investigated the relationship between sleep SWA and anatomical markers of cortical maturation during adolescence in the same subject population in a cross-sectional study. To do this, we collected all-night sleep EEG during 1-2 nights of sleep using a 128-channel high-density EEG system and anatomical MRI data from a group of 41 healthy children and adolescents between 8 and 19 years of age and addressed the following questions: 1) Do sleep SWA and cortical gray matter volume decrease in an age-dependent manner in our subjects? 2) Are the changes in sleep SWA and gray matter

volume during adolescence correlated? 3) Do correlations between the sleep EEG and gray matter volume show regional (lobes) and frequency-specific aspects?

## Materials and Methods

### Subjects

Of 41 subjects enrolled in the study, we excluded 1 subject, who was a habitual short sleeper (sleep duration shorter than the 95th percentile of the age group); 2 subjects left the study before we could collect sleep EEG data, resulting in 38 subjects with at least 1 night of EEG data. Another 2 subjects were excluded from the correlations with magnetic resonance (MR) data because 1 refused the MRI scan and the image quality of 1 subject was very low due to technical problems with the scanner. The final sample consisted of 36 children and adolescents (mean age: 13.5 years, standard deviation [SD]: 3.3 years; 15 girls, 21 boys). We defined puberty between age 10 and 15.9 years (based on the Tanner score; Tanner 1962) and adolescence between 16 and 19 years. Written informed consent was obtained from participants and parents. The study was approved by the local ethics committee according to the declaration of Helsinki.

### Sleep EEG

Sleep recordings for 2 nights were performed by means of a 128-channel EEG amplifier (Electrical Geodesics Inc.). The 2 nights were separated by at least 1 week and took place on the same day of the week. Sleep EEG recordings in girls with menstruation were performed during the follicular phase (except for 1 girl). All subjects but one were recorded for the entire night. In 1 subject, the electrodes were taken off after 5 h due to discomfort. EEG recordings were sampled at 500 Hz and band-pass filtered between 0.5 and 50 Hz (except for 1 subject, where a 0.75-Hz high-pass filter was used to suppress low-frequency sweating artifacts). Sleep stages were visually scored for 20-s epochs according to American Academy of Sleep Medicine criteria (Iber et al. 2007). Mean sleep latency of both nights was 20.2 min (SD: 12.4). Amount of sleep in stage 2 was 151.9 min (SD: 36), and amount in sleep stage N3 was 84.7 min (SD: 31) for the first 4 sleep cycles.

For a quantitative analysis of the sleep EEG, a spectral analysis of consecutive 20-s epochs (Fast Fourier Transform routine, Hanning window, averages of five 4-s epochs) was performed for 109 channels (excluding the channels below the ears) over 4 NREM sleep episodes after visual and semiautomatic artifact removal (except for 1 subject, who slept for 2 whole cycles only). Analyses were performed with the software package MATLAB (The Math Works, Inc., Natick, MA). With the aim to optimize stability across nights, in a first step, we varied the number of cycles (1–4) and stages (N2 or N3 or N2 and N3) for which we calculated SWA (EEG power between 1 and 4.5 Hz). The most stable composition was SWA for stages N2 and N3 for the first 4 NREM sleep episodes. In a next step, we averaged the 2 nights. In 6 subjects, only one night was included due to missing data or bad data quality. Mean difference in SWA between nights was 15.1% for the electrode C4 (Pearson's  $r = 0.977$ ,  $P < 0.001$ ,  $n = 32$ ). SWA measures were logarithmized to obtain a linear relationship with age. Age-related changes were analyzed in all nineteen 10–20 electrodes (Fp1, Fp2, Fz, F3, F4, F7, F8, C3, C4, T3, T4, T5, T6, P3, P4, Pz, O1, O2, and Oz).

To assess the stability of the relationship between SWA and gray matter during the night, we calculated SWA for the first cycle and the fourth cycle separately. The subject with only 2 cycles was excluded from this analysis.

We assessed the frequency specificity of the results by separate analyses for average absolute power in the following EEG bands (for sleep stages N2 and N3 of the same time window): low delta (0.75–1.5 Hz), high delta (2–4.5 Hz), theta (5–7 Hz), alpha (8–11 Hz), sigma (12–15 Hz), and beta (20–25 Hz).

To assess the sleep state specificity of the results, we compared theta power (5–7 Hz) during NREM sleep with theta power during REM sleep for the same time intervals (first 4 sleep cycles, electrode C4). We used theta power for this comparison because it predominates REM sleep.

### Structural MRI

All images were obtained on the same 3-T scanner, a General Electric Signa HDx. We used a  $T_1$ -weighted gradient-echo whole-brain image, time repetition 8.928 ms, time echo 3.496 ms, and flip angle  $13^\circ$ ; image resolution in  $x$ - $y$ - $z$  direction was  $256 \times 256 \times 140$  voxels, resulting in a resolution of  $0.938 \times 0.938 \times 1.2$  mm. The  $T_1$  images were further processed using standard methods. However, because MR-based evaluation methods have never been anatomically validated in children and adolescents, we followed a precautionary approach and used 2 very different methods, which both should be suitable for the evaluation of children's data: a voxel-based morphometry (VBM) analysis using a priori maps tailored for the children's data included in our study and a surface-based analysis that uses limited a priori knowledge of the brain anatomy.

