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Original Article

Sleep and slow-wave activity in depressed adolescent boys: a preliminary study

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ABSTRACT

Objective: Adolescence is a vulnerable period of life that is characterized by increasing incidence of depression. Sleep disturbance is one of the diagnostic symptoms of depressive disorder. Adolescence is also characterized by dramatic maturational changes in sleep and its regulation. The goal of this study was to assess sleep macroarchitecture and slow-wave activity (SWA) in depressed adolescent boys.

Methods: Eight non-medicated adolescent boys meeting the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for depressive disorder and 10 age-matched healthy controls (average age 16.0 years) underwent polysomnography in their home environment for two consecutive nights. Sleep macroarchitecture, SWA, and SWA dissipation were assessed in all subjects.

Results: Depressed boys showed a flattened pattern of SWA dissipation through the night. SWA power was lower during the first non-rapid eye movement (NREM) episode in the frontal derivation and higher during the third NREM episode in the central derivation in the group of depressed boys as compared to healthy boys. The SWA dissipation pattern correlated with the severity of depressive symptoms, and the correlation was strongest in the frontal derivation. In addition, total sleep time was shorter in patients as compared to the control group, but no other differences were found in the macroarchitecture of sleep.

Conclusion: Depression in adolescent boys is characterized by more evenly distributed SWA through the night as compared to healthy subjects, and we showed for the first time that this pattern of SWA distribution is associated with severity of depressive symptoms. These findings suggest that homeostatic regulation of sleep may be impaired in adolescent depression.

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1. Introduction

The incidence of both depressive disorder and insomnia increases rapidly across adolescence [1–5]. According to epidemiological research, the prevalence of major depressive disorder (MDD) among adolescents ranges from 5 to 12% [1,6–8], and the prevalence of insomnia is about 11–13% [4,9]. Depression during adolescence frequently recurs or persists into adulthood, which, in

addition to causing considerable human suffering, induces a substantial economic burden for society [3,10–12].

Sleep disturbance is one of the diagnostic symptoms of depressive disorder. In depressed adults, sleep is characterized by a range of changes in sleep structure [13], which can be divided into three groups [14]: impaired sleep continuity (prolonged sleep latency, increased number of night awakenings), rapid eye movement (REM) sleep disinhibition (shortened REM sleep latency, elevated REM sleep frequency and duration), and non-rapid eye movement (NREM) sleep changes (decreased NREM sleep duration and reduced slow-wave activity (SWA)). Moreover, different REM and NREM sleep parameters have been previously shown to correlate with the severity of depressive symptoms in adults [15].

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Depressed adolescents frequently complain about their sleep [16,17], but the results from objective polysomnographic studies remain controversial. Some polysomnographic studies in depressed adolescents have shown the same sleep alterations which are consistently found in depressed adults [18–23], but others have failed to demonstrate any abnormalities in sleep architecture [24–26]. The differential findings can be explained by, for example, small sample sizes and the heterogeneity of studied samples in terms of gender, age/pubertal status, and the variable clinical features/symptoms of depression (such as inpatient/outpatient status, imposed vs free sleep schedules, comorbid psychiatric disorders, medication use).

Adolescence is characterized by dramatic maturational changes in sleep and its regulation [27–29]. The most remarkable change in sleep architecture during typical adolescence is the reduction in the amount of SWS (by up to 40%) and SWA (by up to 60%) [28,30–34]. The changes in sleep occur during adolescence go hand in hand with major maturation of the psychosocial and physical processes, including a massive reorganization of the brain neuronal networks (synaptic pruning) [27]. It has even been suggested that the observed decline in SWA across adolescence can be explained by a reduction in synaptic density [35,36]. Thus, sleep, and particularly SWA, and brain maturation during adolescence are tightly interconnected.

