



## Increased frontal sleep slow wave activity in adolescents with major depression



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### ABSTRACT

Sleep slow wave activity (SWA), the major electrophysiological characteristic of deep sleep, mirrors both cortical restructuring and functioning. The incidence of Major Depressive Disorder (MDD) substantially rises during the vulnerable developmental phase of adolescence, where essential cortical restructuring is taking place. The goal of this study was to assess characteristics of SWA topography in adolescents with MDD, in order to assess abnormalities in both cortical restructuring and functioning on a local level. All night high-density EEG was recorded in 15 patients meeting DSM-5 criteria for MDD and 15 sex- and age-matched healthy controls. The actual symptom severity was assessed using the Children's Depression Rating Scale–Revised (CDRS-R). Topographical power maps were calculated based on the average SWA of the first non-rapid eye movement (NREM) sleep episode. Depressed adolescents exhibited significantly more SWA in a cluster of frontal electrodes compared to controls. SWA over frontal brain regions correlated positively with the CDRS-R subscore “morbid thoughts”. Self-reported sleep latency was significantly higher in depressed adolescents compared to controls whereas sleep architecture did not differ between the groups. Higher frontal SWA in depressed adolescents may represent a promising biomarker tracing cortical regions of intense use and/or restructuring.

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### 1. Introduction

Depression is one of the leading causes of disease burden worldwide (Hyman et al., 2006). It is a highly disabling, often chronic illness, associated with increased risk of suicide (Ferrari et al., 2013). The incidence of Major Depressive Disorder (MDD) is relatively low in younger children (Kessler et al., 2001), yet rises substantially throughout adolescence (Green et al., 2005), with an almost twofold increase of the lifetime prevalence between age 13 (8.4%) and 18 (15.4%) (Merikangas et al., 2010). This increasing emergence of depression during a vulnerable developmental period (Blakemore and Choudhury, 2006) coincides with pronounced structural and functional modifications in the brain (Paus et al., 2008). These alterations are not paused during sleep, in contrast, sleep is considered an active process, also in the development of the central nervous system (Hobson and Pace-Schott, 2002). Increasing evidence suggests a close relationship between sleep and cortical plasticity (Diekelmann and Born, 2010; Tononi and Cirelli, 2014).

Specifically, the slow fluctuations of cortical activity during deep sleep, visible in the surface electroencephalography (EEG) as slow waves (Steriade et al., 1993) and measured as slow wave activity (SWA; frequency range 0.75–4.5 Hz), have been shown to mirror the extensive synaptic reorganization of cortical areas from early childhood to late adolescence (Campbell and Feinberg, 2009; Kurth et al., 2010). SWA is further closely related to efficient cognitive functioning (Born et al., 2006; Tononi and Cirelli, 2014) and may be involved in the consolidation of memories related to emotions, thoughts and actions (Rasch and Born, 2013). Reported sleep disturbances as a core symptom of MDD and altered sleep structure have long been a major area of research in depression. In depressed adults, alterations in sleep structure such as decreased slow wave sleep are quite consistently observed (Benca et al., 1992; Borbely and Wirz-Justice, 1982) and have been proposed as biomarkers predicting treatment response to a specific antidepressant or even the course of the disorder (Steiger and Kimura, 2010). Findings related to sleep structure in youth have been inconsistent so far (Riemann et al., 2001; Tesler et al., 2013).

As a major marker of the homeostatic regulation of sleep, several studies investigated sleep SWA in the context of MDD. Results of these studies in adults are inconsistent showing reduced (Armitage et al.,

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2001), but also increased SWA at baseline (Frey et al., 2012) as well as after sleep deprivation (Frey et al., 2012). To our knowledge, only one study up to now focused on SWA in depressed adolescents, reporting lower SWA in depressed males compared to controls (Lopez et al., 2012). However, none of the previous studies used high-density EEG (hdEEG) to investigate topographical aspects of the SWA distribution.

Therefore, the main emphasis of our study was to investigate SWA topography in adolescents diagnosed with MDD by means of hdEEG, to detect abnormalities in both cortical restructuring and functioning on a local level.

## 2. Methods

### 2.1. Participants

Fifteen children and adolescents (age range: 12.9–16.6 years, mean  $\pm$  SEM: 15.1  $\pm$  0.3) meeting criteria of a Major Depressive Disorder, single episode or recurrent, according to DSM-IV and DSM-5 (American Psychiatric Association, 1994, 2013) were recruited from in- and outpatient settings at the University Clinics for Child and Adolescent Psychiatry, University of Zurich, Switzerland.

