Published in final edited form as:

Neuroimage. 2012 November 1; 63(2): 959–965. doi:10.1016/j.neuroimage.2012.03.053.

Mapping the electrophysiological marker of sleep depth reveals skill maturation in children and adolescents*

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Abstract

Electroencephalographically (EEG) recorded slow wave activity (SWA, 1–4.5 Hz), reflecting the depth of sleep, is suggested to play a crucial role in synaptic plasticity. Mapping of SWA by means of high-density EEG reveals that cortical regions showing signs of maturational changes (structural and behavioral) during childhood and adolescence exhibit more SWA. Moreover, the maturation of specific skills is predicted by the topographical distribution of SWA. Thus, SWA topography may serve as a promising neuroimaging tool with prognostic potential. Finally, our data suggest that deep sleep SWA in humans is involved in cortical development that optimizes performance.

Keywords

High density EEG; Sleep slow wave activity; Topography; Development

Introduction

Children not only sleep for longer hours than adults, but they also sleep much deeper. The depth of sleep can be quantified by the activity of electroencephalographic (EEG) slow waves (i.e., slow wave activity, SWA, EEG power between 1 and 4.5 Hz). For a long time it was known that the activity of slow waves dramatically changes during development (Feinberg, 1982): Sleep SWA reaches a maximum during the middle of childhood and exponentially declines during adolescence. Because the development of SWA parallels major changes in cortical maturation (e.g., the formation and subsequent elimination of

*Classification: Systems Neuroscience.

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synapses (Huttenlocher and Dabholkar, 1997)), slow waves were proposed to be related to these brain plasticity processes (Campbell and Feinberg, 2009; Feinberg, 1982). In fact, SWA was recently suggested to reflect and contribute to the regulation of short term (<24 h) synaptic plasticity (Tononi and Cirelli, 2006). Such a relationship between sleep slow waves and brain plastic changes was also proposed for the long term cortical plasticity taking place during development. We recently showed by means of high density EEG recordings that the cortical region displaying maximal SWA shifts from back to front (Kurth et al., 2010). This postero-anterior maturation of SWA topography parallels the structural maturation of the cortex (e.g. cortical gray matter thickness; (Shaw et al., 2008)) and fits to the development of functions (Luna and Sweeney, 2004), i.e. early maturation of children's vision originating from posterior areas of the cortex (Teller, 1981), late for executive control functions situated in anterior cortex (Munoz et al., 1998).

However, how the maturation of SWA, anatomical changes and behavioral development are related has not been addressed directly. Thus, in the current study we used high-density EEG, anatomical magnetic resonance imaging and behavioral assessments in children and adolescents to explore the direct relationship between sleep SWA, anatomy and skills with the aim to test whether SWA topography can serve as a neuroimaging tool with diagnostic and/or prognostic potential. Moreover, such an approach should shed light on the role sleep may play during cortical maturation. Our results show that the topographical distribution of sleep SWA can predict the development of specific skills. These age dependent changes of SWA topography closely parallel structural and behavioral maturation, however, precede both skill and gray matter maturation by several years.

Material and methods

Sleep recordings

We performed all-night electrooculogram, electromyogram, and high-density EEG recordings (128 channels, Electrical Geodesics Sensor Net for long-term monitoring) in 63 subjects (2–26 y, 38 males). 49 subjects were recorded at the University Children's Hospital Zurich (Zurich, Switzerland; 8–26 y, 32 males), 14 subjects were assessed at home (Providence, RI, USA; 2–8 y, 6 males). Of the sample, 4 pairs were siblings, and twice, four children were siblings (two boys were monozygotic twins). For more detailed information on subjects, see Table S1 and the age distribution in Fig. S1. A telephone screening excluded the occurrence of personal or family history of psychopathology, chronic diseases, sleep disorders and current use of medication or psychoactive agents. No crossing of more than one time zone was allowed in the 4 months prior to the study. During the week prior to the study, daily sleep diaries were kept by participants or parents and participants wore wrist actigraphs to monitor schedule compliance. Neither medication nor alcohol nor napping was allowed before the recording night. Except for two children (both about 5 y old) who were used to regular napping, the subjects were permitted to nap on the day of the assessment to prevent heightened sleep pressure (for more details see Kurth et al., 2010). Recordings in postpubertal females were performed during follicular phase.

