

Sex differences in slow-wave electroencephalographic activity (SWA) in adolescent depression

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Abstract

Sleep disturbances, present in more than 90% of major depressive disorder (MDD) patients, are moderated by sex in adult MDD. In particular, slow-wave electroencephalographic activity (SWA; 0.5-4 Hz) accumulation is low and dissipation impaired. This SWA abnormality in depressed adult males does not change with age, suggesting that SWA abnormality appears at early ages. The present study evaluated sex differences in SWA in adolescents with MDD compared to healthy controls. We evaluated regularized sleep-wake schedules at home for 5-7 days, followed by two consecutive nights of sleep EEG recording. The study included 104 participants, 52 symptomatic and depressed subjects (MDD: 20 males and 32 females) and 52 healthy controls (HC: 20 males and 32 females), aged 13-18 years. SWA power and dissipation, and duration and latencies to each Non-Rapid Eye Movement (NREM) sleep period were calculated for each group. Results showed that SWA accumulation in the first NREM period was lower and its dissipation across the night more irregular in MDD males compared to HC males ($P < 0.009$). By contrast, SWA was equivalent in MDD and HC females. In conclusion, as reported in adult MDD, the accumulation and dissipation of SWA was abnormal in depressed adolescents, but only in males. SWA abnormalities in adolescent MDD may relate to different depressive symptoms in females and males. These results underscore the need to develop sex-specific therapies to enhance and restore SWA in depressed adolescents.

Introduction

Major depressive disorder (MDD) is a pervasive illness affecting nearly 11% of adolescents, and it has been suggested to have a more severe and chronic clinical course with

onset at this age than in adulthood.¹ Higher rates of recurrence,^{2,3} suicide,⁴ and substance abuse disorder⁵ are evident in early-onset depression compared to late-onset depression.⁶ It is also during these stages of human development that sex differences in MDD become apparent, with a 2:1 female to male ratio of incidence.^{7,8} Several factors have been implicated in the etiology of MDD, but sleep disturbances have received considerable attention as a factor in the onset and maintenance of this disorder.⁹

Subjective sleep complaints are evident in more than 90% of child and adult patients.¹⁰ Persistent sleep disturbances increase the risk of relapse and recurrence of depressive episodes and the risk of suicide.^{11,12} Moreover, recent research indicates that the most common residual symptom of adolescent depression is sleep disturbance.¹³ Although polysomnographic (PSG) measures have been successfully utilized to differentiate adults with depression from healthy controls, results in adolescents have been more equivocal.^{14,15} However, quantitative sleep electroencephalographic (EEG) analysis constitutes a useful tool to examine changes in specific EEG frequencies through the night,¹⁶ and has generally provided a better discrimination between depressed patients from healthy individuals than PSG measures alone.¹⁷

Power spectral analysis of delta EEG activity (0.5-4Hz) in non-rapid eye movement (NREM) sleep, also known as slow-wave activity (SWA), is considered a proxy for sleep homeostasis, with the initial SWA accumulation after sleep onset reflecting sleep drive or sleep need, and the dissipation of SWA reflecting the progression of recovery from the sleep debt that accumulated over the day.^{18,19} Sleep deprivation results in an SWA rebound that is directly proportional to the amount of prior wakefulness, while napping reduces sleep pressure and SWA generation after sleep onset.²⁰

Studies of SWA on MDD have proved useful in distinguishing adults with MDD from healthy control even in the absence of PSG differences.²¹⁻²³ Specifically, SWA power is lower in adults with MDD and dissipates more slowly across the night, resulting in a shift in the relative distribution to the latter part of the night.²¹⁻²³ These SWA abnormalities are strongly associated with severity of depressive symptoms.^{24,25} Recent studies have shown that lower SWA power and a slower dissipation across NREM sleep is more characteristic of men with MDD, perhaps indicative of sex differences in the mechanisms underlying sleep dysregulation in depressed men and women.^{22,26} An earlier study evaluating age effects on SWA in depressed young adults (aged 18-40 years), found no relationship between age and SWA measurements in depressed males, suggesting that delta

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declines earlier in depressed males than in healthy males.²¹ Altogether, these relevant findings underscore the need to understand the relationship between SWA and MDD and developmental changes in brain regulation that may impact the consequences of reduced SWA or impaired function. Studying potential

sex differences in SWA and its regulation may also be helpful in understanding differential prevalence and risk factors in males and females across the life cycle. These study results could lead to the development of behavioral or pharmacological interventions to enhance SWA in depressed patients and to identify sex-specific depressive symptoms related to SWA decline. Furthermore, it may raise awareness of the need to design specific therapies addressing sex differences underlying depressive symptomatology.