DSM diagnoses were assessed by two child and adolescent psychiatrists using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID), a semi-structured interview for children and adolescents (Sheehan et al., 2010). Past psychiatric illness and treatment information was obtained from the parent/guardian and augmented by medical chart information. The actual symptom severity was further assessed using the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski and Mokros, 1996); (Keller et al., 2011). The total sum score as well as five subscores (Guo et al., 2006) (observed depressive mood; anhedonia; morbid thoughts; somatic symptoms; reported depressive mood) were derived. Clinical and functional impairment were assessed using the Clinical Global Impression

Scale (CGI) (Guy, 1976) and the Global Assessment of Functioning (GAF) (Hall, 1995). Self reported pubertal status and parental socioeconomic status of all participants were assessed using the Tanner scales (Carskadon and Acebo, 1993) and the Hollingshead socioeconomic state scale (Hollingshead, 1975), respectively. The Wechsler Intelligence Scale for Children WISC IV (Daseking et al., 2007) and for 2 control participants the TONI-IV (Brown et al., 1997), were used to assess overall cognitive performance.

Exclusionary psychiatric disorders were: schizophrenia, bipolar disorder, autism spectrum disorder, eating disorder, and substance-dependence. Other comorbidities frequently present in adolescents with MDD such as anxiety or attention-deficit disorders were permitted (Kessler et al., 2003), given that MDD was the primary diagnosis (see Table 1 for details). Participants with an intelligence quotient (IQ) < 85 (Brown et al., 1997; Daseking et al., 2007) and a medical/neurological condition known to affect the brain were also excluded.

At the time of the sleep recordings, adolescent patients with depression had an actual severity of depressive symptoms between 21 and 61 (mean score 41.7  $\pm$  3.0). The mean ( $\pm$  SEM) duration of the current MDD episode was 39.5 ( $\pm$  7.8) weeks and the total illness duration was 95.3 ( $\pm$  18.6) weeks (Table 1). The depressed patients were mostly treated in an inpatient setting ( $n = 8$ , 53%), followed by day-clinics ( $n = 4$ , 27%) and outpatient settings ( $n = 3$ , 20%). The majority of the patients received selective-serotonin-reuptake-inhibitors (SSRIs) ( $n = 9$ , 60%) (Table 1). One patient additionally received a tricyclic antidepressant (Mirtazapine), one patient was treated with atypical antipsychotic medication (Quetiapine) and five patients ( $n = 5$ , 33%) were medication naive (Table 1).

Fifteen healthy controls were sex- and age-matched to the patient group (age range: 12.8–16.4 years, mean  $\pm$  SEM: 15.3  $\pm$  0.3). They underwent a telephone and questionnaire screening to exclude personal and family history of psychiatric disorders, chronic diseases, learning disabilities, sleep disorders and use of psychotropic medication.

**Table 1**  
Sample characteristics.

Sample characteristics	Depressed (N = 15)	Controls (N = 15)
Age, years, mean $\pm$ SEM, range	15.1 $\pm$ 0.3, 12.9 - 16.6	15.3 $\pm$ 0.3, 12.8 - 16.4
Sex, female, N (%)	8 (53)	8 (53)
IQ, mean $\pm$ SEM, range	113.5 $\pm$ 2.6, 98.0 - 129.0	115.8 $\pm$ 6.1 <sup>a</sup> , 102.0 - 131.0
Socio Economic State Scale, mean $\pm$ SEM, range	5.3 $\pm$ 0.4, 2.0 - 8.0	3.5 $\pm$ 0.4 <sup>b</sup> , 3.0 - 4.0
Tanner Pubertyscale, mean $\pm$ SEM, range	9.7 $\pm$ 0.3, 7.0 - 11.0	9.5 $\pm$ 0.8 <sup>c</sup> , 7.0 - 12.0
Current DSM-5 Diagnoses, N (%)		
Major Depressive Disorder (MDD)	15 (100)	N/A
Anxiety Disorders	6 (40)	
Panic Disorder	1 (7)	N/A
Social Phobia	4 (27)	N/A
Specific Phobia	2 (13)	N/A
Neurodevelopmental and conduct disorders <sup>d</sup>	4 (27)	
ADHD	4 (27)	N/A
Conduct Disorder	2 (13)	N/A
Characteristics of illness and functioning, mean $\pm$ SEM, range		
Total duration of illness, weeks	95.3 $\pm$ 18.6, 13.0 - 295.0	N/A
Duration of current MDD episode, weeks	39.5 $\pm$ 7.8, 13.0 - 108.0	N/A
Actual Severity of Depression, CDRS-R Sum Score	41.7 $\pm$ 3.0, 21.0 - 61.0	N/A
Illness Severity: Clinical Global Impressions-Severity Scale	4.5 $\pm$ 0.2, 3.0 - 6.0	N/A
Current Functional Level: Global Assessment of Functioning-Scale	52.8 $\pm$ 4.0, 21.0 - 90.0	N/A
Treatment setting and medication at time of the sleep recordings		
Inpatients/Day-Clinics/Outpatients (%)	8/4/3 (53/27/20)	none
Receiving psychotropic medication, N (%) <sup>e</sup>	10 (67)	none
Medication class, N (%)		
Selective-Serotonin-Reuptake-Inhibitors <sup>f</sup>	9 (60)	none
Noradrenergic and Specific Serotonergic Antidepressant (Mirtazapine)	1 (7)	none
Atypical Antipsychotic (Quetiapine)	1 (7)	none

N/A = not available;

<sup>a</sup> Data available for 8 adolescents.