Written informed consent was obtained from the parents or from the participants of full age after explanation of the study methods and aims. The procedures were approved by the local ethics committee, and the study was performed according to the Declaration of Helsinki.

The electrode nets were adjusted to the vertex and filled with gel electrolyte (ECI, Electro Gel), impedances were set below 50 k Ω . Sleep episodes were scheduled to individually reported bedtimes, and subjects were awakened in the morning to allow school or job participation. As a result our subjects had variable bed and rise times.

The EEG was sampled at 500 Hz (0.01–200 Hz) and referenced to the vertex (Cz). Data were offline bandpass filtered (0.5–50 Hz), down-sampled to 128 Hz (except for one subject, where a 0.75–50 Hz bandpass filter was used to exclude sweating artifacts in the lower frequencies). Artifacts were rejected (on a 20 s basis) after visual inspection and if power exceeded a threshold based on average power in the 0.75–4.5 and 20–30 Hz bands (see Huber et al., 2000). Poor quality electrodes were excluded (on average 4 channels per subject) and 11% (average) of the epochs were rejected as artifacts. All analyses are based on re-referenced data to the average reference. Visual scoring for sleep stages (20-s epochs) was performed according to standard criteria (Iber et al., 2007). SWA (1–4.5 Hz) was calculated by power spectral density analysis (pwelch, signal processing toolbox, MATLAB, MathWorks) for all artifact free 20-s epochs. Initial 60 min of non-rapid eye movement (NREM) sleep stages N2 and N3 were included in the analysis.

Regions of interest (ROIs)

In a subset ($n = 40$) of participants, electrodes were digitized and co-registered with the subject's MRI (Fig. 1A) using SofTatic Optic (EMS Inc.) and the three dimensional optical digitizer (Polaris Vicra; Northern Digital). Brodmann areas (BA) were detected using the Talairach Client (Lancaster et al., 1997; Lancaster et al., 2000). For more details on the anatomical electrode localization see Kurth et al. (2010). 6 regions of interest (ROI) were defined according to BAs associated with a skill (Fig. 1B). The ROI “simple motor” was specified by BAs 1–4, representing the primary sensory and the motor cortex. “Complex motor” included BA 1–4 and 6, representing premotor and supplementary motor areas. The ROI “visuomotor” included electrodes over the right parietal lobe (BAs 7 and 40) since these areas were shown to be responsible for visuomotor rotation learning as used with our task (Ghilardi et al., 2000). These data show that rotation adaptation has a lateralized representation in the right parietal lobe, irrespective of the arm used to perform the task. The ROI “vision” represented the primary and secondary visual cortex (BAs 17–19), “language” included auditory cortex, Wernicke's area and Broca's area (BAs 22, 39, 44, 45), and “cognitive control” represented the prefrontal and orbitofrontal cortex (BAs 9, 10, 11, 46, 47). In sum, BAs and electrodes were defined for the ROIs “vision”, “visuomotor”, “simple motor”, “complex motor”, “language” and “cognitive control” (Fig. 1B). Not all BAs were represented in our 128 electrodes.

Quantification of skills

21 skill variables were derived from several tasks (see below) and, based on their anatomical representation, categorized into 5 predefined groups: 1) simple motor skills [$n = 41$, 8.7–

