Sex and Age Differences in Sleep Macroarchitecture in Childhood and Adolescent Depression

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Subject Objective: To evaluate age and sex differences in sleep macroarchitecture in children and adolescents with major depressive disorder.

Design: Ninety-seven (50 F, 47 M) symptomatic unmedicated depressed outpatients were compared with 76 healthy controls (42 F, 34 M) matched for age and sex.

Setting: Participants spent 2 consecutive nights in the sleep laboratory. Participants: One hundred seventy-three children and adolescents, aged 8 to 18 years.

Measurements and Results: Significant group-by-age-by-sex interactions were evident for total sleep period, percentage of Stage 1 sleep, percentage of Stage 2, percentage of slow-wave sleep, and rapid eye movement (REM) sleep latency. The depressed adolescent boys had the greatest sleep disturbance with the highest amount of percentage of Stage 1 sleep, the shortest REM latency, and the least percentage of slow-wave sleep and number of minutes of slow-wave sleep in the first non-REM period. There were minimal age differences in sleep parameters between depressed children and adolescent girls. Within age groups, the sex differences were minimal in the healthy controls. The sex differences within the depressed group were substantially larger than controls.

Conclusions: These findings suggest a differential developmental influence on sleep in early-onset depression that is heavily dependent on sex. Sex differences are substantially smaller in healthy individuals compared with those with depression, in agreement with previous studies in depressed adults.

Keywords: Sleep, depression, sex, children, age, adolescence

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INTRODUCTION

THE LIFETIME PREVALENCE FOR MAJOR DEPRESSIVE DISORDER (MDD) IN CHILDREN AND ADOLESCENTS IS ESTIMATED AT 8% TO 15%, WITH HIGHER rates among adolescents.1,2 Depression is a major factor in suicide, school failure and drop out, and substance use in children and adolescents.3-6 Sleep disturbances are a large contributing factor to risk for depression.

In recent prospective studies, sleep problems during childhood were associated with behavioral and emotional disorders, alcohol or substance abuse, and depression in later childhood.7,8 Sleep problems during adolescence have also been shown to correlate with both suicidal ideation and attempts. What’s more, suicidality is more common in those adolescents with significant sleep complaints.9-12 Risk of relapse and recurrence is also higher in patients with persistent sleep disturbances, throughout the life cycle.13,14 Moreover, subjective sleep complaints are evident in the vast majority of patients with MDD from childhood throughout adulthood.15,16

Laboratory studies of sleep abnormalities in adults with MDD have identified prolonged sleep latency, an early onset of rapid eye movement (REM) sleep (< 65 minutes), decreased deep sleep, and increased wakefulness and sleep fragmentation as characteristic of adults with MDD.17 However, no single sleep measure may reliably differentiate patients from controls.17 Nevertheless, the laboratory-based findings in children with MDD are more equivocal. Some investigators have found longer sleep latency and shorter REM latency in depressed children and adolescents.18-20 Other studies have reported few significant differences from healthy controls.21-24 Considering all published laboratory studies, sleep abnormalities are more prevalent in adolescents with MDD than in younger children.

The inconsistencies across sleep-laboratory studies in early-onset MDD may be due to several factors, including fewer studies among young depressed patients, small sample sizes, age-related changes in sleep, and the failure to examine sex differences. As noted in several studies, sex differences in adults with MDD are substantially greater than those observed in healthy subjects.15,28-30 The idea that the a different pathophysiology underlies depression in males and females has been introduced previously.31

A recent review of the data on sleep and sex in healthy children has suggested that the interaction of age and sex may be a more important statistical consideration than sex alone.32 Comparing the data from children to adults with MDD, it appears that the largest age-related differences are occurring in males, suggesting a differential maturational time course between males and females with depression. On the other hand, other studies have suggested that sex differences in healthy children are minimal if they are matched on developmental age.33 Thus, it would seem that the maturational influences on sleep are both disease- and sex-dependent. Note, that none of the previous studies on sleep considered this interaction in children and adolescents with MDD. Taken to-
together, these findings provide strong support for evaluating the influence of age and sex on sleep macroarchitecture in children and adolescents with depression.