<sup>b</sup> Data available for 2 adolescents.

<sup>c</sup> Data available for 9 adolescents.

<sup>d</sup> The total number of patients in one diagnostic category can be smaller than the sum of the individual diagnoses due to comorbidity.

<sup>e</sup> The total number of patients receiving psychotropic medication is smaller than the sum of the agents due to one patient who received Sertraline and Mirtazapine.

<sup>f</sup> Selective-Serotonin-Reuptake-Inhibitors include Fluoxetine (N = 4), Citalopram (N = 1), Sertraline (N = 4). Differences were compared by using two tailed, unpaired Student's t-test.

Written informed consent was obtained from the legal guardian of minors, and an additional written assent was obtained from each minor after careful 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. All subjects were non-smokers. One week prior to the study, all participants were instructed to maintain regular sleep–wake schedules according to their habitual bedtimes and to keep their caffeine consumption on restricted levels. Compliance was monitored with self-reported sleep logs and wrist motor actigraphy (Actiwatch Plus, AW4, Cambridge Neurotechnology, Cambridge, England). Visual inspection of this data showed in none of the subjects deviations from the instructions. To investigate the process of differential adaptation to the sleep laboratory in the two groups, we analyzed the reported prior total time in bed and total sleep time during both, weekdays and weekends. In addition, all participants were asked to protocol their alcohol consumption, their smoking habits as well as use of medication, by indicating time of the day and amount of drug intake or state ‘no drug consumption at all’ in a diary. According to these protocols, all participants were non-smokers and did not drink alcohol one week prior to measurement night. Twenty-four hours before the sleep assessment, they were asked to refrain from alcohol, caffeine and to avoid naps. At study entry, participants underwent a questionnaire screening where they were asked to report on their habitual sleep parameters, including total sleep time and sleep latency.

## 2.2. Recording and preprocessing of EEG data

All EEG data were collected in the sleep laboratory of the University Children’s Hospital Zurich with a hd EEG device (Electrical Geodesic Inc. Sensor Net for a long-term monitoring, 128 channels). The net sizes were selected according to the head circumference of each participant. Next, the nets were adjusted to the vertex and the cap electrodes were filled with gel electrolyte. The nets were adjusted to each participants’ head to ensure stability of the nets in the course of the night. Impedances were measured at the beginning and end of the recording and were stable below 50 k $\Omega$ . The sleep episode of each participant was scheduled according to habitual bedtimes.

EEG recordings were sampled at 500 Hz (filtered between 0.01–200 Hz) and referenced to the vertex (Cz). The data was then band-pass filtered between 0.5 and 50 Hz and downsampled to 128 Hz. After visually scoring for sleep stages (20 s epochs, American Academy of Sleep Medicine standard criteria (Iber et al., 2007)), artefacts were rejected on a 20 s basis after visual inspection and if power exceeded a threshold based on a mean power value in the 0.75–4.5 and 20–30 Hz bands (Kurth et al., 2010). After exclusion of EEG channels of insufficient quality (on average, 2 channels per participant) the data was rereferenced to average reference. Sleep cycles including NREM and REM sleep episodes were defined according to the criteria of (Feinberg and Floyd, 1979).

## 2.3. EEG power analysis, spectral analysis and statistics

We performed spectral analysis of consecutive 20 s epochs (fast Fourier transform routine, Hanning window, averages of five 4 s epochs, frequency resolution of 0.25 Hz). To assess topographical differences between the groups, SWA was calculated as mean power in the range of 1–4.5 Hz during the first NREM sleep episode. We selected this time interval to account for differences in sleep episode durations and because it belongs to the most consolidated part of sleep. To assess significant topographical differences in SWA between the groups and to define a specific region of interest, we applied statistical nonparametric mapping (SnPM) using a suprathreshold cluster analysis for multiple comparisons (Nichols and Holmes, 2002) as done in previous studies (Huber et al., 2004; Kurth et al., 2010; Ringli et al., 2013). To evaluate a possible effect of medication, we performed an exploratory analysis,

by splitting the patient group into a group with (N=10) and a group without medication (N=5) (for more details see Supplemental Figures 2 and 3). Anatomical localization of electrodes was verified in previous studies (Kurth et al., 2012) using magnetic resonance imaging (MRI) and the positioning software SofTactic Optic (EMS Inc). Electrodes were digitized and co-registered with the subject’s MRI (for details see (Kurth et al., 2012)). We found a high agreement between the alignment of the electrode location and the corresponding anatomical area in a previous study (Kurth et al., 2012). To correct for multiple comparisons across the 0–20 Hz frequency band (0.25 Hz steps), we used a false discovery rate (FDR) correction. Two-way analysis of variance (ANOVA) was performed with group and sex as independent factors and SWA as dependent factor. Pearson product–moment correlation coefficients were calculated to assess relationships between SWA and actual symptom severity (CDRS-R total score and subscores) in the affected sample. Because the data was normally distributed all other variables were compared between the groups by using unpaired t-tests. Data variability is described as standard error of the mean (SEM) and range. All analyses were performed with the software package MATLAB (MathWorks) and SPSS 20.0.