The present study examined the influence of MDD on SWA in adolescents with depression compared to healthy controls, with special emphasis on sex differences. Based on the above mentioned findings, we hypothesized that SWA power would be lower in depressed than in healthy adolescents, and with a slower dissipation across NREM sleep time. We also expected males with MDD to show the lowest SWA power.

Materials and Methods

Participants

For this study, 52 depressed subjects (MDD: 20 males and 32 females) and 52 healthy controls (HC: 20 males and 32 females) aged between 13-18 years with a Tanner developmental score of 3 or over were recruited for a total of 104 participants. Study participants were recruited through published advertisements and posted flyers at community centers, hospitals, outpatient psychiatric clinics, and pediatric clinics in Texas or Michigan. Self-referral or referral from a community clinician was also permitted. Specifically, 64 participants were recruited and studied in Texas (35 MDD and 29 HC) and 40 in Michigan (17 MDD and 23 HC). However, recruitment procedures, study design, and equipment utilized for sleep recordings were identical in both sets of the sample. The study was approved by the Institutional Review Board committee of the University of Texas Southwestern and University of Michigan. Inclusion criteria for all participants consisted of ability to provide informed written consent (parent) and assent (child), and no medication (for at least four weeks) or counseling at the time of the clinical interview. Additional inclusion criteria for healthy controls were no personal or family history of psychopathology in first-degree relatives. For the MDD group, inclusion required a current diagnosis of non-psychotic MDD, single or recurrent, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, 4th ed.) and being symptomatic at the time of enrollment. Exclusion criteria for all participants included significant head injury or unconsciousness for more than five min-

utes (lifetime), independent/intrinsic sleep disorder based on history or polysomnogram (PSG), significant previous or concurrent medical illness determined by history, and lifetime diagnosis of anorexia or bulimia, or substance abuse in the last six months.

Clinical assessment

A brief telephone screen was administered to determine potential eligibility. All participants were then scheduled for a full clinical structured interview. Prior to the initial interview, the study was explained and written informed consent was obtained from the parent(s) and assent from the participant. All study participants underwent the same initial psychiatric evaluations. At the initial visit, each participant and parent(s) was interviewed separately using the Schedules for Affective Disorders and Schizophrenia for School-Aged Children: Present and Lifetime.²⁷ Additionally, depressive-symptom severity was assessed using the Children's Depression Rating Scale-Revised (CDRS-R).²⁸ A minimum score of over 40 on the CDRS-R was required for entry into the study, indexing moderate depressive-symptom severity and matching the criterion of our previous work.²⁹⁻³² While the child was being interviewed, a separate interviewer obtained family history from parents using the Family History Diagnostic Interview. The Children's Global Assessment Scale (CGAS)³³ and the Family Global Assessment Scale (FGAS)³⁴ assessed overall functioning of the child and the family, respectively. Tanner maturation (1-5 scores) was self-assessed by participants using the *Typical Progression of Pubertal Development Chart* adapted from Tanner.³⁵ Breast and pubic hair development were assessed for girls, and genital and pubic hair development for boys.

Procedures

Sleep recording and scoring

All participants agreed to follow their usual school week bed- and rise-time schedule throughout the study, established by sleep history at enrollment. Actigraphs (Actiwatch-L™, Mini-Mitter) were worn throughout the week and sleep/wake diaries were kept daily during the home recording period. Data from the actigraphs were downloaded prior to their first night in the laboratory to ensure participant adherence to their regularized rise- and bed-times.