25.9 y] included repetitive finger (dominant extremity), hand and foot movements (both extremities), as well as alternating foot or hand movements (both extremities) all part of the Zurich Neuromotor Assessment (ZNA for details see Gasser et al., 2010; Largo et al., 2001). Timed motor performances of the ZNA are standardized measures used in the clinic and research to assess developmental changes of the motor system. The test battery consists of distinct motor tasks of variable difficulty (Gasser et al., 2010; Largo et al., 2001). 2) Complex motor skills [n = 56, 4.4–25.9 y] included sequential finger tapping (both extremities, ZNA (Gasser et al., 2010; Largo et al., 2001)) and reaction time (auditory oddball paradigm (Kerr et al., 2010)). Reaction times in an auditory oddball paradigm undergo a developmental decrease (Kerr et al., 2010). fMRI data obtained during an oddball task showed that a motor reaction is associated with increased activity in somatic perception and motor regions (Clark et al., 2001). A cluster analysis in our data confirmed the proximity of the reaction time to both sequential finger tapping variables (see below). 3) Visuomotor skills [n = 38, 8.7–25.9 y] were assessed by means of a simplified version (4 targets) of an implicit rotation learning task involving the right arm (Huber et al., 2004). Targets were presented every second in a pseudorandom order on a computer screen. Subjects reached for the targets using a handheld cursor while unconsciously adapting to systematic rotations imposed on the perceived cursor trajectory (Huber et al., 2004). The rotation degree was increased stepwise from 0 to 60° (3 blocks each, 44 movements per block). The internal model was subsequently tested during 1 block with 0 degree rotation (B0). This implicit learning task was chosen because it allows to quantify the maturation of the visuomotor system, i.e. the representation of the internal model: The ‘aftereffect’ represents the implementation of the rotated internal model (mean of the first 4 movements in B0) (Kagerer et al., 1997), ‘washout’ the re-adaptation to baseline after rotation (first 4 minus last 4 movements in B0) (Seidler, 2007), and ‘responsivity’ the susceptibility of the internal unrotated model (first 4 minus last 4 movements in the first block with 15 degree rotation). 4) Language skills [n = 21, 9.1–16.9 y] and 5) cognitive control skills [n = 21, 9.1–16.9 y] were derived from the WISC IV intelligence test (German version (Petermann and Petermann, 2007)) including 3 verbal comprehension subtests (‘finding similarities’, ‘vocabulary’, and ‘general understanding’, denominated as language skills), and 3 perceptual reasoning and processing speed variables (‘matrices’, ‘digit-symbol’ and ‘symbol search’), respectively. WISC IV scores are widely used for diagnostics and thus represent reliable measures for language and cognitive skills. In order to observe maturational (i.e. age-related) changes in performance, we included non-normalized raw performance scores in the analysis. No skills for vision were assessed. Due to task specific age limits not all subjects contributed to each group (see square brackets for number of subjects and age range). A cluster analysis ensured the similarity of the different skill variables contributing to a group (data not shown; binary hierarchical cluster tree based on Manhattan distance; see Finelli et al., 2001). Behavioral data were z-scored and averaged for each skill. More specifically, for each of the 21 behavioral variables, data were z-scored across subjects. Next, all variables within one (of the five) groups were averaged within subjects. For the analysis of pooled data, the z-scores of the five groups were averaged within each individual.

Slow wave activity topography

In contrast to our previous analysis, we performed a normalization to account for stable regional differences in SWA across ages (i.e. SWA for each electrode and subject was divided by the mean SWA across all subjects for this electrode). This normalization has the advantage that the time point (age) of highest SWA can be identified for each cortical region. In contrast, in our previous analysis (Kurth et al., 2010), temporal regions, for example, always exhibited power minima, because absolute EEG power along the medial postero-anterior axis exceeded power at temporal regions at any time. For the analysis of the maturational changes in SWA topography (Fig. 2) a Kruskal–Wallis test was used (group ‘ROI’, i.e. the 6 SWA-based ROIs, ‘age’ as dependent variable), since the data tended to be not normally distributed (Lilliefors test, Statistics Toolbox, MATLAB, MathWorks, $p=0.06$). We found significant age differences across the ROIs (Fig. 2C; $p<0.0001$, $\chi^2 = 28.4$ with $df = 5$ numerator, $df = 57$ denominator). For each skill and each individual we calculated an index, based on the SWA topography, indicating whether for a specific skill an individual was delayed or ahead in maturation — the *SWA maturation index* (SWAMI). More specifically, for a specific skill an individual received an index of 0 if its SWA maximum was found within the ROI linked to that skill. If, however, the SWA maximum was in a ROI ahead or behind the maturation order of the ROIs (Fig. 2C), the individual received a positive or negative index, respectively. This procedure exemplified for the complex motor skill looks as follows: The maturational stage based on the SWA topography was ‘timed’ when the SWA maximum was located in the ROI ‘complex motor’ ($SWAMI_{\text{complex motor}} = 0$), ‘delayed’ when the SWA maximum was located in the ROI ‘vision’ ($SWAMI_{\text{complex motor}} = -3$), ‘visuomotor’ ($SWAMI_{\text{complex motor}} = -2$), or ‘simple motor’ ($SWAMI_{\text{complex motor}} = -1$), and ‘ahead’, if the SWA maximum was located in the ROI ‘language’ ($SWAMI_{\text{complex motor}} = +1$) or ‘cognitive control’ ($SWAMI_{\text{complex motor}} = +2$).