## 3. Results

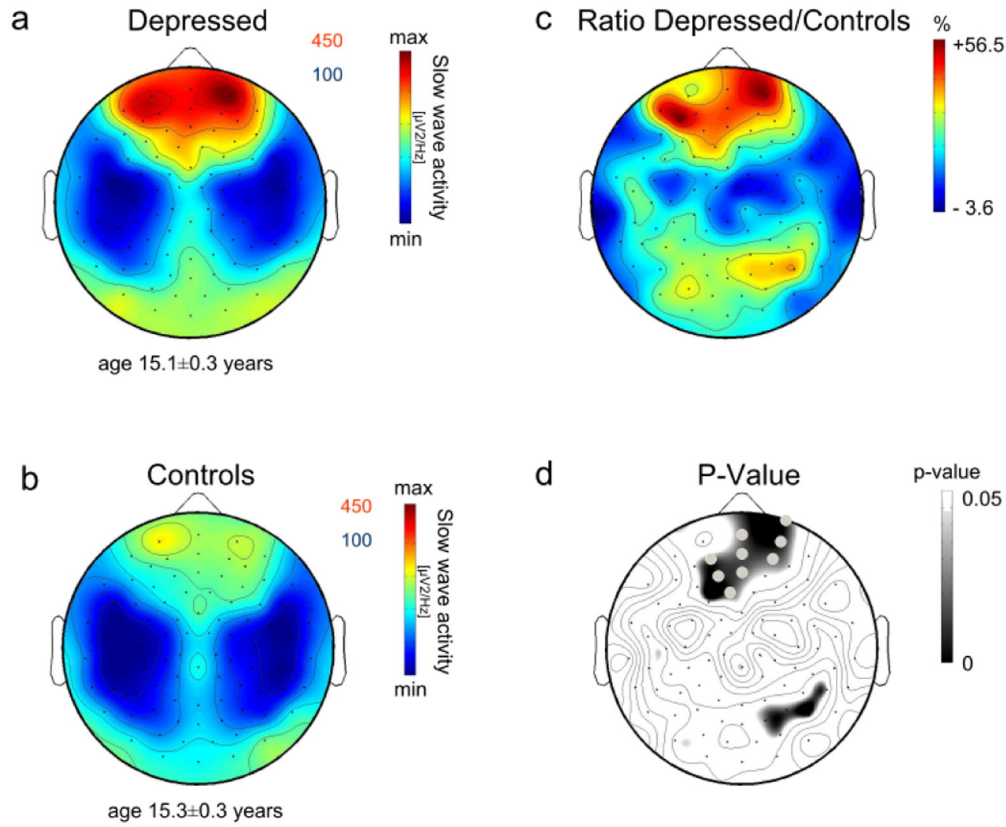
### 3.1. Sleep architecture

First, evaluate any potential differences in sleep duration before entering the study, we compared the reported habitual total time in bed and total sleep time for both groups. There were no significant group differences ( $p = 0.1 - 0.7$ , range of p-values for the four comparisons) (Table 2). Next, we examined visually scored sleep variables of the experimental night to evaluate the sleep quality of the samples. Sleep quality was comparably good in both groups, thus showing high sleep efficiency (>90%). All other sleep stage measures were comparable between the groups with no significant differences (Table 2). Only the self-reported sleep latency was significantly higher in depressed adolescents compared to controls ( $31.2 \pm 6.9$  vs.  $19.0 \pm 2.3$  min,  $p = 0.05$ ) (Table 2).

**Table 2**  
Reported and visually scored sleep variables.

	Depressed mean $\pm$ SEM, range	Controls mean $\pm$ SEM, range
<i>Reported sleep times</i>		
Reported sleep latency (min)	$31.2 \pm 6.9^*$ , 10.0–120.0	$19.0 \pm 2.3$ , 5.0–30.0
Total time in bed (weekdays)	$8.9 \pm 0.4$ , 6.7–11	$9.6 \pm 0.2$ , 8.8–10.9
Total time in bed (weekends)	$10.3 \pm 0.4$ , 7.3–12.2	$10.4 \pm 0.2$ , 9.0–11.8
Total sleep time (weekdays)	$7.3 \pm 0.2$ , 5.8–8.5	$7.9 \pm 0.2$ , 6.9–8.9
Total sleep time (weekends)	$8.9 \pm 0.4$ , 6.8–10.8	$9.5 \pm 0.2$ , 8.8–10.3
<i>Visually scored sleep variables</i>		
Sleep latency (min)	$18.5 \pm 3.6$ , 4.7–50.3	$22.3 \pm 4.1$ , 6.3–55.3
REMS latency (min)	$109.1 \pm 8.3$ , 62.3–172.0	$140.4 \pm 13.4$ , 78.3–220.3
Wake after sleep onset (min)	$13.2 \pm 3.4$ , 2.7–55.0	$21.2 \pm 4.4$ , 4.7–66.7
Sleep stage 1 (%)	$6.3 \pm 1.0$ , 2.8–14.1	$6.7 \pm 0.6$ , 3.6–10.6
Sleep stage 2 (%)	$50.3 \pm 1.7$ , 36.8–59.3	$52.8 \pm 1.1$ , 43.9–58.3
Sleep stage 3 (%)	$22.7 \pm 2.0$ , 14.2–44.0	$22.7 \pm 1.3$ , 14.4–32.3
REMS (%)	$20.7 \pm 1.8$ , 12.2–28.7	$17.7 \pm 1.3$ , 10.7–26.9
Total sleep time (min)	$429.6 \pm 23.8$ , 344.0–529.3	$427.9 \pm 17.6$ , 272.7–540.3
Total time in bed (min)	$462.4 \pm 21.4$ , 407.0–552.0	$468.8 \pm 14.5$ , 365.3–565.0
Sleep efficiency (%)	$92.0 \pm 2.0$ , 84.5–98.8	$90.9 \pm 1.5$ , 74.6–97.7