The primary aim of the present study was to evaluate sex and age differences in sleep macroarchitecture in healthy and depressed children and adolescents. Our approach was to assess the statistical influence of age and sex directly, rather than control for, or eliminate, the influence of either variable on sleep architecture. The largest age-related differences in sleep measures were expected in boys with depression. Secondarily, we compared the influence of chronologic age versus maturation age on sleep macroarchitecture.

METHODS

Subjects

Study participants were recruited over a 5-year period through published advertisements and posted flyers at community centers, hospitals, outpatient psychiatric clinics, and pediatric clinics. Self-referral or referral from a community clinician was also permitted. Almost all study participants were self-referred. Each potential participant called the laboratory expressing an interest in the study. A brief telephone screen was administered to determine potential eligibility. All participants were then scheduled for a full clinical interview. Diagnostic and interview procedures are described below. Participants were paid $100 for participating in the study.

Target enrollment was 200 subjects: 8- to 18-year-old males and females, divided equally among MDD and controls, matched according sex and age (within 6 months) between those 8 to 12 years old and 13 to 18 year olds. All participants were recruited specifically and exclusively for this study and were not participating in any other study at the time of enrollment.

For all participants, inclusion criteria were willing and able to provide informed written consent (parent) and assent (child); normal intelligence, as assessed clinically (or by psychometric testing if evidence of IQ < 80); and no medication (for at least 4 weeks) or counseling at the time of the clinical interview. Additional inclusion criteria for healthy controls were no personal or family history from parents using the Family History Diagnostic Procedures. In addition to these standard pictures.

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Final Sample

Of the 200 participants enrolled in the study, data were excluded from analysis for the following reasons: incomplete or missing clinical or diagnostic data (n = 10); missing sleep diaries (n = 4); technical problems due to power outages, electrode loss, battery back-up failure (n = 8); “no-show” on Night 2 (n = 2) evidence of sleep-disordered breathing (n = 6); or actigraphy problems (n = 4). Note that in some instances there was more than 1 reason for exclusion after enrollment, but the unique number of exclusions was 27. Thus, the final sample reported here consisted of 173 children and adolescents, aged 8 to 18 years, who participated in the study, including 97 MDD and 76 healthy controls. The details on the final sample are reported in the results section.

Diagnostic Procedures

Patients for the study were scheduled for a full evaluation after a telephone screen for inclusion and exclusion criteria. In addition to a structured psychiatric interview, the initial evaluation for the MDD children and adolescents included a medical review of systems, a physical, routine laboratory tests, and neurologic examination. The evaluation was completed during a 3-week period.

All healthy controls and children and adolescents with MDD underwent the same initial psychiatric evaluations. All controls had an absence of any lifetime psychiatric disorder based on clinical interview. There was also no evidence of psychopathology in first-degree relatives. At the initial visit, each participant and parent or parents were interviewed separately using the Schedules for Affective Disorders and Schizophrenia for School-Aged Children: Present and Lifetime, a revision to the Schedules for Affective Disorders and Schizophrenia for School-Aged Children. The Schedules for Affective Disorders and Schizophrenia for School-Aged Children: Present and Lifetime is a semistructured DSM-IV-based diagnostic interview to establish that the patient met DSM-IV criteria for MDD and to identify other concurrent and lifetime psychiatric disorders. The final diagnoses were based on information from interviews of the parent or parents and child. Additionally, depressive-symptom severity was assessed using the Children’s Depression Rating Scale-Revised. 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 assessed overall functioning. Tanner maturation (1-5 scores) was self-assessed by participants using the “Typical Progression of Pubertal Development Chart” adapted from Tanner. Breast and pubic hair development were assessed for girls, and genital and pubic hair development was assessed for boys. Note that Duke et al have shown that children can reliably self-rate sexual maturation using these standard pictures. A third interview was conducted just prior to sleep study to review psychiatric assessment and inventories. A minimum score of > 40 on the Children’s Depression Rating Scale-Revised was required for entry into the study, indexing moderate depressive-symptom severity and matching the criterion of our previous work. Further detail on the clinical evaluation procedures is reported elsewhere.

