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Electroencephalographic Sleep and Hypothalamic–Pituitary–Adrenal Changes from Episode to Recovery in Depressed Adolescents

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Abstract

Objective: The study examined electroencephalographic (EEG) sleep and hypothalamic–pituitary–adrenal (HPA) changes associated with depressive episode and during recovery in adolescent depression.
Methods: Sixteen adolescents with major depressive disorder and 16 volunteers with no personal or family history of psychiatric disorder participated in a three-night EEG sleep protocol along with nocturnal urinary free cortisol (NUFC). Depressed subjects also were restudied during stable remission from the depressive episode.
Results: Compared with controls, depressed adolescents had significantly reduced sleep efficiency, shorter latency to rapid eye movement (REM) sleep, increased phasic REM sleep, and elevated NUFC excretion. Among depressed subjects, EEG sleep values did not change significantly from episode to remission. NUFC excretion reduced significantly during remission from the depressive episode.
Conclusions: The findings that EEG sleep measures are independent of clinical state, whereas HPA variables are state dependent, suggest that sleep and HPA measures make a differential contribution to our understanding of the pathophysiology and prognosis of mood disorders in adolescent patients.

Introduction

ELECTROENCEPHALOGRAPHIC (EEG) SLEEP CHANGES associated with adult major depressive disorder are well-replicated findings in biological psychiatry (Benca et al. 1992; Kupfer 1995). The most reliable sleep abnormalities of adult depression include sleep continuity disturbances, earlier onset of rapid eye movement (REM) sleep, increased phasic REM sleep, and diminished slow-wave sleep. Numerous investigations also have presented evidence of hypothalamic–pituitary–adrenal (HPA) dysregulation, typically manifested as cortisol hypersecretion, in adult major depression (for reviews, see Stokes and Sikes 1991; Barden 2004). From various adult samples with depression, including cross-sectional comparison of remitted patients with healthy controls (Hauri et al. 1974; Poland et al. 1997), single-episode cases versus those with recurrent illness (Giles et al. 1989; Thase et al. 1995) and prospective follow up of individual patients through recovery (Schulz et al. 1979; Rush et al. 1986; Kupfer et al. 1988; Riemann and Burger 1989; Steiger et al. 1989; Steiger et al. 1991; Buysse et al. 1992; Giles et al. 1993; Kupfer et al. 1993; Lee et al. 1993; Thase et al. 1994; Jindal et al. 2002; Rao et al. 2004), there is emerging consensus that EEG sleep disruptions associated with major depressive illness are remarkably stable from episode to recovery. In contrast to the stability of EEG sleep measures, studies examining HPA function highlight the state-related quality of this physiological system in association with depression (Barden 2004). The delineation of state-independent and state-dependent correlates of depressive disorder will be relevant for models of neurobiological vulnerability, course of illness, and prediction of response to various treatment strategies.

Consistent with findings in adults, in a pilot investigation of adolescents with depression, we previously reported that EEG sleep variables remained stable from episode to recovery whereas HPA dysregulation normalized during remission (Rao et al. 1997). The present study was undertaken to replicate and extend these initial observations. In contrast to

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the consistent EEG sleep and HPA changes associated with adult depression, controlled studies of child and adolescent cohorts have been highly variable and showed relatively few abnormalities (see Kaufman et al. 2001; Ivanenko et al. 2005). Therefore, replication of EEG sleep and HPA findings in pediatric samples is critical for understanding developmental continuities and discontinuities. Knowledge of developmental influences on biological correlates of depressive illness potentially can be helpful in developing more effective preventive and treatment interventions for this highly morbid condition (Rao 2006).

Methods

Participants

The participants for the study included 16 adolescents with depression and 16 controls. Prior to performing the research procedures, all adolescents signed a written assent form and parents signed an informed consent document, approved by the Institutional Review Board at the University of California at Los Angeles. The depressed subjects met criteria for major depressive disorder based on the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association 1994), with a minimum duration of 4 weeks and a score of ≥15 on the first 17 items of the Hamilton Depression Rating Scale (HDRS) (Hamilton 1960). Adolescents with a current or prior history of mania, hypomania, substance use disorder symptoms, schizophrenia, schizoaffective disorder, or autism were excluded from the study. Subjects also were excluded if there was a family history of bipolar disorder. All subjects were free from antidepressant drugs and other psychotropic agents for at least 4 weeks (8 weeks for fluoxetine). The controls were free from any type of psychopathology over their lifetime. The controls were not included in the study if any first-degree relative had history of a major psychiatric disorder. All participants were medically healthy and free from alcohol or illicit drug use, as determined by physical examination, full chemistry panel, thyroid function tests, electrocardiogram (ECG), and urine drug screens. Subjects with a personal history of sleep disorder(s), or those with a family history of narcolepsy, and females with suspected pregnancy were excluded from the study.