To date, the literature regarding SWA changes in adolescent depression is scarce. Currently, there are only a few studies regarding SWA abnormalities in NREM sleep of depressed adolescents. In one mixed-gender study a lower delta power in the first NREM sleep episode and an irregular SWA dissipation through the night in depressed adolescents boys compared to healthy subjects have been observed [20]. In the only study using a homogeneous sample in terms of age, gender and medication use, a lower delta amplitude and power has been shown in depressed adolescent girls as compared to healthy girls [37]. Recently, it has also been shown that the topographical pattern of SWA distribution in depressed adolescents is characterized by increased SWA over the frontal cortex compared to healthy controls [38]. However, currently there are no studies that measure SWA abnormalities using a homogeneous sample of depressed boys. Moreover, none of the previous studies have looked at the association between severity of depressive symptoms and SWA dissipation.

Therefore, the aim of our study was to examine sleep macro-architecture, SWA power, and SWA dissipation and their relationship with depression severity in a sample of non-medicated depressed adolescent boys as compared to a healthy control group. Furthermore, as an additional marker of sleep homeostasis, we calculated the rise rate of SWA during the initial stage of sleep, which has been shown to be associated with homeostatic sleep pressure [39].

2. Materials and methods

2.1. Participants

A total of 20 (10 patients and 10 healthy controls) non-medicated adolescent boys aged between 14 and 17 years were recruited for a research project focusing on adolescent depression, sleep, and brain maturation (the ADSLEEP project). Patients suffering from depressive and/or sleep symptoms were recruited from the Helsinki University Central Hospital Department of Adolescent Psychiatry outpatient units, and healthy controls were recruited via advertisements in a newspaper for the hospital staff. Exclusion criteria for all participants consisted of mental retardation, insufficient knowledge of the Finnish language, current use of medication, age over 17.5 or under 14.5 years, chronic somatic

illness, substance abuse/dependence, principal Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnosis other than depressive/sleep disorder.

All subjects underwent detailed clinical and psychiatric evaluation. All adolescents were free of psychotropic and other medication during the study, and the presence of somatic conditions and structural brain pathologies were ruled out based on brain magnetic resonance imaging (MRI) and blood samples. One patient was excluded from the analyses presented in this paper because he was diagnosed with a circadian rhythm sleep disorder only.

Nine patients were diagnosed with depressive disorder according to the DSM-IV. Diagnostic assessment was performed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime version (K-SADS-PL) by one of the authors (A.S.U.) [40]. Depression symptom severity was further evaluated with two different scales: the self-administered, 21-item Beck Depression Inventory (BDI-21) [41], and the Hamilton Depression Rating Scale (HDRS), administered by one of the authors (A.S.U.) [42]. Insomnia symptoms were assessed by the Athens Insomnia Scale (AIS) [43]. Polysomnographic data were not available for one patient due to drop out, leaving eight patients and 10 control subjects in the analyses of the current study.

The study protocol conformed to the Declaration of Helsinki and was approved by the ethics committee of the Helsinki University Central Hospital. Written informed consent for study participation was received both from the participants and their parents or legal guardians.

2.2. Sleep recording and scoring

Polysomnographic recordings were conducted in subjects' home environments with ambulatory recording devices (Embla, Flaga Hf. Medical devices; electroencephalogram (EEG) positions according to the International 10–20 system; derivations F4-M1, C4-M1, O2-M1 and backup derivations F3-M2, C3-M2, and O1-M2; sampling rate 200 Hz) for two consecutive nights. EEG, electro-oculogram, and electromyogram were recorded according to standard criteria and the whole recording period was manually scored for sleep stages in 30-s epochs by a certified sleep technician blinded to the patient/control status of the subjects. Night 1 served as an adaptation night and night 2 has been used for the sleep and power spectral analyses presented in this paper.

Total sleep time (TST), sleep efficiency (time asleep relative to sleep period, which was calculated as time from sleep onset through last epoch of sleep), SWS and REM sleep latencies (time from sleep onset until first SWS or REM sleep episode, correspondingly), and number of awakening episodes were calculated from the scored data.