The Institutional Review Boards at the University of Texas Southwestern Medical Center and the University of Michigan approved this study. Prior to the initial interview, the study was explained and written informed consent was obtained from the parent or parents and assent from the patient.

Procedures

All participants agreed to follow their habitual school-week bedtimes and rise times, established by sleep history, throughout the entire study. They were informed that a deviation of more than one-half hour during the week prior to lab study would result in discontinuation from the study. With the exception of 2 children,
and 3 adolescents, the lab sleep studies were conducted on Friday and Saturday nights during the regular school year and outside of holiday and vacation schedules. Actigraphs (Actiwatch-1™, Mini Mitter Co., Inc., Bend, OR.) were worn throughout the week, and sleep-wake diaries were collected daily during the home-based recording period. Data from the Actiwatch™ were downloaded prior to their first night in the laboratory to ensure that the participants adhered to their habitual schedule. On lab nights, lights-out and lights-on time followed the habitual schedule. Spontaneous morning awakenings only occurred in 3 of the 173 subjects and were within one-half hour of habitual rise times.

Night 1 served as laboratory adaptation and as an additional screen for the presence of independent sleep disorders. Night 1 recordings also included chest and abdomen respiration bands, nasal-oral thermistors, and leg electrodes. Electrode placement on the subsequent night included F1, F2, C3, C4, O3, O4, P3, P4, left and right electrooculogram, recorded from the upper and lower canthi, and a bipolar electromyogram recorded from under the chin and on the cheek. Electroencephalogram electrodes were referenced to the ear lobes linked through a 10-kΩ resistor to minimize nonhomogeneous current flow and potential artifactual hemispheric asymmetries, as is standard in our laboratory.

The electroencephalogram was transduced by GRASS™ P511 A/C amplifiers set at a sensitivity of 5 (50-μV, 0.5-second 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. The respiratory signals were also digitized to further assess potential reductions in airflow and effort. Any subject who showed 5 or more instances of >50 % reduction in airflow of at least 5 seconds in duration per hour was excluded from further study. This, coupled with visual assessment of respiratory signals, exclusion for parental report of snoring, or evidence of snoring in the lab, minimized the likelihood of including those children with sleep-disordered breathing. Further, 6 participants that we excluded for having a respiratory disturbance index > 5 per hour were referred to an accredited sleep disorders center for full evaluation. Only one was judged to have clinically significant sleep-disordered breathing.

Visual stage scoring of 30-second epochs was conducted according to standard sleep-staging criteria, by research personnel trained at better than 90 % agreement on an epoch-by-epoch basis. Sleep latency was defined as the first consecutive 10-minute block of any sleep stage (except REM) with no more than 2 minutes of wake time, reflecting persistent sleep onset. Total sleep period 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. REM density was scored on a 5-point scale for each epoch, ranging from no eye movements (0) to more than 4 per epoch (4). These scores were then averaged per minute of REM. Sleep efficiency was calculated as the total amount of sleep time divided by the total sleep period. The number of awakenings of at least 30 seconds in duration was also calculated. The personnel who scored the records were blind to the diagnostic group, age, or sex.

Statistical Analysis

Data were coded for group (MDD vs NC) and sex. For the first set of analyses, a cutoff of 12 years was used to contrast children and adolescents, corresponding with previous work and with the definition of adolescence. For the second set of analyses, average Tanner scores assessed potential maturational differences, first using a cutoff of 3 and then contrasting those Tanner 1 and 2 with Tanner 4 and 5. This analysis was used to evaluate whether the chronologic-age cutpoint of 12 years captured the same between-group differences as maturational age and how sleep differed between prepubertal and pubertal children. Split plot analysis of variance (ANOVA) evaluated statistical differences, testing the 3-way interaction first and 2-way interactions and main effects only if 3-way interactions were not significant. Least-squares multiple comparisons contrasted differences between individual means only if a significant overall ANOVA effect was obtained to protect against Type I errors.

