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# 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.



## 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 ± SEM: 15.1 ± 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 socio economic 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 ± 3.0). The mean (±SEM) duration of the current MDD episode was 39.5 (±7.8) weeks and the total illness duration was 95.3 (±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 ± SEM: 15.3 ± 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 ± SEM, range | 15.1 ± 0.3, 12.9 - 16.6 | 15.3 ± 0.3, 12.8 - 16.4 |
| Sex, female, N (%) | 8 (53) | 8 (53) |
| IQ, mean ± SEM, range | 113.5 ± 2.6, 98.0 - 129.0 | 115.8 ± 6.1[a], 102.0 - 131.0 |
| Socio Economic State Scale, mean ± SEM, range | 5.3 ± 0.4, 2.0 - 8.0 | 3.5 ± 0.4[b], 3.0 - 4.0 |
| Tanner Pubertyscale, mean ± SEM, range | 9.7 ± 0.3, 7.0 - 11.0 | 9.5 ± 0.8[c], 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[d] | 4 (27) | |
| ADHD | 4 (27) | N/A |
| Conduct Disorder | 2 (13) | N/A |
| *Characteristics of illness and functioning, mean ± SEM, range* | | |
| Total duration of illness, weeks | 95.3 ± 18.6, 13.0 - 295.0 | N/A |
| Duration of current MDD episode, weeks | 39.5 ± 7.8, 13.0 - 108.0 | N/A |
| Actual Severity of Depression, CDRS-R Sum Score | 41.7 ± 3.0, 21.0 - 61.0 | N/A |
| Illness Severity: Clinical Global Impressions-Severity Scale | 4.5 ± 0.2, 3.0 - 6.0 | N/A |
| Current Functional Level: Global Assessment of Functioning-Scale | 52.8 ± 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 (%)*[e] | 10 (67) | none |
| Medication class, N (%) | | |
| Selective-Serotonin-Reuptake-Inhibitors[f] | 9 (60) | none |
| Noradrenergic and Specific Serotonergic Antidepressant (Mirtazapine) | 1 (7) | none |
| Atypical Antipsychotic (Quetiapine) | 1 (7) | none |

N/A = not available;
[a] Data available for 8 adolescents.
[b] Data available for 2 adolescents.
[c] Data available for 9 adolescents.
[d] The total number of patients in one diagnostic category can be smaller than the sum of the individual diagnoses due to comorbidity.
[e] 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.
[f] Selective-Serotonin-Reuptake-Inhibitors include Fluoxetin (N = 4), Citalopram (N = 1), Sertraline (N = 4). Differences were compared by using two tailed, unpaired Student's t-test.