NREM periods used for power spectral analysis were determined as a succession of sleep stages 1, 2, and 3 with a duration of 15 min or more and terminated by REM sleep or wakefulness of least 5 min. No minimum REM sleep duration was required for the first REM sleep episode. Only the first three episodes of NREM sleep were included in the power spectral analysis, because all the subjects had at least three NREM sleep episodes during the night.

2.3. Power spectral analysis

The EEG (sampling rate 200 Hz) was subjected to spectral analysis off-line using a fast Fourier transform (FFT) routine with the help of Spike 2 software (version 8.07 CED, Cambridge). Power spectra (Hanning window) from central C4-M1 and frontal F4-M1 channels were computed, using FFT size of 512 Hz giving a resolution of 0.39 Hz. The spectral power was averaged in 30-s epochs to be of identical length with the stage-score epoch length. Power

spectra of SWA range (delta frequencies 0.39–3.91 Hz) were calculated separately for NREM episodes 1, 2, and 3 from each derivation. Spectral powers were normalized in each recording to the mean SWA power across two derivations during the first three NREM episodes to enable comparisons of the recordings between persons, ie, the SWA power values in each channel were divided by the mean SWA across two channels (frontal and central) of the analyzed time interval. To evaluate SWA dissipation, the difference in SWA power between the first and the third NREM sleep episodes was calculated. The rise rate of SWA was calculated during the initial 10 min of the first NREM sleep episode. Artifacts were excluded by visual inspection and only artifact-free epochs were included in the power spectral analysis (artifacts comprised on average 1.6% of the total recording time).

2.4. Statistical analysis

All statistical analyses were performed with SPSS v.22 (IBM Corp., Armonk, NY, USA). One-way ANOVA was used to analyze the differences between groups of healthy controls and depressed patients. Repeated measures ANOVA was used to compare SWA power in different NREM sleep episodes and SWA dissipation. The rise rate of SWA was modeled by a linear least-squares regression on individual data and the slopes were compared between groups using linear mixed model of repeated measurements. Pearson correlation coefficients were calculated to assess the relationship between SWA dissipation and severity of depression (evaluated by HDRS and BDI-21). The values reported in the figures represent mean $\pm$ standard error of mean (SEM).

3. Results

3.1. Sample description

Participants were on average 16.0 ± 0.8 (mean $\pm$ SD) years old. The subgroups of patients and healthy controls did not differ in terms of their age, body mass index (BMI), or serum testosterone levels (ANOVA, not significant, Table 1). No axis-I diagnoses were found among the controls according to a semi-structured diagnostic interview. The cases were confirmed to suffer from depressive disorder and they expectedly showed more symptoms of depression than controls both in the BDI-21 and HDRS (ANOVA, $p < 0.05$ and $p < 0.001$ correspondingly; Table 1). Depressed patients also demonstrated higher AIS scores as compared to controls indicating the presence of more insomnia symptoms (ANOVA, $p < 0.05$; Table 1). None of the patients suffered from bipolar disorder nor manifested psychotic features of depression. A comorbid anxiety disorder was present in one, and comorbid disruptive behavior disorder was present in another of the patients.

Table 1
Sample characteristics.

Variable	Controls (N = 10)	Patients (N = 8)
Age	16.2 $\pm$ 0.7 (14.8–17.2)	16.9 $\pm$ 1 (14.7–17.3)
BMI	20.6 $\pm$ 1.7 (17.8–23.8)	16.9 $\pm$ 3.9 (16.8–27.6)
S-Testo	19.4 $\pm$ 3.6 (15.3–27.6)	16.9 $\pm$ 4.1 (15.0–26.3)
BDI-21*	2.8 $\pm$ 4.0 (0–12)	16.9 $\pm$ 12.0 (1–33)
HDRS**	0.3 $\pm$ 0.7 (0–2)	12.9 $\pm$ 4.4 (7–19)
AIS*	2.1 $\pm$ 2.2 (0–7)	9.4 $\pm$ 6.2 (1–18)

Data are reported as mean $\pm$ SD (range). Significant differences between control and depressed patients subgroups are marked with asterisks (* $p < 0.05$, ** $p < 0.001$; ANOVA). AIS, Athens insomnia scale; BDI-21, 21-item Beck Depression Inventory; BMI, body mass index; HDRS, Hamilton Depression Rating Scale; S-Testo, serum testosterone level (nmol/l; N = 9 for controls).