### VBM Analysis

Global gray and white matter volumes (as well as gray/white matter ratios, which were the simple ratio between the volume of all gray matter voxels by all white matter voxels) and whole-brain gray matter maps were calculated with the SPM5 software (<http://www.fil.ion.ucl.ac.uk/spm>) for Matlab using the VBM5 toolbox (<http://dbm.neuro.uni-jena.de/vbm/vbm5-for-spm5>) by Christian Gaser. Images were individually masked for non-brain tissues, normalized, segmented, and hidden Markov random field corrected using custom-made a priori maps. Images were modulated to reverse nonlinear transformations used for the normalization and then smoothed with a 10-mm full-width at half-maximum (FWHM) Gaussian kernel.

The custom-made a priori maps were obtained by averaging segmented images of all subjects used in the study, normalized using the same procedure with a priori maps contained in SPM5 (Montreal Neurological Institute space), and smoothing the mean images for gray matter, white matter, and cerebrospinal fluid with a Gaussian kernel of 10-mm FWHM.

Image statistics were calculated on a voxel-by-voxel basis. Gaussian distribution of the data is provided by the smoothing of the images. Images were masked explicitly using a relative threshold of 0.1 to exclude voxels that are unlikely to belong to the gray matter segment. Differences lying outside the brain (meninges are not fully excluded by the procedure) or between white matter and liquor were excluded.

### Surface-Based Analysis

Local gray matter volumes (cortical and subcortical), cortical areas, thicknesses, and curvatures were calculated using Freesurfer version stable v4.5.0 for Mac OS 10.5.2 (<http://surfer.nmr.mgh.harvard.edu>; see also Dale et al. 1999; Fischl et al. 1999). In this software, the  $T_1$  images are analyzed using the recon-all procedure, which treats subcortical structures and cortical hemispheres separately. The procedure for the cortical hemispheres uses intensity gradients to model gray-white border and measures cortical thicknesses perpendicularly to the gray-white border up to the outer liquor space. The procedure corrects the topology automatically until each hemisphere is one contiguous sheet without holes. Extracted surfaces were checked for topological faults (holes and knots). Images had only few, very small defects, which did not have to be corrected manually. With the completed models for the hemispheres, the hemispheres are registered with a spherical atlas, which utilizes individual cortical folding patterns to match cortical geometry across subjects, which allows parcellation of the cerebral cortex into gyral and sulcal units. It has been shown that Freesurfer statistics are robust against white noise in the images and that results are similar if using multiple  $T_1$  images to using 1 image (Han et al. 2006; Jovicich et al. 2009). Since the measured thicknesses have a small variability and are consistent with anatomical studies (i.e., they are slightly thicker than adult values and converge against adult values) and the measured gyral and sulcal volumes are consistent with adult values, the method is believed to be valid for our age range. Finally, Freesurfer statistics were evaluated with SPSS 16.0 for Windows.

### Lobewise Analysis

Areas from the surface-based analysis were fused to form the 4 main lobes (prefrontal, temporal, parietal, and occipital lobes) left and right. The orbitofrontal cortex was not included in the prefrontal lobe.

### Statistics

EEG power values and gray matter variables were compared with multiple correlations accounting for sex and total brain size (gray matter plus white matter plus liquor).

The statistical threshold assumed was  $P = 0.001$  uncorrected for the SPM analysis and  $P = 0.05$  uncorrected for the surface-based analysis.

### Colocalization

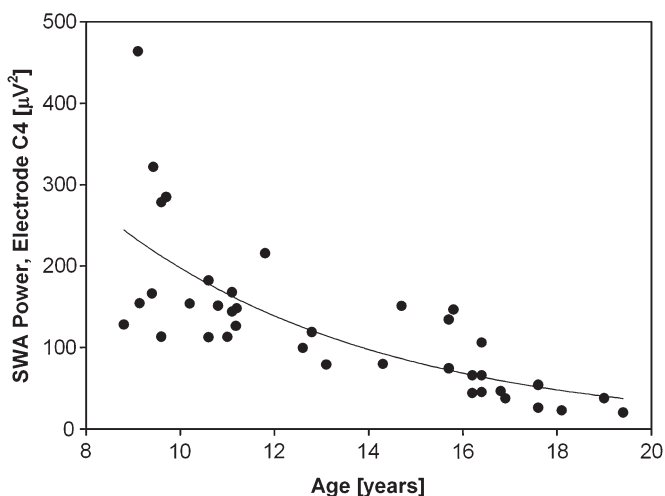
The degree of colocalization between the correlation spots over all predefined areas for 2 variables was defined as the scalar products of the beta weights for all predefined cortical areas ( $n = 62$ ) divided by the Euklidian length of the beta weight vectors (0 = independent, 1 = collinear, i.e., the cosine between the vectors). The values for the structural modalities (volume, area, and thickness) were treated separately. The significance of these scalar products was assessed with a permutation test: the actual scalar product was compared with the distribution of theoretical scalar products, which were obtained as 100 000 scalar products between the first vector and random permutations of the second vector. Consequently, a 5% significance level was defined as 5000 theoretical scalar products being larger than the measured scalar product.