Each participant spent two consecutive nights in a sleep laboratory. Night 1 served as laboratory adaptation and as an additional screen for the presence of independent sleep disorders, and night 2 as the study night. Electrode placement on the study night included F3, F4, C3, C4, O1, O2, P3, P4, left and right electrooculogram (EOG), recorded from the

upper and lower canthi, and a bipolar, chin-cheek electromyogram (EMG). Night 1 recordings also included chest and abdomen respiration bands, nasal-oral thermistors, and leg electrodes. EEG electrodes were referenced to the ear lobes linked through a 10 K Ω resistor to minimize non-homogeneous current flow and potential artifactual hemispheric asymmetries, as is standard in our laboratory. EEG was transduced by Grass™ P511 A/C amplifiers set at a sensitivity of 5 (50 μ V, 0.5 s calibration), corresponding to a gain of 50,000. The half-amp low- and high-bandpass filters were set at 0.3 and 30 Hz, respectively. A 60-Hz notch filter attenuated electrical noise.

Visual stage scoring was conducted in 30 sec epochs, according to standard sleep staging criteria, described in Rechtschaffen and Kales,³⁶ by research personnel trained for more than 90% agreement on an epoch-by-epoch basis. Sleep latency was defined as the first consecutive 10 min block of any sleep stage (except REM) with no more than 2 min of waking time, reflecting persistent sleep onset. Total sleep period (TSP) was defined as the time from lights out to lights on. The REM latency was defined as the minutes from sleep onset to the first epoch of REM sleep with no minimum duration criterion. Sleep efficiency is calculated as the total amount of sleep time divided by the total sleep period. The number of arousals was defined as the total number of waking episodes of at least 30 sec duration. Percentages of each of the sleep stages within TSP were also computed. The personnel who scored the records were blind to the diagnostic group, age or gender.

Non-REM period definition

The definition of NREM periods closely followed that outlined by Dijk *et al.*³⁷ and Feinberg and Floyd.³⁸ NREM periods were defined as the succession of stages 2, 3, or 4 of 15 min or more duration, and terminated by stage REM or a period of wakefulness of at least 5 min. Stage 1 sleep epochs were excluded. No minimum REM duration was required for the first or last REM period. Latency to each of the NREM periods was measured in minutes from sleep onset. For statistical purposes, only the first four NREM periods were included for analysis, since not all subjects had more than 4 NREM periods through the night.

Power spectral analysis (PSA)

The PSA algorithm was taken from Press *et al.*³⁹ processing data in 2 sec epochs. Following their recommendation that PSA be computed where the sample size is an integer power of two, the digitized data values based on 250 Hz were padded with six zeros to produce 512 samples/2 s.⁴⁰ Spectral estimates were tapered and a Hanning window mini-

mized band overlap.⁴⁰ The present paper was restricted to spectral power in the 0.5 to 3.9 Hz delta band. SWA power was then averaged in 30 sec epochs to provide identical epoch lengths to the stage-score data. Data were then inspected on an epoch by epoch basis to ensure that only artifact-free epochs were included in the statistical analyses. To estimate SWA dissipation through the night, the difference in SWA power between successive NREM periods was calculated.

Statistical analysis

Data were coded for group (MDD or HC) and sex. The statistical analysis software (SAS) version 9.1.3 for Windows was utilized for all analyses. Repeated-measures analysis of variance (ANOVA) was conducted for SWA power, SWA dissipation, and NREM period latency and duration, treating NREM periods as a four-level repeated measure. Separate ANOVAs evaluated between-group differences for the dependent variables: SWA power, SWA dissipation, and duration and latency to each NREM period, if a statistical NREM period by group by sex interaction and NREM period main effect were obtained with the repeated-measures ANOVA. Least-squares multiple comparisons tested differences between individual means at an experiment-wise $P < 0.05$, only in the NREM periods when a significant overall ANOVA effect was obtained. Data are provided as mean ± standard deviation unless otherwise specified.

Results

Demographic and clinical data

Demographic and clinical information is shown in Table 1. There were no significant between-group differences in age ($F_{3,103}=0.5$; $P > 0.05$) or Tanner developmental scores ($F_{3,103}=0.7$; $P > 0.05$). There were between-groups differences for CGAS ($F_{3,103}=495.8$; $P < 0.0001$), FGAS ($F_{3,103}=55.3$; $P < 0.0001$) and CDRS ($F_{3,102}=278.8$; $P < 0.0001$). As expected, the MDD adolescents showed lower CGAS and FGAS, and higher CDRS scores than HCs ($P < 0.0001$). It should be noted that CDRS scores were missing for one MDD female and thus analyses were based on 31 subjects.