3.2. Sleep architecture

Among all studied sleep parameters only TST was significantly shorter in depressed patients as compared to control subjects ($F_{1,15} = 6.61$, $p = 0.02$) (Table 2).

3.3. Slow-wave activity power

Repeated measures ANOVA (within-subject factors: EEG derivation and NREM episode, between-subject factor: group) revealed that SWA was significantly different in different NREM sleep episodes ($F_{2,32} = 22.06$, $p < 0.001$) (Fig. 1a and b) with the biggest values in the first NREM and the smallest in the third NREM episode. SWA power was higher in frontal compared to central derivation ($F_{1,16} = 63.49$, $p < 0.001$).

SWA in the group of depressed patients was lower during the first NREM episode in the frontal derivation ($F_{1,16} = 6.8$, $p = 0.02$) and higher during the third NREM episode in the central derivation ($F_{1,16} = 5.37$, $p = 0.03$) compared to healthy subjects.

3.4. Slow-wave activity dissipation

Repeated measures ANOVA (within-subject factors: EEG derivation, between-subject factor: group) revealed a significant effect for both factors. The difference in SWA power between the first and the third NREM episode was higher in the frontal derivation compared to the central derivation ($F_{1,16} = 30.93$, $p < 0.001$) and in the healthy group it was higher compared to the depressed group ($F_{1,16} = 5.21$, $p = 0.04$).

In the frontal derivation the decline of SWA from the first to the third NREM episode was significantly smaller in depressed patients than in healthy controls ($F_{1,16} = 5.32$, $p = 0.04$); in the central derivation it tended to be smaller ($F_{1,16} = 4.09$, $p = 0.06$) (Fig. 2). These results show that SWA power was more evenly distributed through the night in depressed patients compared to healthy subjects.

3.5. Slow-wave activity rise rate

The analysis of the rise rate of SWA during the initial 10 min of the first NREM sleep episode revealed that depressed patients demonstrated slower build-up of SWA compared to healthy subjects in the frontal derivation ($p = 0.03$). This was not observed in the central derivation ($p = 0.16$).

3.6. Association of SWA dissipation with depression severity

To assess the relationship between SWA dissipation and the severity of depression symptoms, we performed Pearson

Table 2
Sleep parameters in control and depressed patient groups of adolescents.

Sleep parameters	Controls (N = 10)	Patients (N = 8)
TST, min*	481.05 $\pm$ 11.84	426.57 $\pm$ 25.40
Sleep efficiency	97.15 $\pm$ 0.96	93.81 $\pm$ 3.42
N1, %	4.00 $\pm$ 0.84	4.86 $\pm$ 0.80
N2, %	51.68 $\pm$ 1.31	49.27 $\pm$ 2.71
N3, %	27.47 $\pm$ 1.79	29.30 $\pm$ 3.77
R, %	16.86 $\pm$ 1.93	16.56 $\pm$ 2.20
SWS latency, min	14.85 $\pm$ 2.66	35.79 $\pm$ 17.56
REM sleep latency, min	151.35 $\pm$ 17.26	113.50 $\pm$ 22.09
Awakenings, number	11.40 $\pm$ 2.50	8.00 $\pm$ 1.68

Data are reported as mean $\pm$ standard error of the mean (SEM). Significant difference between control group and depressed patients group, * $p < 0.05$ (ANOVA). N, NREM sleep stage; R, rapid eye movement sleep; SWS, slow-wave sleep; TST, total sleep time.