RESULTS

There were 50 females and 47 males in the sample of outpatients with MDD and 42 female and 34 males in the sample of healthy nondepressed controls. None of the final participants had an independent sleep disorder (e.g., sleep-disordered breathing, bruxism, periodic limb movements, or restless legs), based on history and confirmed on the first night in this study. There were 25 girls and 24 boys in the 8- to 12-year-old-MDD group and 17 girls and 16 boys in the 8- to 12-year-old healthy control group. The adolescent group had 25 girls and 23 boys with MDD and 25 healthy control girls and 18 boys in the 13- to 18-year-old age range.

Demographic and clinical information are shown in Table 1. Note that there were no significant differences in age or Tanner developmental maturation scores between the MDD and control groups. The MDD group was significantly more impaired than controls on the Family Global Assessment Scale and the Children’s Global Assessment Scale, where values below 60 indicate mild to moderate dysfunction on both scales (p < .05). Depressive symptom severity was also significantly higher in the MDD group, with Children’s Depression Rating Scale scores in the 90th percentile compared with the tenth percentile in controls (p < .05), as would be expected. There were a number of children and adolescents in the depressed groups who had psychiatric comorbidity, who also met diagnostic criteria for other psychiatric illness. These are identified in Table 1. We excluded diagnoses of dysthymia, evident in 9 girls (18 %) and 10 boys (21.2 %), as this diagnosis also reflects depressive symptomatology. About 20% of the sample also met criteria for attention-deficit/hyperactivity disorder. There were also 7 other participants who had secondary diagnoses. Note that comorbid psychiatric illness is generally quite high in early-onset depression, and the amount of comorbid illness in the present sample is lower that that reported in other studies.

Sleep Macroarchitecture: Chronologic Age

The means and SD for all of the sleep measures are shown in Table 2, separated by group and the chronologic-age cutpoint.

Three-Way Interactions

The ANOVA revealed a significant 3-way sex-by-diagnostic group-by-age interaction for total sleep period (F[2,156]=8.69; p < .01). Least-squares multiple comparisons indicated that adolescents had significantly (p < .001) shorter total sleep periods than...
Sleep in Depressed Children  

Robert Metzger, MD, MPH; Elissa T. Tannenbaum, PhD; Ann E. Diamond, MD; et al.

Sleep in Depressed Children  

Sleep in Depressed Children

Table 1—Demographic and Clinical Features of the Sample by Diagnostic Group and Sex

<table>
<thead>
<tr>
<th>Major Depressive Disorder</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>Age, y*</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>12.4±2.8</td>
</tr>
<tr>
<td>≤ 12</td>
<td>10.0±1.4</td>
</tr>
<tr>
<td>≥ 13</td>
<td>14.8±1.5</td>
</tr>
<tr>
<td>Tanner scorea</td>
<td>3.3±1.5</td>
</tr>
<tr>
<td>FGAS*</td>
<td>58.9±10.7</td>
</tr>
<tr>
<td>CGAS*</td>
<td>53.5±10.6</td>
</tr>
<tr>
<td>CDRS-R*</td>
<td>58.9±10.0</td>
</tr>
<tr>
<td>Age of Onset, y*</td>
<td>11.2±3.1</td>
</tr>
<tr>
<td>Length of current</td>
<td>15.5±19.6</td>
</tr>
<tr>
<td>depressive episode, mo.*</td>
<td></td>
</tr>
<tr>
<td>Suicide attempts, no.</td>
<td>1</td>
</tr>
<tr>
<td>Ideation, 1-5 scalea</td>
<td>2.4±0.9</td>
</tr>
<tr>
<td>Family history of</td>
<td>16 (32.0)</td>
</tr>
<tr>
<td>MDD*</td>
<td></td>
</tr>
<tr>
<td>Comorbid psychiatric</td>
<td>12 (24.0)</td>
</tr>
<tr>
<td>diagnosisb</td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>9</td>
</tr>
<tr>
<td>Enuresis</td>
<td>0</td>
</tr>
<tr>
<td>SAD</td>
<td>1</td>
</tr>
<tr>
<td>Generalized Anxiety</td>
<td>0</td>
</tr>
<tr>
<td>Conduct Disorders</td>
<td>0</td>
</tr>
<tr>
<td>Phobia</td>
<td>0</td>
</tr>
<tr>
<td>Obsessive-Compulsive</td>
<td>1</td>
</tr>
<tr>
<td>Separation Anxiety</td>
<td>1</td>
</tr>
</tbody>
</table>