## Results

### EEG SWA and Gray Matter Decrease with Age in Healthy Children

As expected, averaged EEG power in the slow-wave frequency range (SWA, 1–4.5 Hz, both nights) showed a marked decrease during adolescence, consistently with earlier studies (see Introduction). The decrease was present in all 10–20 electrodes (with interelectrode correlations between 0.852 and 0.992; all  $P < 0.001$ ), however, variable in its extent. We found the largest decreases of SWA over central and parietal regions. Because of the high correlation between electrodes, in a first step, we refer to the classically used electrode C4. For this electrode, as for the others, the decrease of SWA was consistent with an exponential model, with a power loss of around 12% per year between 8 and 19 years of age (Fig. 1).

We first used the conventional VBM (voxelwise analysis of whole-brain maps) analysis to detect changes in gray matter volume during childhood and adolescence. On the global level, the changes in cortical organization are best reflected in a significant decrease of the gray-to-white matter ratio (mean



**Figure 1.** Decrease of SWA (EEG power between 1 and 4.5 Hz) across adolescence (electrode C4, first 4 sleep cycles, mean over 2 nights) with a fitted exponential function.

2.07; decreasing 0.03 per year). Moreover, consistent with published data, we found regional gray matter volume decreases with age by means of the VBM analysis (Fig. 2). Between the ages 8 and 19, the spots with the most significant volume decreases were found in the prefrontal lobe bilaterally, in the left anterior temporal lobe, the right posterior cingulate, and in the left superior parietal lobe.

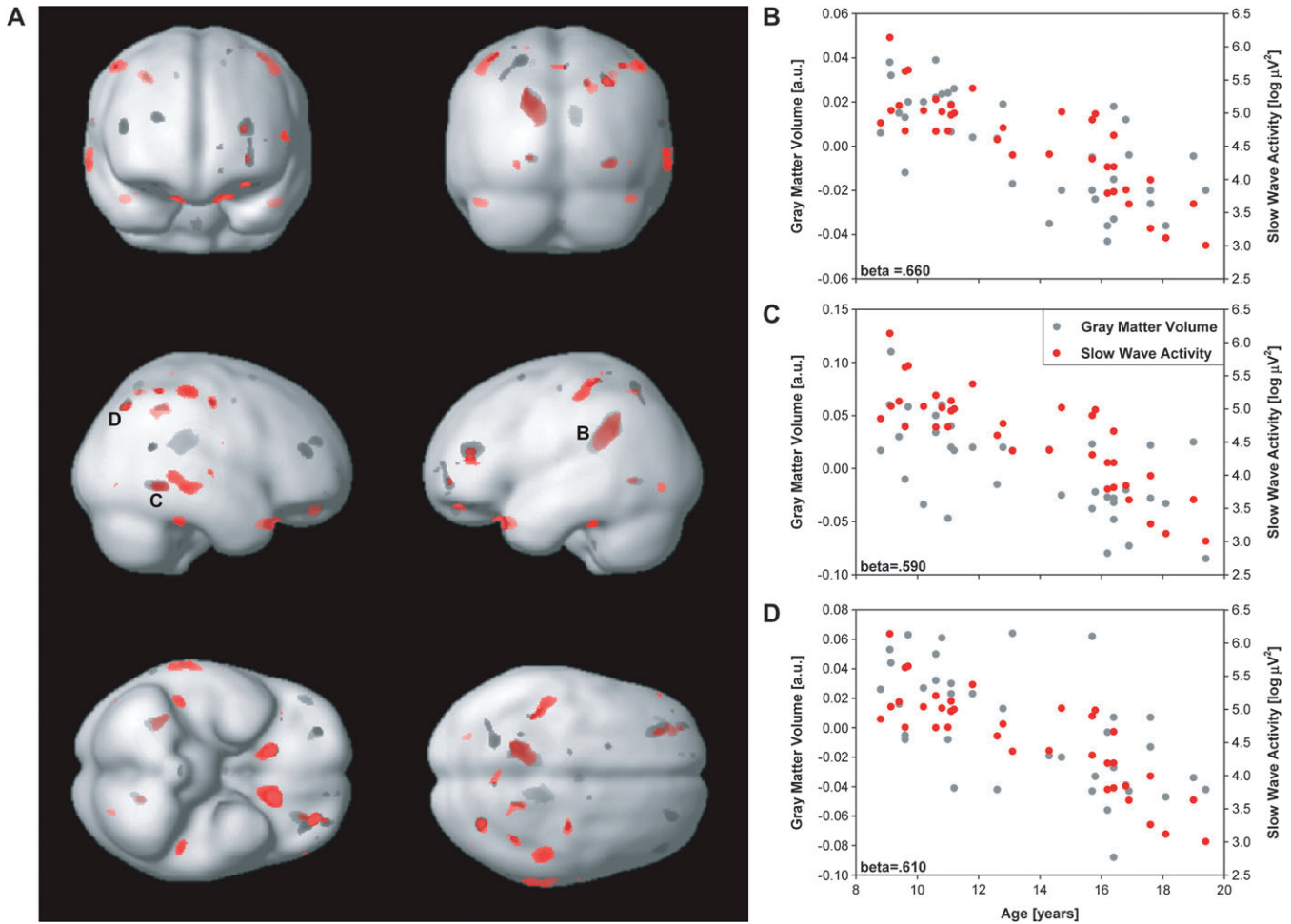
In the surface-based analysis, we found a small, nonsignificant global decrease of cortical thickness over the observed age range (mean 2.79 mm [standard error of the mean 0.17]; decrease  $-0.007$  mm per year,  $P = 0.173$ ). Analysis for the main lobes showed strongest thickness decreases with age in the parietal lobes (0.4% per year), followed by the frontal (0.3%), temporal (0.3%), and occipital (0.2%) lobes. Whereas the volume of the left orbital gyrus, the main part of the orbitofrontal cortex, was quite stable, the right orbital gyrus showed a marked decrease in volume; this asymmetry is supported by the observation that the left–right asymmetry between the sulci increases during adolescence in this region (Sowell et al. 2002). Other individual regions with age-related increases or decreases are listed in Table 2 (last column). Most correlations with age were found for cortical thickness, where the strongest negative correlation was present for the left middle frontal gyrus (standardized beta =  $-0.68$ ) and the strongest positive correlation for the right temporal pole (beta = 0.54; Table 2). Thus, the observed volume changes are primarily due to changes in cortical thickness.