Next, in order to contrast the maturation of SWA topography and behavior, Spearman correlations were calculated between the SWAMI and the skill variables (Fig. 3, Fig. S2). Skills were averaged within subjects, resulting in one overall skill value for each ROI and correlated with the SWAMI. For pooled data points, both, skills and SWAMI were averaged within subjects.

For a comparison of the developmental trajectories, $SWAMI_{\text{complex motor}}$ and $skill_{\text{complex motor}}$ versus age were fitted by a double exponential function [$f = a \cdot (1 - \exp(-b \cdot x)) + c \cdot (1 - \exp(-d \cdot x))$], $R_{SWAMI} = 0.59$, $p_{SWAMI} < 0.0001$, $R_{\text{skill}} = 0.82$, $p_{\text{skill}} < 0.0001$, Fig. 4]. Both variables were z-scored across subjects.

Neuroimaging

To include an anatomical marker of cortical maturation in the comparison of developmental trajectories, we estimated gray matter thickness based on magnetic resonance images in a subgroup of subjects in which data was available (8–26 years). For this analysis, we used T1-weighted images obtained with General Electric Signa HDx 3T scanner. The sequence used was a 3-dimensional gradient-echo whole brain image (resolution 0.938 0.938 1.2 mm, TR = 8.928 ms, TE = 3.496 ms, FA = 13°). The Freesurfer version 4.5.0 for Mac OS 10.5.2

(<http://surfer.nmr.mgh.harvard.edu>) was used to extract the neocortices of each hemisphere. For between-subject comparisons, this software uses a spherical model for each hemisphere in the normalized Talairach–Tournoux space, which shows only the gyri and sulci most consistently found in different subjects. Cortical thicknesses are defined as the distances from the gray–white border to the pia mater, measured perpendicularly to the cortex. Since we wanted to compare anatomical and EEG measures as closely as possible, we measured the cortical thickness at the average Talairach coordinates of each electrode (average error 3.7 mm, SD 2.4 mm) (Lancaster et al., 1997; Lancaster et al., 2000). Note that these points were most often situated on the crowns of the gyri. Common for EEG measures are that not all neurons contribute equally to the signal (Nunez and Srinivasan, 2006). Thus, because of their small distance to the electrodes and the favorable orientation of their apical dendrites, the pyramidal neurons directly under the electrodes should contribute more to the EEG signal, as compared to more distant and deep neurons. Cortical thicknesses at neighboring points tend to be correlated significantly. Therefore, gray matter thicknesses below all electrodes in the ROI ‘complex motor’ were averaged for each subject, z-scored across subjects and contrasted with $SWAMI_{\text{complex motor}}$ and $skills_{\text{complex motor}}$ (Fig. 5). Negative gray matter values were used in order to directly compare the maturation of the three variables (i.e. the decrease in cortical thickness is represented as a maturational increase). We used regression analyses (double exponential) to uncover the maturational time point for each parameter (Supplementary methods).

Results

All of our subjects slept well, with sleep efficiency around 90%. They also showed expected age-related changes in sleep architecture, like an increase in REM sleep and a decrease in slow wave sleep (see Table S1 for details). In agreement with our previous analysis (Kurth et al., 2010), we found a shift of maximal SWA from posterior to anterior regions across age (Fig. 2A). For an anatomical localization of these regional changes, we co-registered the electrodes with the subject's magnetic resonance images (Fig. 1 and Fig. 2B). We found SWA maxima at the early ages over the visual cortex, later over visuomotor regions, followed by the primary and secondary motor cortex, language areas and finally over the frontal cortex (Fig. 2C).