Sleep macroarchitecture

A MANOVA of polysomnographic (PSG) variables (Table 2) yielded a significant group by sex interaction ($F_{9,95}=2.6$; $P < 0.01$) group ($F_{9,95}=2.1$; $P < 0.04$), and sex ($F_{9,95}=2.9$; $P < 0.004$) main effects. The latency to the first REM period ($F_{3,103}=4.4$; $P < 0.006$), percentage Stage 1 sleep ($F_{3,103}=5.7$; $P < 0.002$), percentage

Stage 2 ($F_{3,103}=4.7$; $P < 0.004$), and percentage REM sleep ($F_{3,103}=2.7$; $P < 0.05$) differed between groups. Least-square multiple comparisons indicated that MDD males showed shorter REM latency ($P < 0.004$) and higher percentage REM ($P < 0.03$) than HC males. MDD females spent more time in Stage 1 than healthy females ($P < 0.05$), and more time in Stage 2 than MDD males ($P < 0.04$). MDD males also had significantly more Stage 1 than MDD females ($P < 0.03$).

Slow-wave activity power and dissipation across NREM periods

Slow-wave activity power

Repeated-measures ANOVA of SWA power yielded a significant NREM period by group by sex interaction ($F_{9,300}=2.5$; $P < 0.009$) and an

NREM main effect ($F_{3,300}=215.0$; $P < 0.0001$). Separate ANOVAs revealed between-group differences in the first ($F_{3,103}=4.1$; $P < 0.009$), third ($F_{3,103}=2.8$; $P < 0.05$), and fourth NREM periods ($F_{3,103}=2.8$; $P < 0.05$), but only a trend in the second NREM period ($F_{3,103}=2.6$; $P = 0.06$). Multiple comparisons showed that SWA power was significantly lower in MDD males compared to HC males in the first ($P < 0.007$) and third ($P < 0.02$) NREM periods (Figure 1A). However, there were no differences in SWA power between MDD and HC females ($P > 0.05$) in any of the NREM periods. Our results also confirmed previous studies showing different developmental time periods between healthy males and females during adolescence. Thus, HC males expressed higher SWA power than HC females in the first, third, and fourth NREM periods ($P = 0.002-0.03$). There was no

Table 1. Demographic and clinical features of the sample by diagnosis and sex.

	HC-M (n=20)	HC-F (n=32)	MDD-M (n=20)	MDD-F (n=32)
Age	14.7±1.2	15.1±1.6	15.3±1.6	15.0±1.5
Tanner scores	4.2±0.7	4.4±0.5	4.4±0.7	4.4±0.6
FGAS	91.0±8.1	89.9±6.2	66.1±13.0	64.4±11.7
CGAS	92.2±5.8	91.0±4.0	51.3±5.6	53.4±5.2
CDRS-R*	18.0±1.3	18.5±1.6	55.7±7.4	56.5±10.1
Age of onset	–	–	13.4±2.9	12.9±2.6
Length of current depressive episode ^o	–	–	16.0±26.7	20.2±21.8
Family history of MDD (n)	–	–	13	27
Comorbid psychiatric diagnosis (n)	–	–	6	15
ADHD	–	–	3	6
Generalized anxiety	–	–	3	4
Phobias	–	–	–	2
Oppositional defiant dis.	–	–	–	5
OCD	–	–	–	2

*Missing data n=31 for MDD females. ^oIn months. HC, healthy control; MDD, major depressive disorder; M, males; F, females; FGAS, family global assessment scale; CGAS, clinical global assessment scale; CDRS-R, children’s depression rating scale - revised; ADHD, attention deficit hyperactivity disorder; OCD, obsessive compulsive disorder.

Table 2. Means and standard deviations of sleep macroarchitecture by diagnoses and sex.