*Reported sleep times:* Reported sleep latency in minutes, total time in bed on weekdays in hours, total time in bed on weekends in hours, total sleep time on weekdays in hours, total sleep time on weekends in hours; *Visually scored sleep variables:* Sleep latency in minutes, rapid eye movement (REM) sleep latency in minutes, wake after sleep onset in minutes, sleep stage 1 in percent (%), sleep stage 2 in %, sleep stage 3 in %, REM sleep in %, total sleep time in minutes, total time in bed in minutes and sleep efficiency in %. Differences were compared by using two tailed, unpaired Student’s t-test. \* Represent significant differences ( $p \leq 0.05$ ).

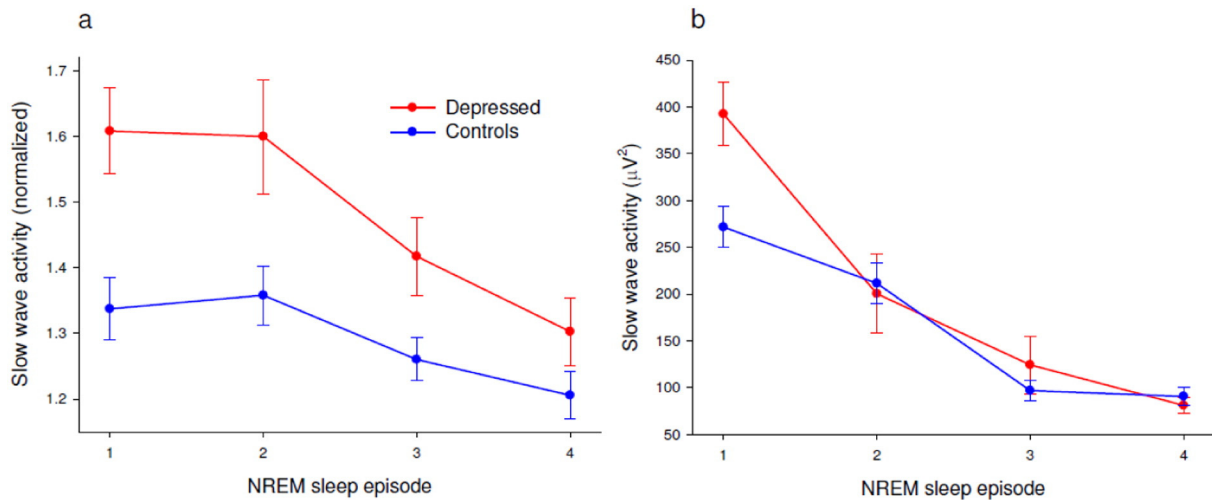


**Fig. 1.** (a, b). Topographical distribution of SWA (EEG power between 1–4.5 Hz) for the first NREM sleep episode in depressed subjects (a) and healthy, age- and sex-matched control subjects (b). Values are colour coded (maxima in red, minima in blue) and plotted on the planar projection of the hemispheric scalp model. The numbers in the right upper corner of each topographical plot represent the maximal (red) and minimal (blue) value of SWA. (c, d). Topographical distribution of the difference in SWA between depressed and control subjects (ratio depressed/controls). Values are colour coded (group differences in percentage %). SWA was increased by 43.7% ( $\pm 1.7\%$  SEM) at a frontal cluster of 9 electrodes (c), indicated as grey dots ( $p < 0.05$ , SnPM, suprathreshold cluster test controlling for multiple comparisons, *Nichols and Holmes, 2002*) (d).