Fig. 1. SWA power in frontal (a) and central (b) electroencephalogram (EEG) derivations in first three non-rapid eye movement (NREM) sleep episodes. $N = 10$ /control group, $N = 8$ /depressed patients group. Data are illustrated as mean $\pm$ SEM. Repeated measures ANOVA (within-subject factors: derivation and NREM episode, between-subject factor: group), $*p < 0.05$. SWA, slow-wave activity.

Fig. 2. Slow-wave activity (SWA) dissipation in frontal and central electroencephalogram (EEG) derivations from the first to the third non-rapid eye movement (NREM) sleep episode. $N = 10$ /control group, $N = 8$ /depressed patients group. Data are illustrated as mean $\pm$ standard error of the mean (SEM). Repeated measures ANOVA (within-subject factors: derivation, between-subject factor: group), $*p < 0.05$, $#p = 0.06$.

product–moment correlation analysis. A negative correlation between SWA dissipation and HDRS was found in the frontal ($r = -0.505$, $p < 0.05$) derivation, meaning that more severe symptoms of depression are associated with more evenly

distributed SWA through the night. For the central derivation this correlation was not significant ($r = -0.437$). Correlation coefficients between SWA dissipation and BDI scores did not reach the level of significance either (for frontal ($r = -0.30$) and central ($r = -0.33$) derivations).

4. Discussion

The major finding of this work was that depressed adolescents demonstrated a slower pattern of SWA dissipation as compared to healthy controls. The SWA distribution through the night was more even in depressed boys as compared to healthy subjects. SWA power was lower during the first NREM episode in frontal derivation and higher during the third NREM episode in central derivation in the group of depressed boys as compared to healthy boys. The SWA dissipation pattern in the frontal area correlated with the severity of depressive symptoms so that more severe depressive symptoms were associated with more evenly distributed SWA power through the night.

NREM sleep and particularly SWS is considered to be the most restorative stage of sleep which is known to be one of the physiologically measured determinants of sleep quality [44,45]. SWA and its temporal distribution through the night are physiological markers of sleep homeostatic regulation (process S) [46]. SWA power increases following prolonged wakefulness (sleep deprivation) [47,48], and is reduced after naps [46]. Further, in the course of spontaneous sleep, the highest SWA is observed in the beginning of the night and it declines towards the end of the night [45]. Such a

declining pattern of SWA distribution was observed in the group of healthy controls in our study, but in the group of depressed boys the SWA dissipation pattern was less clear and had a much flatter shape.

According to the S-deficiency hypothesis of depression [49] homeostatic sleep regulation is impaired in depression and is normalized after sleep deprivation. It suggests that depressed subjects fail to accumulate a sufficient sleep drive during the daytime, but sleep deprivation, an efficient but short-term depression treatment [49–51], may improve mood via transiently suppressing SWA and increasing homeostatic sleep drive. Studies in rodent models of depression have also shown decreased SWA during both spontaneous and recovery sleep [52,53] and, further, in early-life stress models a decline in all frequency ranges, including the SWA range, has been reported [54]. Our results are in line with earlier studies in adults [13,55] and adolescents [20,37] showing that depressed boys have lower SWA power in the first NREM sleep episode and an irregular SWA dissipation pattern compared to healthy individuals. Moreover, the slower rise of SWA during the initial stage of sleep after sleep onset in the group of depressed adolescents also indicates a lower homeostatic sleep drive [39] compared to the healthy group. Taking all this into account, we conclude that our results give support to the S-deficiency hypothesis of depression.

In the depressed adolescents, in the central derivation SWA remained at a higher level after three NREM episodes as compared to healthy controls. This may be interpreted as a partially incomplete dissipation of SWA, which means that the core restorative process of sleep is unsuccessful and part of sleep pressure remains. This resembles the sleep deprivation-like state in healthy individuals, which is known to affect mood and performance [56,57]. It should be noted, however, that in our study SWA was assessed only during the first three NREM episodes, and the majority of the participants had four (or sometimes even five) episodes of NREM in total. It is therefore possible that during the following episodes the levels of SWA in controls and depressed subjects reached the same level. To verify this assumption a bigger sample size is needed to be able to match control and depressed participants by the number of NREM episodes during the night.