Sleep variables	HC-M (n=20)	HC-F (n=32)	MDD-M (n=20)	MDD-F (n=32)
Total sleep time, min.	449.2±35.3	458.4±42.0	445.5±44.5	465.2±41.7
Sleep latency, min.	9.5±9.9	13.7±10.7	14.6±11.2	18.1±20.2
REM latency, min.	111.1±57.1	84.7±38.6	69.6±23.7	107.6±50.3
% Stage 1*	8.4±5.0	4.8±3.0	10.6±7.2	7.4±5.0
% Stage 2*	47.0±6.4	52.6±5.9	45.4±8.2	50.0±8.5
% SW (stages 3+4)*	20.8±8.1	18.0±7.7	17.9±10.5	18.3±8.7
% REM*	18.3±3.9	21.2±4.0	22.3±4.9	20.6±5.1
% awake and movement*	5.1±4.7	3.1±1.6	3.6±1.6	3.4±2.2
Sleep efficiency	93.0±4.9	93.8±2.4	93.2±2.5	93.0±4.5
Number of arousals	23.4±7.7	19.1±8.9	20.4±6.1	19.7±8.4

*Relative to total sleep time. Minutes of stages 3+4. HC, healthy control; MDD, major depressive disorder; M, males; F, females; REM, rapid eye movement sleep; NREM, non-rapid eye movement sleep; SW, slow wave sleep.

such difference between MDD males and females. Data are shown in Table 3.

Slow-wave activity dissipation

Repeated-measures ANOVA for SWA dissipation yielded a significant NREM period by group by sex interaction ($F_{6,206}=2.8$; $P<0.02$) and an NREM period main effect ($F_{2,206}=26.2$; $P<0.0001$). Individual ANOVAs revealed statistically significant results for the decrease in SWA power from the first to the second NREM period ($F_{3,103}=4.4$; $P<0.006$), and a trend from the second to the third NREM period ($F_{3,103}=2.5$; $P=0.059$). Multiple comparisons showed the smallest SWA decline from the first to the second NREM period in MDD males compared to HC males ($P<0.0005$) where HC males dissipated an excess of $190\mu V^2$ of SWA power more than MDD males (Table 3). There was no SWA dissipation between MDD and HC females. In addition, no difference was seen between HC males and females or between MDD males and females. Data are shown in Table 3.

Non-REM sleep period characteristics

To ensure that the between group differences in SWA power and its dissipation were not influenced by differences in the characteristics of the individual NREM periods, we contrasted the latency to each NREM and the duration of each NREM period across group and sex.

No NREM by group by sex interaction was evident for the duration measures ($F_{9,300}=1.3$; $P>0.05$). Data are shown in Table 3.

The latencies to each NREM period did show a significant NREM period by group by sex interaction ($F_{9,300}=3.0$; $P<0.002$) and an NREM period main effect ($F_{3,300}=1937.8$; $P<0.0001$) from repeated-measures ANOVA. Separate ANOVAs of each NREM period confirmed that it was the latencies to the third ($F_{3,103}=4.1$; $P<0.009$) and fourth ($F_{3,103}=3.5$; $P<0.02$) NREM periods that showed group differences. MDD males showed a shorter latency to the third ($P<0.003$) and fourth ($P<0.005$) NREM period compared to HC males. No differences were seen between MDD and HC females. Also, HC females showed shorter NREM latency than HC males ($P<0.02$) in the third NREM period, but no difference was noted between MDD males and females. Data are shown in Table 3.

In summary, neither the latency to the first two NREM periods nor the difference in duration according to group and sex ruled out differences in NREM period as a contributor to the group by sex interactions obtained with SWA power and its dissipation in the first half of the night.

Table 3. Means and standard deviations of slow-wave activity power and dissipation, and non-REM period characteristics by diagnosis and sex.