### The SWA Decrease Correlates with Gray Matter Changes in Healthy Children

Our data set allowed a direct correlation of gray matter and SWA during sleep. In the whole-brain analysis, the ratio between all gray matter and white matter voxels in the entire brain, which showed a marked decrease over the age range, correlated significantly with SWA at electrode C4 (beta = 0.367,  $P = 0.025$ ).

Using VBM analysis, we found significant positive correlations between SWA at electrode C4 and gray matter volumes in the posterior cingulate, bilateral parietal, and left dorsolateral prefrontal lobes as well as sensorimotor, occipital, and posterior temporal areas. There were no significant correlations with the volumes of the large subcortical core structures (basal ganglia, thalamus, and amygdala). Moreover, the positive correlations colocalized to a large extent with a subset of the regions showing the most pronounced age-dependent decrease in gray matter (Figs 2A and 3; see also below). The strongest positive correlations between SWA and gray matter, which overlapped with regions exhibiting age-dependent decreases in gray matter volume of the parietal (posterior cingulate), temporal (fusiform gyrus), and occipital lobes (cuneus/precuneus border), explain up to 45% of the variability (Fig. 2B–D). Only few regions showed negative correlations between gray matter volume and SWA, that is, the right temporal pole and the left hippocampus. Note that the hippocampus is among the few brain structures that increases in volume at this age range and might be an interesting target for further investigation because of its role in learning and memory processes (Moscovitch et al. 2006).

As found in the VBM analysis, the surface-based analysis revealed predominately positive correlations between local gray matter measures and sleep SWA at electrode C4. We



**Figure 2.** Correlation between cortical gray matter and sleep SWA during adolescence (mean of 2 nights, first 4 sleep cycles, electrode C4). (A) Overlay of gray matter decrease with age (gray) and regions with positive correlation between gray matter volume and sleep SWA (red). (B–D) Time course of gray matter and logarithmized sleep SWA for 3 example regions: (B) posterior cingulate, (C) fusiform gyrus, and (D) cuneus/precuneus border. Beta values refer to standardized weights of the multiple correlation between SWA at electrode C4 and gray matter volume, corrected for sex and whole-brain volume;  $P < 0.001$ , uncorrected for multiple comparisons.

observed similar results for other electrodes with a large overlap between cortical regions correlating with SWA (data not shown, see Materials and methods for electrode details). The main associations were found for cortical thickness and SWA, whereas surface area revealed only few associations with SWA (Table 1 for pooled N2 and N3; the correlations with separate SWA for sleep stages N2 and N3 can be found in Supplementary Table S1). Virtually all areas showing a positive correlation between gray matter volume and sleep SWA using the VBM analysis also showed a positive correlation in the surface-based analysis, that is, for cortical thickness, but with more prefrontal regions involved. We believe that surface-based assessment of cortical thickness is the more sensitive measure for changes in cortical structure because it does not rely on spatial correspondence of individual structures via normalization of the brain to an averaged template but maps the individual gyri and sulci of each subject (see Materials and methods for more details). This might be of particular importance for the complicated gyrification in the prefrontal cortex.

Next we tested whether the close relationship between gray matter measures and sleep SWA exists independent of age. Thus, we applied an age correction to the multiple correlations. Even when controlling for age, we found significant correla-

tions between gray matter measures and SWA (with smaller effect sizes), again with a preponderance of positive correlations (Table 1). Another contributing factor might be head size because it consistently showed positive correlations with SWA. Thus, all calculations were corrected for whole-brain volume (sum of gray matter, white matter, and liquor). Finally, the distance between the electrode and the cortical tissue might influence the signal strength. In this respect, it is noteworthy that the thickness of non-brain tissues failed to show any significant effects.

To assess the relationship between the time course of SWA and cortical gray matter measures, we calculated multiple correlations between SWA in the first and the fourth sleep cycle (see Materials and methods) and parcellated gray matter measures from the surface-based analysis. For both the first and the fourth sleep cycle, we obtained qualitatively similar results in terms of regions and beta weights as for the average across the first 4 cycles with no statistical differences (data not shown).