Behavioral data (e.g. finger movements) collected in the same subjects allowed examining the direct relationship between the maturation of a specific skill and SWA topography. To do so, we defined a subject's maturational stage based on the topography of SWA, i.e. in which region of interest (vision, visuomotor, simple motor, complex motor, language, and cognitive control) a subject showed maximal SWA. This *SWA maturation index* (SWAMI) showed a positive correlation with skill performance ($R = 0.41$, $p < 0.002$, $n = 56$ when all skills were pooled; Fig. 3 for ‘complex motor’, Fig. S2). Thus, individuals with a higher SWAMI (i.e., with a more “mature” SWA topography), had also better skills.

Next, we compared the time course of SWA topography and skills across age (Fig. 4). We found that the maturation of SWA preceded the maturation of skills by ~3.7 years. Finally, in a subgroup of subjects we assessed the time course of gray matter thickness across age in relation to the time course of SWA topography and skills. In order to compare our

behavioral variables with the observed decrease of gray matter thickness, we presented this data in an inverted manner. This initial investigation suggests that cortical gray matter thickness matures after skills (Fig. 5, Supplementary methods).

Discussion

We found that the topography of SWA changed across age in a specific manner, as previously shown (Kurth et al., 2010). SWA maxima at the early ages were located over the visual cortex, then showed a spatial shift to anterior regions, reaching the frontal cortex in late adolescence. This finding is in line with behavioral observations that children's vision matures early and executive control functions late during development (Luna and Sweeney, 2004; Teller, 1981). Furthermore, anatomical changes, e.g. in cortical thickness, follow a similar spatial maturation (Shaw et al., 2008). Thus, our findings indicate that brain areas, which are currently maturing, display more sleep SWA than the rest of the cortex.

Compared to the analysis in Kurth et al. (2010) we used normalized SWA across all subjects (see Materials and methods for details). Such a normalization controls for stable regional differences in absolute EEG power and allows to better observe the regional changes in SWA across maturation. Most obviously, the SWA maximum not only shows a maturational shift from posterior to anterior along the midline (as shown in Kurth et al., 2010), but also additionally illustrates the maturation over temporal regions. This approach allowed us to assess direct relationships between the regional changes in SWA topography and skill maturation across the entire cortex (for example including language areas of the temporal cortex). The analysis showed that the maturation of SWA topography predicted the maturation of skills. Thus, the more mature, i.e. the more frontal, the topography of SWA was, the better subjects performed in behavioral tasks. We have defined ROIs for 'simple' functions (e.g. simple motor, complex motor) whose cortical representation should remain rather stable across development. However, performing tasks involving for instance cognitive control may activate differential prefrontal cortical regions in childhood, adolescence and adulthood, as shown in fMRI studies, e.g. (Luna and Sweeney, 2004). Such an age dependent change in cortical activation is a possible explanation why correlations with SWAMI were strong for complex motor skills but weaker for cognitive control. Another explanation for the strong relationship of SWAMI and complex motor skills might be that for this skill behavioral data were available from a large number of subjects ($n = 56$) and covered a broad age range of subjects (4–26 y). Task restrictions limited the age range for other skills and as a consequence reduced statistical strength and may not have equally covered the developmental window.

A clear limitation of our study is that it only includes cross-sectional data and thus conclusions about development may be confounded (Kraemer et al., 2000). Moreover, a general challenge in the interpretation of maturational findings is that many behavioral and neural mechanisms undergo parallel maturation. This complicates the distinction between correlated and causal maturational factors. Accordingly, whether a causal relationship exists or whether the two variables follow parallel changes cannot be concluded from this analysis. However, support for a causal relationship is given by the *Synaptic Homeostasis Hypothesis*, which proposes a close relationship between neuronal plasticity during waking and sleep