Homeostatic sleep regulation is constantly interacting with the circadian regulation of sleep. Not only the homeostatic process by itself, but rather its interaction with the circadian system has been suggested as crucial for the regulation of mood [51,58]. Molecular circadian mechanisms, namely a flattened circadian gene expression pattern, have been observed in the brain of depressed patients [59]. The shifting of SWA power from the first half of the night closer to the end of the night observed in our study might indirectly indicate a circadian phase shift in depressed adolescent patients, supporting the phase-shift hypothesis of depression [60]. According to this hypothesis mood disturbances result from a phase advance or delay of the central pacemaker and related peripheral circadian rhythms.

We found that a flatter SWA dissipation was associated with more severe depression symptoms. Notably, the distribution of SWA across the first two NREM sleep episodes (the delta sleep ratio) has been previously linked to clinical outcome and symptom severity in depressed adult patients [61,62]: a better response to therapy was observed in subjects with a higher delta sleep ratio, although the association between severity of depression and SWA distribution was not assessed in these studies. To our knowledge, our study is the first to show the association between SWA dissipation through the night and severity of depressive symptoms in adolescent depressed boys. Further intervention studies are needed to examine whether flatter SWA dissipation is linked to worse treatment response in adolescents.

The association between SWA dissipation and depression severity was more pronounced in the frontal compared to the central derivation. From topographical studies on SWA regulation and distribution, it is known that slow waves during sleep are more prevalent in frontal areas in both humans [63,64] and animals [65]. The prevalence of SWA in the frontal area was also observed in all subjects from our study. Furthermore, morphometric and functional brain imaging studies [66–70], including studies in adolescents and young adults [71,72], have shown that the frontal cortex, which plays a key role in emotion regulation, is affected by depression. Thus, our results are in line with earlier findings on the involvement of the frontal cortex in depression, and support the idea that sleep regulation and depression might share common neurobiological mechanisms [73–75].

The shorter TST observed in our sample of depressed adolescents as compared to healthy controls may be due to insomnia symptoms (difficulties in falling asleep, disrupted sleep continuity, and early morning awakenings), which is evidenced by significantly higher AIS scores in depressed boys compared to controls. We could not find any other differences in sleep macroarchitecture between depressed and healthy participants, which was not surprising based on previous literature showing controversial findings [22]. The small sample size might have limited our possibilities to detect subtle differences in sleep macroarchitecture. Furthermore, it should be noted that the group of depressed patients in our study had a larger variability of sleep parameters as compared to the group of healthy adolescents which could partly explain why no other significant differences in sleep parameters between the two groups were observed, and which might reflect the typically heterogeneous phenomenology of adolescent depression [76,77].

The strengths of our study include most notably the homogeneous sample in terms of gender and age, and the lack of medication use among all participants. Further strengths are the detailed psychiatric evaluation, relatively low instances of psychiatric comorbidities among the depressed adolescents, and the use of two nights of ambulatory recordings in the home environment, which likely minimized the effects of stress on the results.

The limitations include most notably the small sample size, because of which the results should be considered as preliminary. The results should, therefore, be confirmed in studies with larger sample sizes. Further limitations include the inclusion of only male participants, which limits the generalizability of the findings to female adolescents. Indeed, gender differences have been observed in SWA of depressed adolescents with depressed girls showing no changes in SWA [20] or even higher SWA [78] as compared to an age- and gender-matched control group, and thus it is advisable to study the two genders separately.

5. Conclusions

Depressed adolescent boys had lower SWA power and showed a slower rise of SWA power in the course of the first NREM episode, and a flatter SWA dissipation through the night in the frontal area compared to age-matched healthy boys. The pattern of SWA dissipation was associated with severity of depressive symptoms. These findings suggest that homeostatic sleep regulation may be impaired in depression.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <http://dx.doi.org/10.1016/j.sleep.2017.06.029>.

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