#### **Regional Aspects of the Correlation between MRI Markers of Cortical Maturation and Sleep SWA**

Imaging studies show a specific progression of cortical brain development reflected in a region-specific time course of

**Table 1**

Brain regions showing significant correlations between gray matter measures and SWA at electrode C4 (beta: standardized weights of the multiple correlation corrected for sex and brain size)

Region	Hemisphere	Measure	Beta	<i>P</i> (uncorrected)
Without age correction				
Inferior frontal gyrus, triangular part	L	Thickness	0.388	0.023
	R	Thickness	0.423	0.040
Middle frontal gyrus	L	Thickness	0.572	0.029
Superior frontal sulcus	L	Area	-0.485	0.010
Superior frontal gyrus	L	Thickness	0.476	0.026
	R	Thickness	0.623	0.014
Orbital gyrus	R	Volume	0.470	0.006
		Area	0.451	0.019
		Thickness	0.519	0.008
Middle temporal gyrus	R	Thickness	0.445	0.015
Superior temporal sulcus	R	Thickness	0.383	0.034
Fusiform gyrus	R	Thickness	0.582	0.001
Postcentral gyrus	R	Volume	0.392	0.029
Supramarginal gyrus	L	Thickness	0.409	0.014
	R	Volume	0.407	0.027
Intraparietal sulcus	L	Thickness	0.345	0.036
	R	Thickness	0.533	0.002
Superior parietal gyrus	L	Thickness	0.537	0.003
	R	Thickness	0.437	0.019
Precuneus	L	Thickness	0.354	0.041
	R	Thickness	0.506	0.006
With age correction				
Inferior frontal gyrus, orbital part	R	Volume	-0.195	0.042
		Area	-0.194	0.049
Orbital gyrus	L	Area	0.360	0.031
Parahippocampal gyrus	L	Volume	0.241	0.023
	R	Thickness	0.261	0.010
Fusiform gyrus	L	Volume	0.232	0.020
	R	Thickness	0.224	0.033
Inferior temporal sulcus	R	Volume	0.216	0.016
		Area	0.242	0.017
Central sulcus	L	Thickness	0.222	0.023
	R	Volume	0.240	0.028
Supramarginal gyrus	L	Thickness	0.271	0.012
Intraparietal sulcus	R	Thickness	0.260	0.012

macroscopic gray matter changes (see Introduction). Thus, in a next step, we explored the regional aspects of the relationship between gray matter measures and sleep SWA. Even though the age-related decrease in SWA was present in all electrodes, we found some region-specific differences in its expression. We found the fastest decrease rate of SWA in centroparietal (slope of the linear regression  $b = -32 \mu\text{V}^2/\text{year}$ ) and occipital and dorsal frontal ( $b = -28$ ) electrodes, followed by temporal ( $b = -23$ ) and central and lateral frontal electrodes ( $b = -18$  to  $-19$ ). To account for the global decrease of SWA with increasing age, which might be related to the global decrease of gray matter volume, we normalized SWA at each electrode to the mean overall 10–20 electrodes to investigate regional aspects. Interestingly, we found the strongest relative decrease of SWA in parietal and parietocentral electrodes (slope of the linear regression  $b = -0.025$ ), close to the area where we also found the strongest decrease of gray matter. Moreover, we observed relative increases of SWA in frontopolar and frontocentral regions ( $b = 0.04$ ), which encompasses the observed gray matter volume increases in the superior frontal sulcus. Relative power in the theta and sigma frequency ranges did not show such a close relationship to local gray matter volume changes. With the limited spatial resolution of EEG recordings in mind, our results reveal some regional differences in the relationship between SWA and gray matter, which correspond to previously reported facets of the progression of brain development.

### Correlation between MRI Markers of Cortical Maturation and Other Frequencies of the Sleep EEG

We next examined whether the relationship between sleep EEG activity and gray matter was specific to certain frequencies. This is of interest because the most pronounced age-related changes in the sleep EEG were found for the lower part of the frequency spectrum ( $<8$  Hz; Jenni and Carskadon 2004), in which activity is closely related to sleep depth. Thus, to test for the frequency specificity of our results, we investigated also other classical frequency ranges of the sleep EEG. As found in previous studies, other frequency ranges showed also age-dependent decreases in power. In our subjects, we observed the steepest slopes of annual decrease in the low delta and theta ranges, followed by the high delta, alpha, sigma, and beta ranges. The highest negative correlations between power and age were found in the high delta ( $r = -0.728$ ) and low delta ( $-0.696$ ) ranges, followed by the theta ( $-0.668$ ), alpha ( $-0.606$ ), beta ( $-0.588$ ), and sigma ( $-0.538$ ) ranges (all  $P < 0.001$ ). However, it is noteworthy that power values in all frequency bands depend on each other (i.e., correlations between band power ranged from  $r = 0.415$ ,  $P < 0.01$ , for low delta and sigma to  $r = 0.926$ ,  $P < 0.001$ , for low and high delta; all correlations between the frequency bands are provided in Supplementary Table S2). Next we correlated power in the different frequency ranges with changes in MRI markers of cortical maturation. On the global level, the gray-to-white ratios correlated only with power in the low delta (standardized beta =  $0.484$ ,  $P = 0.003$ ) and high delta (beta =  $0.427$ ,  $P = 0.009$ ) bands, but not with power in the higher frequency bands. On the local level, however, we found a similar preponderance of positive correlations between EEG power and gray matter volumes for all other frequency ranges, as for SWA (Table 2). To assess the significance of the overlap of age-related gray matter changes and EEG power—gray matter correlations—we calculated the degree of colocalization (see Materials and methods). Colocalization with age-related thickness decreases was most pronounced for positive correlations with power in the slow frequency ranges (low delta and high delta) and least pronounced for the spindle frequency range (sigma), with intermediate values for alpha and beta (Fig. 3). This pattern was similar for gray matter volumes and cortical surface areas. Colocalizations for all frequency ranges were highly significant using a permutation test ( $P < 0.001$ ; see Materials and methods).