(Tononi and Cirelli, 2006). The hypothesis links the well-known homeostatic regulation of sleep (Borbély and Achermann, 2005) to the homeostatic regulation of synaptic strength. Studies in various species (*Drosophila melanogaster*, mouse, rat and human) using state of the art methodologies (Western blots and confocal microscopy, recording of miniature excitatory post-synaptic currents, local field potential recordings and transcranial magnetic stimulation) indeed indicate that wakefulness is associated with a net increase in synaptic strength (Bushey et al., 2011; Gilestro et al., 2009; Huber et al., 2012; Liu et al., 2010; Vyazovskiy et al., 2008). In contrast, sleep results in a re-normalization of such increased synaptic strength after waking (Bushey et al., 2011; Gilestro et al., 2009; Huber et al., 2012; Liu et al., 2010; Vyazovskiy et al., 2008).

The reason for the close relationship between slow waves and changes in synaptic strength is based on the generation of such sleep oscillations on the neuronal level. Intracellular recordings showed that EEG slow waves stem from slow oscillations of the membrane potential, alternating between hyperpolarized “down” states and depolarized “up” states (Steriade et al., 1993a; Steriade et al., 1993b). Multiunit recordings in the rat now show that when sleep pressure is high, and presumably synaptic strength is increased (Vyazovskiy et al., 2008), the synchronization of “up” (ON) or “down” (OFF) states is high across units (Vyazovskiy et al., 2009). Such synchronized fluctuations of membrane potentials across large neuronal networks give rise to large amplitude slow waves on the scalp EEG. In the course of a sleep period, when sleep pressure dissipates, and presumably synaptic strength re-normalizes, unit activity becomes less synchronized giving rise to lower amplitude slow waves (Vyazovskiy et al., 2008; Vyazovskiy et al., 2009). Thus, brain areas which undergo extensive plastic changes during maturation, resulting in large changes in synaptic strength and/or densities should show largest amplitude slow waves.

Aside from that, the above mentioned hypothesis claims that SWA not only reflects synaptic strength but also plays an important role in its regulation (Tononi and Cirelli, 2006). Namely, SWA was suggested as an active component triggering the downscaling of synaptic strength. Because of this possible direct impact of slow waves on synaptic plasticity we investigated the temporal relationship between SWA maturation and maturation of skills. We found a time lag of about 3.7 years between the maturation of SWA topography and the maturation of skills. This time lag of skill maturation to SWA topography maturation may indicate that sleep slow waves are involved in or potentially even contribute to the development of skills and thus supports a role of slow waves also during the long-term plastic changes during development. Thus, high SWA would not only reflect increased synaptic strength/density but also be related to its reduction due to slow wave dependent synaptic re-normalization. Indeed, recent research provides evidence for the impact of specific burst firing, the characteristic firing pattern of sleep slow oscillations (Steriade et al., 1993a; Steriade et al., 1993b), on the functional change of glutamatergic synapses (Birtoli and Ulrich, 2004; Lante et al., 2011). The application of burst firing in pyramidal neurons of cortical slices induced the elimination of AMPA receptors, and input-specific long-term depression (Birtoli and Ulrich, 2004; Lante et al., 2011). Since synaptic plasticity of neural circuits represents a continuum from strengthening or weakening of existing synapses to structural plasticity, including synapse formation and elimination (Holtmaat and

Svoboda, 2009), the impact of sleep SWA on synaptic strength may ultimately result in changes in cortical connectivity. Indeed a recent study provides evidence for the involvement of sleep in structural changes during development: Imaging spine turnover using two-photon microscopy in adolescent mice revealed a net spine loss during sleep (Maret et al., 2011).