aData are shown as mean ± SD.
bData are shown as number of subjects (%).

*p < .05 contrasting subjects with major depressive disorder with healthy controls, collapsed across age and sex.

FGAS refers to Family Global Assessment Scale; CGAS, Children’s Global Assessment Scale; CDRS-R, Children’s Depression Rating Scale, Revised; ADHD, attention-deficit/hyperactivity disorder; SAD, seasonal affective disorder.

Table 2—Sleep Macroarchitecture by Group and Age (Collapsed by Sex)

<table>
<thead>
<tr>
<th>Sleep Variable</th>
<th>Children (8-12 y)</th>
<th>Adolescents (13-18 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MDD</td>
<td>HC</td>
</tr>
<tr>
<td>Total sleep, min*</td>
<td>520.7±48.3</td>
<td>523.7±39.9</td>
</tr>
<tr>
<td>Sleep latency, min*</td>
<td>15.7±14.3</td>
<td>11.7±10.1</td>
</tr>
<tr>
<td>REM latency, min*</td>
<td>131.7±54.7</td>
<td>117.9±43.3</td>
</tr>
<tr>
<td>Sleep stage, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1*</td>
<td>8.0±4.3</td>
<td>7.8±5.5</td>
</tr>
<tr>
<td>2*</td>
<td>49.4±6.9</td>
<td>47.9±6.8</td>
</tr>
<tr>
<td>SWS*</td>
<td>20.5±6.6</td>
<td>22.2±5.5</td>
</tr>
<tr>
<td>REM</td>
<td>17.7±4.7</td>
<td>17.9±4.1</td>
</tr>
<tr>
<td>Awakening</td>
<td>4.5±2.4</td>
<td>4.1±2.2</td>
</tr>
<tr>
<td>movement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>96.9±2.9</td>
<td>97.6±2.1</td>
</tr>
<tr>
<td>REM density</td>
<td>2.3±.6</td>
<td>2.3±.7</td>
</tr>
<tr>
<td>SWS in first NREM period, min*</td>
<td>69.6±25.3</td>
<td>70.1±21.8</td>
</tr>
<tr>
<td>Awakenings, no.*</td>
<td>25.3±8.8</td>
<td>25.4±9.6</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD unless otherwise indicated. MDD refers to major depressive disorder; HC, healthy controls; REM, rapid eye movement; SWS, slow-wave sleep; NREM, non-rapid eye movement.

*p < .05 contrasting subjects with major depressive disorder with healthy controls, collapsed across age and sex.

Table 2—Sleep Macroarchitecture by Group and Age (Collapsed by Sex)

% Stage 1

% TSP

8-12 yrs 13-18 yrs

Figure 1—Mean Stage 1 (expressed as a percentage of total sleep period [% TSP]) in children and adolescents by sex and diagnostic group. HC F refers to healthy control females, (grey hatched line); MDD F, depressed females (black hatched line); HC M, healthy control males (grey solid line); MDD M, depressed males (black solid line).

REM latency (F2,165 = 4.93; p < .01). The largest age-related differences were found in the MDD males, with the smallest age-related differences in MDD females, accounting for the significant 3-way interaction, illustrated in Figure 2. The adolescent healthy

SLEEP, Vol. 29, No. 3, 2006
control and MDD boys had significantly shorter REM latencies than their younger counterparts, as determined by least-squares multiple comparisons (p < .02, p < .0001, respectively).