Finally, we assessed sleep state specificity of our results by correlating theta power during REM sleep in the first 4 cycles of the night with parcellated gray matter volumes, areas, and cortical thicknesses. We compared these results with the results obtained for the analogous correlations with theta power during NREM sleep during the same time period (Table 2). The results involved the same brain structures, and the beta values were similar, without any significant differences (all  $P > 0.1$ ; data not shown).

### Discussion

Our study shows that 1) sleep SWA and cortical gray matter decrease during adolescence as observed previously 2) the decreases in SWA and gray matter are highly correlated, and 3) the relationship between the sleep EEG and gray matter is most pronounced in areas maturing during adolescence and strongest for the SWA frequency range.

**Table 2**

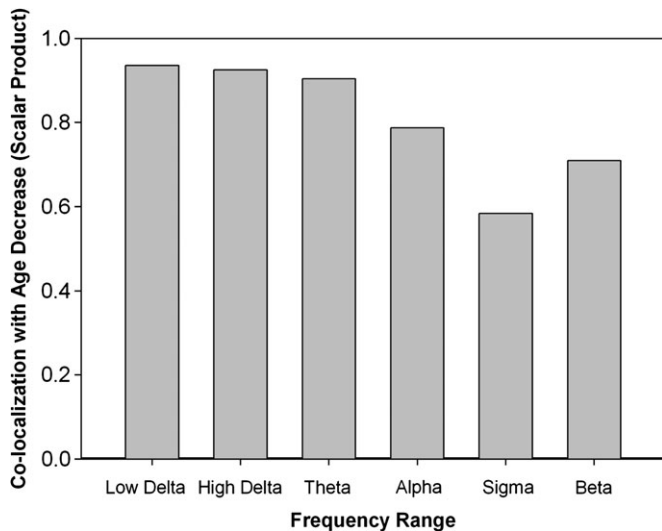
Brain regions showing significant correlations between gray matter measures and power in different frequency bands for electrode C4 (beta: standardized weights of the multiple correlation corrected for sex and brain size)

Region	Hemisphere	Measure	Low delta	High delta	Theta	Alpha	Sigma	Beta	Age
Inferior frontal gyrus, opercular	L	Volume					-0.338		
	R	Thickness				-0.354	-0.351		
Inferior frontal gyrus, orbital	L	Volume							-0.341
	R	Thickness	0.376	0.395	0.383				
Inferior frontal gyrus triangular	L	Thickness	0.420	0.428					-0.428
	R	Thickness							
Middle frontal sulcus	L	Volume		0.403	0.491	0.577	0.508	0.467	
		Area		0.374	0.447	0.514	0.477	0.427	
		Thickness		0.334		0.309			
Middle frontal gyrus	R	Thickness							-0.369
	L	Thickness	0.638	0.521					-0.680
Superior frontal sulcus	L	Volume							0.390
	R	Area	-0.487	-0.458	-0.496	-0.384			0.539
Superior frontal gyrus	L	Thickness	0.519	0.454					-0.555
	R	Thickness	0.655	0.615					-0.575
Orbital gyrus	R	Volume	0.482	0.453	0.388	0.370		0.359	-0.532
		Area	0.455	0.441	0.377	0.436			
		Thickness	0.559	0.467	0.457				-0.586
Temporal pole	L	Volume							0.465
		Thickness						-0.427	
	R	Volume			-0.330	-0.363	-0.380	-0.350	0.456
Inferior temporal gyrus	L	Thickness				-0.563	-0.463	-0.524	0.539
		Area					-0.394		
Inferior temporal sulcus	L	Area		-0.373					0.453
	R	Thickness	0.523	0.431	0.392				
Middle temporal gyrus	L	Thickness	0.360						
	R	Thickness	0.382	0.371					
Cingulate gyrus	L	Thickness							-0.387
	R	Volume	0.393	0.370	0.351				
Postcentral gyrus	L	Thickness							-0.415
	R	Thickness	0.483						
Supramarginal gyrus	L	Volume		0.473	0.435	0.389			-0.397
		Thickness	0.352	0.358					
	R	Thickness	0.496	0.574	0.454	0.346		0.418	-0.549
Intraparietal sulcus	L	Thickness	0.517	0.539	0.389				
	R	Thickness	0.475	0.398					-0.568
Superior parietal gyrus	L	Volume					0.370		-0.490
		Area				0.424			-0.406
	R	Thickness	0.368						-0.375
Precuneus	L	Volume							-0.454
		Area							-0.431
	R	Thickness	0.561	0.472	0.433	0.429		0.443	-0.523
Fusiform gyrus	L	Thickness	0.530	0.435	0.472				-0.400
	R	Thickness	0.544	0.618	0.528	0.446		0.534	-0.463
Parahippocampal gyrus	R	Volume							0.385
		Area							0.494
Lingual gyrus	L	Thickness					0.362		
	R	Thickness							-0.402
Inferior occipital gyrus	R	Thickness			0.415	0.362			

As observed in longitudinal (Campbell and Feinberg 2009) and cross-sectional (Jenni and Carskadon 2004) studies, we confirm in our sample that SWA decreases during childhood and adolescence. The decrease is not confined to the SWA frequency range but, though to a lesser extent, also found for all other frequency ranges. This observation is also illustrated by the intercorrelations between power of frequency bands across the entire spectrum. Also Campbell and Feinberg (2009) reported age-dependent changes in the sleep EEG for other frequency ranges, that is, for theta power. Moreover, confirming other reports (Gogtay et al. 2004; Sowell et al. 2004), we observed age-related changes in cortical gray matter. The changes were most pronounced in the medial parietal lobe and in parts of the prefrontal cortex—areas known to show maturational changes during childhood and adolescence.