A widely used marker of cortical maturation is gray matter thickness as assessed by magnetic resonance imaging (Shaw et al., 2008; Sowell et al., 2003). It is well known that cortical thickness decreases considerably during childhood and adolescence, as shown in cross-sectional and longitudinal studies (Giedd et al., 1999; Gogtay et al., 2004; Shaw et al., 2008; Sowell et al., 2004). This phase of cortical thinning has been hypothesized to reflect neuronal refinement in terms of selective elimination of synapses, resulting in the improvement of cognitive abilities (Giedd et al., 1999; Shaw et al., 2008). Since in a subgroup of subjects we obtained also structural magnetic resonance images, we were wondering how the time course of gray matter thickness across age relates to the time course of SWA topography and skills. In line with the literature, the time course of gray matter reduction did not level off until the mid 20s (Shaw et al., 2008; Sowell et al., 2007). In our data complex motor skills level off at the beginning of the third decade. This corresponds to numerous studies showing a peak for motor functioning in the early 20s and age related changes following a quadratic function (Voelcker-Rehage, 2008). In comparison, our preliminary analysis suggests that cortical gray matter thickness matures after skills, since gray matter thinning took place until the age limit of our sample at 26 years. The observation of gray matter thickness being the latest measure to mature may be explained by the fact that gray matter changes assessed by structural magnetic resonance imaging not only reflect changes in the number of synapses, but are also influenced by changes in hydrophobic lipids and iron content, or the age-related increase in myelination (Paus et al., 2001; Steen et al., 1997). How such microstructural changes are affecting electroencephalographic SWA needs to be investigated. Nevertheless, since numerous structural features (skull thickness, liquid layers, etc.) were excluded to substantially affect EEG power measures (Buchmann et al., 2011), sleep SWA may allow a rather direct quantification of cortical synaptic strength.

Another explanation for our observation that the changes in SWAMI precede skill and gray matter maturation is that the variables reflect different aspects of maturation. The plastic changes related to skill maturation may include several phases: Synapse formation, changes in synaptic strength (i.e. synaptic potentiation), and synaptic pruning. Numerous studies show a close relationship between sleep SWA and synaptic strength (Esser et al., 2007; Vyazovskiy et al., 2008; Vyazovskiy et al., 2007). In line with this observation, are synapse formation and synaptic potentiation reflected by an increase in SWA (Huber et al., 2007; Huber et al., 2004), synaptic pruning, on the other hand, is related to a decrease of SWA (Buchmann et al., 2010). Since the SWAMI depends on maximal SWA it may rather represent the initial phases (formation, potentiation). Another important aspect is that skill maturation not only depends on gray but also on white matter maturation. Thus, in particular for advanced behavioral functions, representing an interplay of several cortical regions, efficient fiber myelination might be an important contributor (Deutsch et al., 2005). However, white matter maturation seems to be reflected by changes in EEG coherence rather than changes in EEG power (Tarokh et al., 2010). Thus, processes of fiber

myelination may significantly affect skill performance but not similarly affect sleep SWA. However, sleep slow waves may also represent an interesting marker for such white matter changes since slow waves were shown to travel across the cortex (Massimini et al., 2004) and thereby revealing the major connectional backbone of the cortex (Murphy et al., 2009). We thus believe that our electrophysiological measure might provide a promising tool to study these processes in more detail.

Conclusions

In conclusion, the mapping of cortical maturation by sleep SWA can serve as a promising intermediate characteristic between genes and behavior, which might contribute to the understanding of complex developmental disorders. We believe that the topographical recording of SWA provides advantages for the following reasons: The noninvasive tool enables the acquisition of spontaneous neuronal activity during natural sleep in sensitive populations such as children and patients with a neurologically pathological phenotype. Confounding factors are minimized, and the recording is not affected by attention levels, permitting an undisturbed assessment of brain activity across the scalp. And finally, the duration of monitoring is merely restrained to the duration of sleep, allowing several hours of data acquisition. The reflection of cortical maturation in SWA, together with increasing evidence of SWA as regulator of synaptic strength outlines the relevance of sleep SWA as marker for cortical changes.

Finally, it might be time to focus also on neuronal activity during sleep and not only during wakefulness. We believe that sleep SWA could be used as a window to gain insight into maturational processes of the cortex. Moreover, SWA might even contribute to these plastic changes and be involved in the “hardwiring” of neuronal connections.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by a Swiss National Science Foundation Grant PP00A-114923 (R.H.), a research grant from the University Research Priority Program of the University of Zurich (R.H., O.G.J.), a National Institutes of Health Grant K01MH074643 (M.L.B.), and by a loan of technical material by Giulio Tononi and Electrical Geodesics.

Appendix A. Supplementary data

Supplementary data to this article can be found online at [doi:10.1016/j.neuroimage.2012.03.053](https://doi.org/10.1016/j.neuroimage.2012.03.053).