	HC-M (n=20)	HC-F (n=32)	MDD-M (n=20)	MDD-F (n=32)
NREM 1				
Latency*	8.9±6.9	9.5±5.8	12.2±13.3	9.5±5.6
Duration*	92.8±36.4	81.9±36.8	65.8±19.7	93.5±40.3
Power ^o	955.4±242.0	738.0±216.7	759.7±270.1	781.3±227.7
Decay ^o	310.2±207.6	224.4±179.3	120.3±142.8	202.5±153.7
NREM 2				
Latency*	125.1±50.7	105.6±41.4	96.7±28.9	121.7±46.3
Duration*	82.7±27.1	76.8±24.7	71.7±14.9	74.6±25.3
Power ^o	645.1±170.5	513.5±134.2	639.4±233.0	578.7±246.1
Decay ^o	100.7±178.2	73.7±133.8	196.1±146.8	121.9±201.6
NREM 3				
Latency*	241.6±55.8	206.7±46.3	192.4±36.0	226.6±54.9
Duration*	67.7±30.4	71.7±14.4	59.7±20.8	71.0±19.1
Power ^o	544.4±157.0	439.7±111.9	443.3±166.0	456.8±140.1
Decay ^o	56.1±135.2	42.7±114.9	6.2±130.7	39.0±132.4
NREM 4				
Latency*	340.8±72.7	307.7±51.2	288.7±38.8	329.5±61.5
Duration*	55.1±22.3	63.0±15.1	53.4±14.0	56.3±15.6
Power ^o	488.3±113.1	397.0±102.4	449.6±159.2	417.7±113.6

*In minutes; ^oin μV^2 . HC, healthy control; MDD, major depressive disorder; M, males; F, females; NREM, non-rapid eye movement sleep.

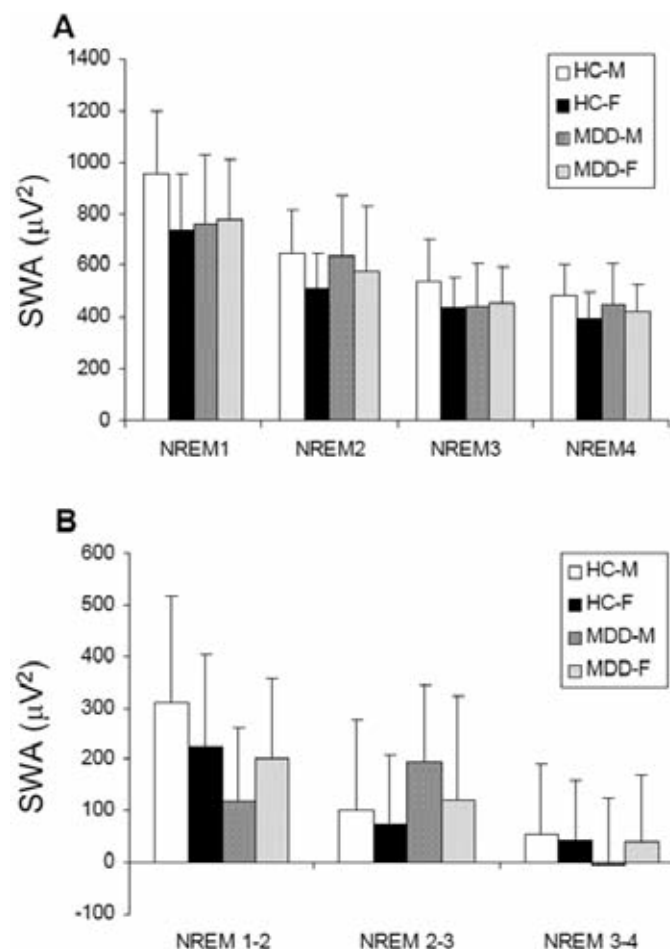


Figure 1. Slow wave activity (SWA), power (A), and SWA dissipation (B) across non-rapid eye movement (NREM) sleep periods for healthy control males (HC-M) and females (HC-F), and depressed males (MDD-M) and females (MDD-F). Error bars represent standard deviations.

Correlation between REM latency and slow-wave activity measures

Pearson's correlations were used to address the contribution of short or long REM latency to changes in SWA between groups. No significant correlations were obtained between SWA power or SWA dissipation and REM latency in any of the groups (r 0.05-.38; $P > 0.05$). Thus, the reduction in SWA power observed in depressed males was not due to a shorter REM latency.