There was also a significant 3-way interaction for percentage of slow-wave sleep (SWS) and minutes of SWS during the first non-REM (NREM) period (F_{7,165} = 4.78; p < .01, F_{7,165} = 8.59; p < .01; respectively). Adolescents had significantly less SWS than their younger counterparts (p range: .0005-.04; see Figure 3). Least-squares multiple comparisons revealed that the MDD adolescent boys had significantly less SWS (p range: .002-.057) than all of the younger age groups. The MDD adolescent boys also had the least number of minutes of SWS in the first NREM period, significantly less than all of the younger age groups, p range: .0001-.0003. Least-squares multiple comparisons confirmed that SWS percentage and minutes of SWS within the first NREM period were significantly less in adolescent healthy control girls compared to younger healthy control girls (p < .001, p < .001, respectively). The adolescent MDD girls had significantly less SWS (p < .03) than the younger MDD girls, with a trend for less (p < .08) SWS in the first NREM period.

Two-Way Interactions

There was a significant group-by-sex interaction (F_{7,166} = 4.24; p < .04) for number of arousals during the night. The MDD males had significantly (p < .03) more arousals from sleep than the MDD females. There were no other significant 2-way interactions for any other sleep variable.

Main Effects

A group main effect was obtained for 1 sleep measure, percentage of REM sleep. Adolescents (17.8%) had significantly less REM sleep than the younger children (19.3%) (F_{4,166} = 4.88; p < .03).

Sleep Macroarchitecture: Maturation Age

To ensure that our arbitrary age cutpoint of 12 years did not produce an artificial distinction between groups, we conducted a secondary ANOVA using Tanner score instead of chronologic age in the model. Groups were stratified by average Tanner scores, an average of upper and lower body scores less than 3 compared with scores greater than or equal to 3.

Group Interactions

The results of the 3-way interactions (diagnostic group-by-sex-by-Tanner) were evaluated, and the outcome was very similar to that obtained with age. The 3-way interactions remained statistically significant for several parameters of sleep macroarchitecture: total sleep period (F_{7,163} = 5.88; p < .0001), REM latency (F_{7,163} = 4.20; p < .001), percentage of SWS (F_{7,163} = 2.87; p < .008), and minutes of SWS during the first NREM period (F_{7,163} = 5.84; p < .0001).

Multiple comparisons indicated that the pubertal males and females in the MDD and healthy control groups slept significantly (p range: .0001-.01) less than the prepubertal children. Multiple comparisons revealed significant developmental age differences, similar to the chronologic-age analyses. The MDD pubertal males (11.5%) had a significantly (p < .04) higher percentage of Stage 1 sleep than the prepubertal MDD males (8.4%).

To further evaluate the influence of developmental age, we conducted an ANOVA contrasting Tanner scores less than 3 to scores greater than or equal to 3. Finally, correlations were computed to determine whether Tanner scores or age accounted for more variance in sleep measures. Overall, the correlations with sleep macroarchitecture were higher for chronologic age than for Tanner scores but differed dramatically by group and sex. For females with MDD, age accounted for significant variance (13%-21%) in total sleep period, SWS percentage, and minutes of SWS in the first NREM period. Tanner scores were not significantly correlated with most measures of

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*SLEEP, Vol. 29, No. 3, 2006*
sleep macroarchitecture, except total sleep period (9%). Among healthy females, age accounted for 10% to 41% of the variance in sleep measures, with highest correlations for total sleep period, SWS percentage, and minutes of SWS within the first NREM period, in contrast with 1% to 29% for Tanner score. Age accounted for 24% to 50% of the variance in total sleep period, percentage of SWS, and REM latency for healthy males. Tanner scores accounted for 38% of the variance for total sleep period but were not significant with any other sleep measure. By sharp contrast, Tanner score (14%-46%) and age (20%-42%) accounted for significant variance in MDD males in sleep measures, and correlations were higher than any other group.