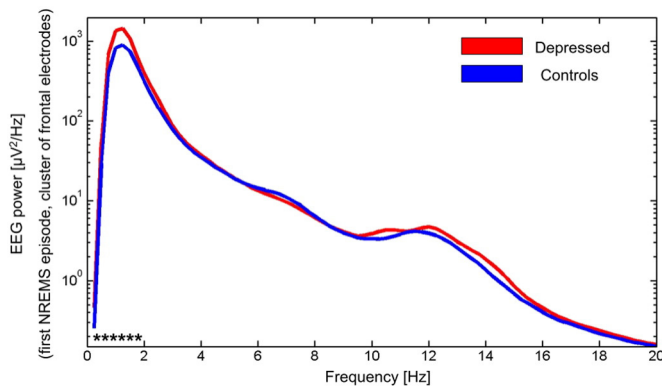
**3.2. Topographical distribution of SWA in depressed adolescents compared to healthy controls**

To investigate the topography of sleep SWA in adolescents with depression, we calculated EEG power maps for each group. The

topographical distribution of absolute values of SWA in the first NREM sleep episode showed regional differences with maxima over the frontal cortex and minima over the temporal lobes (Fig. 1a and b). When contrasting the maps, we found higher SWA over the frontal cortex in depressed adolescents (Fig. 1c and d). Compared to age- and sex-matched



**Fig. 2.** Slow wave activity time course in the cluster of 9 electrodes showing a significant difference between depressed ( $n = 15$ ) and healthy, age- and sex-matched control subjects (see Fig. 1) for the first 4 NREM sleep episodes. When we normalized SWA, by dividing SWA for each electrode by the average SWA across all electrodes, to account for differences in global SWA, SWA in the frontal cluster remained significantly higher from the first to the third NREM sleep episode ( $p < 0.05$ , two tailed, unpaired Student's t-test) (a). SWA was different in the first NREM sleep episode ( $p < 0.01$ , two tailed, unpaired Student's t-test) (b). There were no significant group differences in the timing and length of the NREM sleep episodes (data not shown).



**Fig. 3.** EEG power spectra for the cluster of 9 electrodes showing significant differences in SWA between depressed and control subjects during the first NREM sleep episode. \* indicate frequency bins for which power in the depressed group ( $n = 15$ ) differed significantly ( $p < 0.05$ ) from the controls (two tailed, unpaired Student's *t*-test).

controls, depressed adolescents exhibited 43.7% ( $\pm 1.7\%$ ,  $p = 0.01$ ) more SWA in a cluster of 9 frontal electrodes (SnPM, see [Methods](#) for details; [Fig. 1d](#)).

To evaluate the effects of sex, a two-way ANOVA confirmed a significant group effect with higher frontal SWA in the cluster of 9 frontal electrodes for the first NREM sleep episode in depressed adolescents ( $F(1,26) = 9.7$ ,  $p = 0.004$ ) but showed no effect of sex ( $F(1,26) = 0.8$ ,  $p = 0.4$ ) and no interaction sex  $\times$  group ( $F(1,26) = 1.6$ ,  $p = 0.2$ ).

For an anatomical localization of the frontal cluster, orthogonal projection of the electrodes onto the cortex localized all 9 electrodes to the frontal lobe, superior frontal gyrus (8 electrodes to Brodmann area (BA) 10 and 1 electrode to BA 8).

### 3.3. SWA time course across the sleep cycles

As expected, SWA was increased during the first NREM sleep episode, but we found no statistically significant differences during the following episodes ([Fig. 2](#)). When we normalized SWA for each electrode by the average across all electrodes, to account for differences in global SWA, SWA in the frontal cluster remained significantly higher from the first to the third NREM sleep episode in depressed adolescents compared to age- and sex-matched controls ([Fig. 2](#)).

### 3.4. Frequency-specific frontal increase in depressed adolescents

In order to assess whether the observed frontal increase in SWA was restricted to the SWA frequency range ( $< 4.5$  Hz), we examined the entire frequency spectrum. We found that the increase in SWA in the 9 significant frontal electrodes was specific for the low frequency range ( $< 2$  Hz) in the depressed group ([Fig. 3](#)) compared to controls ( $p = 0.02$ , FDR corrected).

### 3.5. Associations with actual symptom severity

We further investigated the relationship between SWA and actual symptom severity in the affected group. Positive correlations between SWA over frontal brain regions and the CDRS-R subscore for morbid thoughts ( $r = 0.62$ ,  $p = 0.01$ ) were found. Three of 11 electrodes showing a significant correlation were located over BA 10.

## 4. Discussion

Our study found that the topographical distribution of sleep SWA in adolescents diagnosed with Major Depressive Disorder (MDD) shows a particular pattern with increased SWA over the frontal cortex compared to healthy individuals. We further examined the topographical

distribution of EEG power in the alpha, beta, sigma, and theta frequency ranges and found no other frequency range showing such differences (for more details see Supplemental Figure 1). Thus, the differences we observe are specific for the low frequency range. Self-reported sleep history was not different between the groups. Concerning the night spent in the laboratory, both groups slept equally well. Sleep efficiency (group means from 91 to 92%) was concordant with laboratory-based measures reported from other studies ([Mason et al., 2008](#)). Whereas changes in sleep structure in depressed adults such as reduced slow wave sleep and reduced REM latency were quite consistent ([Reynolds and Kupfer, 1987](#)), studies in depressed children and adolescents revealed inconsistent outcomes ([Tesler et al., 2013](#)). In line with our results, several studies reported no significant group differences in any sleep variable ([Dahl et al., 2003](#); [Emslie et al., 1990](#)). In contrast, two longitudinal studies reported altered sleep structure, such as reduced REM sleep latency and more REM sleep, to precede and co-occur in adolescents with depression ([Dahl et al., 1996](#); [Rao et al., 2002](#)).