Our data set allowed to directly evaluate the relationship between the changes in sleep SWA and cortical gray matter. As postulated by Campbell and Feinberg (2009), we observed a tight relationship between sleep SWA and a variety of indexes of cortical maturation derived from MR images. Most significant were correlations with cortical thickness in the right orbital

gyrus, the right fusiform gyrus, both intraparietal sulci, and bilateral precuneus. However, to a lesser extent, some cortical gray matter volumes and surface areas also showed a significant relationship with SWA. It is of particular interest that the highest correlations between sleep SWA and gray matter volume/thickness were found in the same areas showing the largest changes in gray matter, that is, the areas displaying maturational changes during childhood and adolescence. Some of these areas exhibited a significant correlation even after correcting for age, revealing that sleep SWA, in these areas, explains more variability in cortical maturation than age. This might be due to large developmental differences in our age range and thereby signify the importance of good markers of cortical maturation. Moreover, an extension of our analysis to the first and the fourth sleep cycle revealed a stable relationship between cortical gray matter changes and sleep SWA, which supports the validity of SWA as a marker of cortical maturation. Because whole-brain volume and skull thickness might change with age and may affect the EEG signal, we also looked for the influence of these variables on our results. While skull thickness failed to show a significant relationship with



**Figure 3.** Colocalization of the correlation between age and cortical thickness and the correlation between EEG power and cortical thickness for different frequency bands (scalar products; 0 means completely independent, 1 means collinear, see Materials and methods).

SWA, whole-brain volume was correlated positively with SWA. Thus, all reported results are corrected for whole-brain volume.

The major finding of our study is the close relation of SWA, which is an electrophysiological measure of sleep depth and local cortical gray matter volumes. The coincidence between age-related cortical pruning with spots of high positive correlation between sleep SWA and local gray matter volumes suggests that the activity of slow waves during deep sleep can be used as a marker of cortical maturation. However, how may such a close relationship between age-related gray matter changes and changes in sleep SWA arise? It can only be speculated that the larger gray matter volume in children reflects, at least in part, higher synaptic density and possibly also higher cell density. There exists good evidence, however, that children have not only increased synaptic density in higher order (association) areas but probably also more cell activity (Brewer et al. 2009). The increased cell activity fits well to the higher brain energy consumption observed in children (Chugani et al. 1987). Thus, in children, a specific task would involve more neurons/synapses and more action potentials than in adults. To recruit these larger networks needed to carry out a task, input neurons should be able to influence the activity of more postsynaptic neurons. This observation might also be reflected in some common forms of epilepsy starting during childhood, which often vanish in adulthood (Neubauer et al. 2008). Thus, as a result of the spontaneous activity of a given neuron during sleep, the probability of an action potential in postsynaptic neurons is higher, leading to increased synchronicity across the network (always as compared with an adult pruned network). Higher synchronicity leads also to higher EEG power (Vyazovskiy et al. 2009). Such a mechanism may also relate to an observation when manipulating sleep homeostasis: though the homeostatic regulation of sleep is mainly reflected in the SWA frequency range (Borbély and Achermann 2005), it extends also to higher frequencies. For example, the increased sleep depth after sleep deprivation is reflected in an increase of EEG power up to 10 Hz (Finelli et al. 2000). Not surprisingly, however, the strongest correlations

were found for EEG power in the slow-wave frequency range given that this rhythm dominates the EEG during deep sleep. It is noteworthy that the correlation between EEG power and gray matter was especially evident within the low delta band, at frequencies corresponding to the slow oscillations (Steriade et al. 1993). Note that this mechanism is not confined to slow waves but applies to rhythmic oscillations in general, like theta, alpha, and beta waves, which should share the same anatomical substrate for the generation of cortical activity. Indeed, we found similar positive correlations with local gray matter volumes for the higher frequency ranges. Moreover, given the proposed mechanism, a relationship between electrical activity and gray matter may not be restricted to deep sleep but apply to different behavioral states and EEG frequencies as well. Indeed, we found a preponderance of positive correlations between gray matter volumes and EEG power for N2 and N3 separately and for EEG power in the theta range also during REM sleep. This fits to the observation that theta power during NREM and REM sleep were highly correlated ( $r = 0.913$ ,  $P < 0.001$ ). In addition, a similar relationship was reported for the waking EEG: absolute power in quiet waking EEG in slow waves, alpha, and beta correlates positively with gray matter in the 4 main lobes, most strongly at lower frequencies (Whitford et al. 2007). However, power values measured in the waking EEG are more difficult to interpret and presumably more variable because they are strongly affected by general cognitive performance and the specificity of the task or the applied setting.