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Fig. 1. Electrode localization and *regions of interest* (ROIs). (A) Co-registration of electrodes with T1-weighted magnetic resonance images. Standard electrodes are labeled on the right side (RM = right mastoid). (B) Layout of high density EEG electrode net in top view (adapted from the Electrical Geodesics, Inc.). Based on Talairach coordinates (Lancaster et al., 1997; Lancaster et al., 2000), electrodes were assigned to ROIs, which were defined according to Brodmann areas (BA) associated with a skill. The table contains the electrode numbers and BAs for all ROIs (color coded). Remaining electrodes were attributed to closest ROIs (colored open circles, i.e. 5, 12, 38, 121 to ‘cognitive control’; 6, 13, 29, 111 to ‘complex motor’, and 52 to ‘simple motor’; this was the case in n = 11).

Fig. 2.

Maturation of sleep *slow-wave activity* (SWA). (A) SWA distribution for age groups: Top 25% of SWA values are mapped. (B). *Regions of interest* (ROIs) based on anatomical electrode localization using Brodmann areas (see Fig. 1). (C). SWA topography maturation reflected by the ROI with maximal SWA (SWA maxima located in vision in $n = 5$ subjects, visuomotor $n = 3$, simple motor $n = 3$, complex motor $n = 12$, language $n = 6$, cognitive control $n = 34$). The age of subjects with maximal SWA in the same ROI was averaged (thin vertical lines) and variability is presented as mean $\pm 2^* SE$.

Fig. 3.

Relationship between *SWA maturation index* (SWAMI) and skills in 'complex motor'.

SWAMI identified which ROI contained the single electrode with maximal SWA in each subject (see Figs. 1 and 2). SWAMI thus represents the maturational stage of a subject's topographical SWA map. SWAMI predicted complex motor skills (Spearman, $R = 0.31$, $p = 0.02$, $n = 56$, 4.4–25.9 y). Points are color coded for age groups (black = youngest, light blue = oldest, colors refer to same age groups as in Fig. 2). The Spearman correlations between SWAMI and skills for the other ROIs revealed $R_{\text{visuomotor}} = 0.12$, $p_{\text{visuomotor}} = 0.46$; $R_{\text{simple motor}} = 0.27$, $p_{\text{simple motor}} = 0.09$; $R_{\text{language}} = 0.33$, $p_{\text{language}} = 0.14$; $R_{\text{cognitive control}} = 0.21$, $p_{\text{cognitive control}} = 0.35$, see Fig. S2.

Fig. 4.

Maturation of *SWA maturation index* (SWAMI) and skills in 'complex motor'. Data were fitted with a double exponential function [$f = a \cdot (1 - \exp(-b \cdot x)) + c \cdot (1 - \exp(-d \cdot x))$]. The results show that SWAMI (solid, black) increases before skills (dashed, blue, $R_{\text{SWAMI}} = 0.59$, $p_{\text{SWAMI}} < 0.0001$, $R_{\text{skill}} = 0.82$, $p_{\text{skill}} < 0.0001$, both $n = 56$). For example, when y is fixed at -1 , skills are delayed relative to SWAMI by 3.7 years. The dotted line represents the extrapolation of the fit to younger ages. Gray dots represent SWAMI of subjects that were not included in the curve fit ($n = 7$). Both variables were z-scored across subjects.

Fig. 5.

Gray matter (gray, dashed line) and skills (blue, solid line) fitted by a double exponential function [$f = a \cdot (1 - \exp(-b \cdot x)) + c \cdot (1 - \exp(-d \cdot x))$], both $n = 44$, $R_{\text{Skills}} = 0.65$, $p_{\text{Skills}} < 0.0001$, $R_{\text{Gray matter}} = 0.45$, $p_{\text{Gray matter}} = 0.03$]. SWAMI of an extended sample was added ($n = 63$, black, dotted line and open circles (same fit, $R_{\text{SWAMI}} = 0.77$, $p_{\text{SWAMI}} < 0.0001$)). All variables were z-scored across subjects, and gray matter values were inverted.