Regarding sleep SWA, previous findings showed that the topography of SWA is characterized by local maxima with an age-dependent shift from occipital areas during early childhood, central areas in late childhood to frontal areas in late adolescence ([Kurth et al., 2010](#)). This age shift in SWA seems to parallel the anatomical maturation which is supported by magnetic resonance imaging studies showing that cortical development follows a similar posterior-anterior time course ([Sowell et al., 2004](#)). In our adolescent patients with MDD such a typical age-specific frontal predominance was detected, however, compared to healthy controls, we identified significantly higher SWA values over a cluster of frontal electrodes. This cluster of 9 electrodes was localized over the frontal lobe, superior frontal gyrus (BA 8 and 10). To our knowledge, this is the first study investigating the topographical distribution of SWA in depressed adolescents with hdEEG. Using single electrodes, a study found SWA to be lower in male adolescents compared to healthy controls, but reported no differences in female adolescents ([Lopez et al., 2012](#)). However, from this study we do not know whether the reduced SWA in male subjects was specific for a certain region or was present globally. A global difference might indicate a relationship to changes in sleep structure affecting SWA in a similar way at all electrodes. In line with our results, a recent study ([Frey et al., 2012](#)) showed higher SWA in depressed female young adults compared to healthy controls. Even though we statistically ruled out an effect of sex on our findings, larger as well as longitudinal studies of pre- and postpubertal children and adolescents are needed to further disentangle the complex interaction between maturation, sex and onset of depression.

What might the local increase of SWA over frontal regions reflect? Since SWA topographically peaks over areas of extensive synaptic reorganization during healthy development ([Kurth et al., 2012](#); [Wilhelm et al., 2014](#)), the increase of frontal SWA in depressed adolescents may reflect an altered pruning of synapses in this area, such as a failure to reduce irrelevant and/or dysfunctional connections which may then result in more pronounced frontal cortical thickness ([Ducharme et al., 2014](#); [Reynolds et al., 2014](#)). Thus, the increased frontal SWA in adolescent-onset depression may represent an early deviant neurodevelopmental pattern. The observation that SWA is positively associated with cortical thickness ([Buchmann et al., 2011](#)) and a recent structural imaging study showing thicker right and left middle frontal gyrus (BA 46, including portions of BA 9 and BA 10) in depressed adolescents compared to controls further support this hypothesis ([Reynolds et al., 2014](#)). Interestingly, a longitudinal study correlated anxious/depressed symptom scores with thickness of the right ventromedial prefrontal cortex and found a negative association at younger ages, a positive association from 15 years on and a shift in polarity occurring at about age 12 ([Ducharme et al., 2014](#)).

Beside the close association to maturational and structural processes, SWA was also found to be use dependent and regulated on a local

level. More specifically, SWA is locally increased as a result of more intense use during preceding wakefulness (Huber et al., 2004). Therefore, the local increase of SWA in our sample could also reflect an increased use of the frontal cortex during the day, such as maladaptive repetitive ruminative thinking as hypothesized by Frey et al. (2012). Interestingly, functional MRI studies reveal higher activation in the medial and dorso-lateral prefrontal cortex and in limbic structures during rumination (Cooney et al., 2010). Our result of a positive correlation between morbid and suicidal ideation and frontal SWA, may further support the association between ruminative thinking and locally increased SWA. For this use dependency speaks that the local difference was more prominent at the beginning of the sleep period. Typically, use dependent increases of SWA are reduced in the course of the night reflecting the recovery function of sleep (Borbely and Achermann, 2005). However, normalized SWA in the significant cluster is persistently increased across the night which rather supports a stable trait. Thus, the observed SWA changes may reflect short-term use dependent processes which might interact with long-term cortical reorganizational processes. In this regard, frequently increased daytime use of specific brain regions, during a period where major neurobiological modifications occur, could alter the time course of typical healthy cortical restructuring.