**DISCUSSION**

To summarize these findings, there were significant age-related differences in sleep macroarchitecture that were sex and disease dependent. Significant group-by-age-by-sex interactions were evident for total sleep period, percentage of Stage 1 sleep, percentage Stage 2 sleep, percentage of SWS, and REM latency. Consistent with our previous findings, the depressed adolescent boys had the greatest sleep disturbance with the highest amount of Stage 1 sleep, the shortest REM latency, the least amount of SWS, and fewest number of minutes of SWS in the first NREM period and more arousals than depressed females. In contrast, the depressed girls did not differ dramatically from healthy controls in any sleep variable. These findings indicate important sex differences in sleep macroarchitecture in early onset depression.

Previous work by our group found important sex differences in adults with depression. Men with depression had deficiencies in SWS sleep, whereas women with depression did not show any impairment. Although delta abnormalities in adults with MDD have been reported in a number of studies, in particular in the first NREM period, there appear to be important sex differences that begin to emerge during adolescence. Reduced SWS and an altered time course in males may indicate impaired homeostatic regulation of sleep. By contrast, females with MDD show greater desynchronization of ultradian (90-minute) rhythms in quantitative sleep electroencephalogram activity, based on temporal coherence measures. These findings were evident among both adults and children. A recent study of circadian rest-activity cycles in a subset of the children included in the present study revealed damped circadian rhythms and lower levels of light exposure in young girls with MDD. Boys with MDD did not show circadian rest-activity abnormalities until adolescence. Thus, the developmental time course differs in boys and girls with MDD, and at least some elements, such as SWS, are distinct. However, to conclude that it is homeostatic impairment that characterizes adolescent depressed boys, it would be necessary to assess the time course of delta activity across NREM sleep episodes. Such efforts are currently underway.

Secondary to the chronologic-age analyses, we explored the influence of developmental age in sleep macroarchitecture. Groups were stratified by Tanner scores, and the 3-way interactions remained significant. Thus, the between-group differences in sleep variables in the present study cannot be attributed to a confound in developmental maturity between patients and controls. Moreover, chronologic age was often a better correlate of sleep macroarchitecture than maturational age in healthy boys and girls and similarly for females with MDD. Tanner score was more strongly correlated with sleep only in the MDD boys. Moreover, the effect sizes were generally larger when chronologic age was used in the interaction rather than Tanner score.

There are a number of limitations to the present study. Foremost is the cross-sectional comparison of sleep between children and adolescents. A longitudinal design that permitted an assessment of age-related changes in sleep would have been the ideal strategy. Moreover, the clinical relevance of these findings or which symptoms of depression are most strongly related to sleep disturbances remains to be established. Conducting follow-up studies on the clinical status of the children and adolescents with MDD is essential to evaluate whether sleep disturbances predict the course of illness in early-onset MDD. A follow-up study is underway. In addition, this study did not assess the influence of comorbid psychiatric illness on sleep. About 28% of the MDD group met criteria for attention-deficit disorder or other psychiatric illness. Although psychiatric comorbidity is very common in childhood depression research, it is possible that it could impact on the sleep findings. However, contrasting those subjects with and without comorbid diagnoses would have reduced the statistical power to detect sex and age interactions within the depressed group. Further, there were no clinical differences between boys and girls, and, thus, the presence of comorbid illness cannot account for our findings. Nevertheless, this issue does require further scrutiny. One caveat is that a very large sample size would be necessary to evaluate the influence of each comorbid psychiatric illness on sleep.

It should also be noted that our sample of healthy children met extremely stringent inclusion and exclusion criteria. They have no first-degree relatives with psychiatric illness and, as such, are best viewed as super healthy. The findings in our healthy controls may not generalize to a broader population of normal children. However, our depressed participants were also quite healthy medically, aside from psychiatric illness; the depressed group also met stringent inclusion and exclusion criteria. We believe that this makes our findings even more compelling.

There is 1 final limitation: our procedures for screening potential sleep-disordered breathing used a nasal/oral thermistor rather than a pressure transducer for air flow. As such, our methods may be less than optimal in quantifying apnea and hypopnea events. Future research should be sensitive to these potential limitations.

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