There are several limiting factors to our study. First, of course our study, which is correlative in nature, is not able to prove causalities or to exclude mediating factors between cortical gray matter and SWA. A possible class of mediators could be hormones, for example, the growth hormone–insulin-like growth factor 1—axis: these hormones do not only promote brain growth and influence the densities of dendritic trees (Aberg et al. 2006) but also promote sleep in rabbits and rats (Obal et al. 1988). Other possible mediators are neurotrophins like brain-derived neurotrophic factor (BDNF), which is related to synaptic plasticity in an activity-dependent manner (Savitz et al. 2006). BDNF was increased after sleep deprivation (Hairston et al. 2004), and it is more expressed in rats showing more SWA after exploring enriched environments (Huber et al. 2007). In addition, if injected directly into the brain, BDNF promotes sleep SWA (Fragana et al. 2008). Second, our study is purely cross-sectional and cannot show a development of brain structure and electrical cortical activity, which could be achieved with longitudinal data. Third, changes in MRI gray matter volumes can only approximate changes in synaptic density. In humans, synapse numbers can only be counted postmortem. Hence, the valuable studies by Huttenlocher and colleagues show a clear decrease of synapse density during adolescence (Huttenlocher and Dabholkar 1997). Using MRI to approximate changes in synapse density, it seems that cortical thickness is the most sensitive measure because, other than conventional voxel-based morphometry (Hutton et al. 2009), it tracks the changes in the thickness of several cortical layers, which have been observed in a postmortem study (Rabinowicz et al. 2009). However, MRI can assess only macroscopic anatomical structure at a scale of millimeters, but not the remodeling of synaptic structures itself, which has to be assessed with animal or postmortem human studies.

With all these limitations in mind, our study provides convincing evidence that SWA during sleep represents a good electrophysiological marker of cortical maturation during adolescence. It allows for 1) longitudinal data acquired at multiple times on the same subject, with little risk, low costs, and without requiring immobility—all these points are particularly relevant for young subjects and/or patients and 2) SWA might reflect not only synaptic density, that is, number, but also other synaptic properties like synaptic strength and efficacy. This is elegantly illustrated by studies in rats where synaptic strength was, for example, measured as the level of alpha-amino-hydroxy-methyl-isoxazole-priopionic-acid (AMPA) receptors per synapse and synaptic efficacy as the magnitude of the physiological effects, for example, postsynaptic currents (Vyazovskiy et al. 2008). Recently, Vyazovskiy et al. (2009) showed that both synaptic strength and synaptic efficacy are determinants of sleep SWA.

Finally, the activity of sleep slow waves may not only be a consequence of cortical maturation but also play an active role in restructuring networks. Evidence comes from the observation that rhythmic activity can induce plastic processes like synaptic remodeling both during development and learning (Katz and Shatz 1996). Moreover, sleep may represent an ideal state to perform such remodeling (Tononi and Cirelli 2006). Indeed, studies in adults have suggested a role of slow waves in the plasticity of local circuits (Huber et al. 2004, 2006). It was shown that both sleep deprivation (Guzman-Marin et al. 2005) and sleep fragmentation (Guzman-Marin et al. 2007) can reduce neurogenesis in the dentate gyrus of the hippocampus. Studies in kittens have shown that the shift in ocular dominance after monocular deprivation in cats can be strengthened by sleep and correlates with the amount of NREM sleep (Frank et al. 2001). Moreover, blocking neuronal activity during sleep using Na-channel blockers resulted in a reduction of ocular dominance plasticity (Jha et al. 2005). Effects downstream of N-Methyl-D-Aspartat (NMDA) receptor activation (probably via increased phosphorylation of the proteins CaMKII and ERK and the GluR1 subunit of the AMPA receptor) are responsible for these plasticity effects because blocking the NMDA receptor abolishes the shift in ocular dominance (Aton et al. 2009). It can be assumed that the relatively large and dense cortical networks in children allow synaptic pruning, a use-dependent process that makes the networks more efficient in routine processes (Hua and Smith 2004) but less flexible for learning novel processes. As the brain becomes more efficient, the drive for restructuring might decrease, which would explain the exponentially falling curve of SWA, that is, the reduction of sleep depth, into adulthood.

No matter if sleep SWA merely mirrors cortical changes or actively interacts with this process, our study highlights the strength of sleep SWA for the exploration of maturational changes during adolescence. This is of importance because 1) adolescence is an especially sensitive period for synaptic pruning in cortical circuits involved in cognitive functions and 2) adolescence is also a sensitive period for the pathophysiology of many psychiatric disorders, presumably due to this extensive synaptic remodeling (Paus et al. 2008). For example, “overpruning” during adolescence, when schizophrenia symptoms often start (Keshavan et al. 1994), could explain the reduced expression of synaptic proteins and the decreased volume of neuropil in prefrontal circuits observed in schizophrenic patients (Woo and Crowell 2005). Alternatively,

pruning during adolescence may unmask preexisting synaptic deficits (Hoffman and McGlashan 1993). Defects in pruning have also been linked to mood disorders (Saugstad 1994), autism, and mental retardation (Tessier and Broadie 2009). Thus, being able to monitor the extent of synaptic remodeling during adolescence could increase our understanding of pathophysiology, help early diagnosis, and guide potential therapies (Woo and Crowell 2005).

### Supplementary Material

Supplementary material can be found at <http://www.cercor.oxfordjournals.org/>.

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### Notes

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