Discussion

The major finding of the study was that depressed adolescent males showed SWA abnormalities, with lower SWA power in the first NREM period and irregular dissipation of SWA over the night, compared to healthy control males. Low SWA power at the beginning of the night suggests that depressed adolescent males failed to accumulate sufficient sleep drive during the daytime. The irregular dissipation or decline of SWA between consecutive NREM periods further suggests reduced recovery from prior sleep debt in this group. Depressed adolescent males showed maximum SWA loss between the second and third NREM periods, not between the first and second as would be expected if sleep drive was high at sleep onset. Moreover, this group expressed the shortest latency to the third and fourth NREM period of the night. Altogether, these results indicate that depressed adolescent males, like depressed adult males, show reduced SWA power with an abnormal time course.

SWA power and its time course are considered physiological correlates of the recuperative aspect of sleep as evidenced by the increase in SWA power following sleep deprivation⁴¹ and the reduction of SWA power after napping.⁴² Consequently, the SWA abnormalities observed in depressed adolescent males compared to healthy males in the absence of differences in total sleep time between these groups suggest the existence of sleep deficit at a neuronal level that may interfere with mood regulation.

In an earlier study, Reynolds and collaborators reported lower slow-wave sleep and delta wave count, as well as irregular temporal distribution of delta waves, in depressed men compared to depressed women, although the authors attributed the sex differences to variations in skull thickness.⁴³ Our own group has shown that men with depression have lower SWA accumulation in the first NREM period and slower dissipation through the night compared to healthy men.^{21,22} In addition, depressed males showed no relationship

between SWA changes and age (between 20-40 years), suggesting the presence of SWA abnormalities in adolescents with depression. These findings and our present results support the idea that the pathophysiology of depression differs for men and women, and that such differences emerge at very early ages.

The present results highlight the need to develop sex specific therapies to improve sleep quality rather than time spent sleep in adolescents with MDD, and particular emphasis should be given to the enhancement and restoration of Slow-Wave Activity. Interpretation of our initial findings in adults with MDD and the current work raise the possibility that: i) SWA impairment antecedes the onset of MDD in males, underscoring the need to study SWA regulation in children and adolescents at-risk for MDD; and ii) SWA impairment may relate to different depressive symptoms in females and males.

Regarding the analysis of polysomnographic data, we observed a substantial shorter REM latency and higher percentage of REM sleep in depressed male adolescents compared to healthy control males. However, depressed females showed longer REM latency compared to healthy females, although this difference was not statistically significant. Our results suggest that changes in REM latency might be sex-specific and could potentially account for the great discrepancy in studies of sleep in depression examining changes in REM latency. In agreement with our previous findings in adults,²¹ the relationship between REM latency and SWA measures in either depressed or healthy adolescents was negligible, suggesting that changes in REM sleep and SWA mechanisms are not interdependent. Historically, short REM latency has been offered as an explanation for reduced visually scored slow-wave sleep and reduced delta wave count,^{44,45} but this suggestion does not fit the SWA data presented here. However, we did obtain group differences in REM latency in the present study and in several of our previous publications.^{32,46,47} Thus, REM sleep differences may be evident in some MDD adolescents, but they do not appear to contribute to SWA differences between depressed and healthy control groups.

There are several limitations to the current study. It is noteworthy to highlight that it describes baseline sleep and, therefore, only evaluates the time course of SWA, not its regulation. Sleep deprivation or sleep challenge studies will be necessary to evaluate whether SWA regulation and sleep homeostasis is truly impaired in adolescents with MDD. A study of SWA homeostasis in adults indicated that both men and women with MDD showed an abnormal SWA response to a mild sleep challenge, but the effects were inverted, with a blunted response in MDD men and a hyper-response in MDD women.⁴⁸ If the adolescent data are con-

sistent, one would also expect a blunted response to sleep deprivation or sleep challenge in adolescent males with MDD. Ongoing research in our laboratory is investigating sleep homeostasis and regulation in MDD adolescents. Second, the cross-sectional nature of the present study makes it difficult to establish whether SWA abnormalities in depressed adolescents persist in adulthood or whether they lead to a more severe course of illness compared to those with adult onset MDD. Third, we did not analyze clinical data in relationship to SWA, and as such, the clinical relevance of SWA impairment remains to be demonstrated. Nevertheless, the present results constitute the basis for the development of new therapies to improve sleep quality in depressed adolescents, with the caveat that sleep disturbances in MDD may not be of the same nature for males and females.

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