Sleep slow oscillations are also considered an ideal basis for information processing and transfer within a specific circuit (Diekelmann and Born, 2010). Thus, an “over-activation” of slow oscillations may facilitate an engraving of dysfunctional negative biased thoughts and pave the way for the onset of the disease. The observed difference between objective and subjective sleep measures in our depressed adolescents may be an indication for such negative biases and altered memories (Taylor Tavares et al., 2008). This observation fits well with Beck's cognitive model of depression (Beck, 2008), which assigns biased acquisition and information processing a key role in the development and maintenance of depression. A puzzling question is therefore, whether sleep, i.e. sleep slow waves, are actively involved in the formation of maladaptive neuronal responses. Support for a “depressogenic” role of sleep slow waves comes from selective slow wave sleep deprivation in depressed adults which result in an amelioration of depressive symptoms (Landsness et al., 2011). However, so far selective slow wave sleep deprivation has not been investigated in adolescents with MDD. If indeed negative biases are related to frontal SWA, we might expect such a relationship also to be present in healthy participants. In an exploratory analysis of a sample of 31 healthy adolescents and young adults ( $16.9 \pm 0.7$  years) selected from ongoing studies in our laboratory, who had no personal and family history of psychiatric disorders, learning disabilities, sleep disorders or use of medication, we correlated the difference in objective and subjective sleep latency and frontal SWA. Indeed, we found a significant positive correlation between the difference in objective and subjective sleep latency and SWA in the first NREM sleep episode in the same cluster of 9 frontal electrodes ( $r = 0.5$ ,  $p = 0.002$ ; Pearson product-moment correlation;  $r = 0.4$ ,  $p = 0.02$ , partial correlation, controlling for the effect of age). In another preliminary analysis of 7 unaffected siblings of our depressed patients, we found a trend for a higher self-reported sleep latency ( $p = 0.07$ ) and more importantly a similar increase in SWA in the first NREM sleep episode over the cluster of 9 frontal electrodes compared to age- and sex matched controls (group,  $F(1,12) = 7.2$ ,  $p = 0.02$ ). These results support the notion that negative biases and altered memories possibly exist as part of a continuum, depend on the same neurobiological system as sustained depressive symptoms and that SWA may be an early marker to detect alterations within this system.

When discussing these results we should keep in mind some limiting factors of our study. We did not include an adaptation night for our young participants. In this regard, previous studies showed no first night effects in youth, i.e. reported no significant differences in sleep parameters when comparing the first to the second night spent in the laboratory (Browman and Cartwright, 1980; Coble et al., 1974). In our study, both groups showed high sleep efficiency and no

significant differences in sleep structure, especially no group differences in sleep latency. In addition, self-reported total time in bed as well as total sleep time during both, weekdays and weekends, did not significantly differ between our participants with MDD and our healthy controls one week prior to assessment (Table 2). The setting was new and similar for all study participants during the night spent in our sleep laboratory. Thus, we assume no important impact of adjustment processes in our samples of adolescents. Due to the naturalistic design of the study, the use of medication is present in most of the depressed adolescents, and it is unclear how these medications might have influenced SWA. Particularly, 60% of our young patients received SSRIs, which were shown to alter REM sleep and overall sleep efficiency, both of which did not differ between our groups. In contrast, no effects of SSRIs on slow wave sleep have been reported in adults (Nicholson and Pascoe, 1988; Saletu et al., 1991; Tesler et al., 2013). Furthermore, a preliminary report assessing 6 depressed children showed no effects of SSRIs on deep sleep (Armitage et al., 1997). In our exploratory analysis, we split the group of patients into a group with ( $N = 10$ ) and a group without medication ( $N = 5$ ). Both groups show a frontal increase SWA, the lack of statistical power limits a direct comparison (see Supplemental Figures 2 and 3). Interestingly, the unaffected, unmedicated siblings showed a similar frontal increase, thus a direct causative influence of medication on SWA seems unlikely. The high rates of comorbidities in the depressed group reflect a rather typical clinical sample because anxiety disorders are the most frequent comorbid disorders in children and adolescents with MDD. Next to social phobia, ADHD was the most prevalent comorbidity in our sample. Interestingly, in a sample of children with the primary diagnosis of ADHD the SWA topography showed a different pattern with lower SWA in frontal areas compared to healthy controls, contrasting our finding of higher frontal SWA in depressed adolescents (Ringli et al., 2013). However, considering specific depressive cognitions such as morbid and suicidal thoughts, we would assume similar neuronal circuits to be involved irrespective of any comorbidity. Since our results point to an association of increased SWA over frontal brain regions with morbid and suicidal thoughts, we speculate that this association may be similar in all our depressed patient irrespective of comorbidities. Since depression during adolescence may also precede other mental disorders such as bipolar disorder or schizophrenia, follow-up investigations of the topographical distribution of SWA are necessary to tract deviant cortical development. Even though all study participants underwent a screening to exclude personal and family history of psychiatric disorders and none of the controls was in current or past psychiatric treatment, the screening questions were not equivalent to the questions used in the MINI. Thus, we cannot rule out that some individuals would have met criteria for a psychiatric disorder according to the MINI and the prevalence might not exactly match to the number of comorbidities as reported for our patient group. Potential ADHD symptoms as well as sporadic depressive symptoms in the control group at the time of the sleep assessments may have influenced our reported group effects.

In conclusion, SWA topography seems to be a reliable mapping tool that mirrors and/or precedes disturbed processes of cortical brain plasticity and the perceptual disconnection from the environment during sleep seems particularly relevant for research in children with mental diseases. Our finding of increased frontal SWA in adolescents with MDD may represent a promising biomarker tracing cortical regions of extensive reorganization.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.nicl.2015.10.014>.

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