Diagnostic evaluation

The diagnosis of major depressive disorder and other psychiatric disorders was done using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL) (Kaufman et al. 1997). The K-SADS-PL is a semistructured interview designed to ascertain present and lifetime history of psychiatric illness according to DSM-IV criteria. Probes and objective criteria are provided for individual symptoms at both diagnostic and subthreshold levels. Interrater and test–retest reliability have been established, as well as convergent and discriminant validity (Kaufman et al. 1997). The K-SADS-PL was administered separately to the parent and the adolescent, and both were reinterviewed to resolve any discrepancies. Summary scores were tabulated based on the information obtained from both informants. The Children's Global Assessment Scale (CGAS) (Shaffer et al. 1983), a global psychosocial functioning measure, also was completed. The adolescent participants completed the Beck Depression Inventory (BDI) (Beck et al. 1961).

The Family History–Research Diagnostic Criteria (FH-RDC), a semistructured instrument, was used for the evaluation of psychiatric disorders in family members (Andreasen et al. 1977). The mother was interviewed regarding major psychiatric disorders over lifetime in all first-degree relatives of the adolescent subject. The FH-RDC is sensitive for obtaining information from knowledgeable relatives (Thompson et al. 1982).

Regulation of sleep–wake schedule

One week prior to the laboratory assessment, the participants were instructed to go to bed between 10:00 p.m. and 11:00 p.m. and to awake between 6:30 a.m. and 7:30 a.m. The sleep–wake schedules were monitored by daily sleep logs and wrist actigraphy.

Sleep and neuroendocrine protocol

The protocol comprised a three-night study. The participants arrived in the laboratory at 8:00 p.m.. Conventional EEG electrodes were attached by 9:00 p.m., and sleep recordings were made from 10:30 p.m. (lights out) to 7:00 a.m. Subjects were asked to void urine at 10:30 p.m. prior to switching off the lights. All urine voided between 10:30 p.m. and 7:00 a.m. (including the 7:00 a.m. sample) was collected by means of a male urinal or a urinary hat (for females).

To rule out the presence of major sleep disorders, a full sleep polysomnography was performed on the first night, including respiratory, oximetry, and leg movement measurements. The International 10-20 System was used for EEG electrode placement, electromyogram (EMG), electrooculogram (EOG), and ECG. Bilateral EEG recordings were obtained from left (C3) and right (C4) central leads, referenced to the opposite mastoid, A2 and A1, as well as to a linked reference (A1+A2). Bilateral EOG recordings were obtained referenced A1 + A2 along with a submental EMG recording.

Scoring of sleep records and cortisol assays

Sleep records were coded and scored according to standard criteria (Rechtschaffen and Kales 1968). The scorer was blind to the diagnostic status of the participants. REM latency was calculated using both lenient and strict definitions. For the lenient criterion, REM latency was defined as the time between sleep onset (the first minute of any stage of sleep) and the first 30 seconds of REM sleep. The strict criterion was defined as the time between sleep onset (first minute of stage 2 or deeper sleep, followed by at least 9 minutes of stage 2 or deeper sleep, interrupted by no more than 1 minute of waking or stage 1) and the first REM period ≥3 minutes in length. Although both REM latency values were used in the analyses, only the strict definition of REM latency is reported here, with the intervening wake time subtracted. Other REM sleep measures, including REM activity and REM density, and additional sleep variables were scored according to the criteria of Kupfer (1976), as was done previously (Poland et al. 1989; Poland et al. 1997). REM activity was scored on a scale ranging from 0 to 8 units.

Nocturnal urinary free cortisol (NUFC) was assayed using the radioimmunoassay method (Poland and Rubin 1982; Rao et al. 1997). NUFC concentration was calculated from

the total urine sample. Samples from the same subject were analyzed in the same assay. Low, medium, and high cortisol pools were reanalyzed in each assay to assess intra- and interassay variability. The intra- and interassay coefficients of variation for the assays were less than 10%.

Criteria for remission from depressive episode

Adolescents with depression participated in repeated EEG sleep and HPA studies during remission, following the same protocol described above. At the time of remission, the subjects had to have a rating of ≤2 on the Psychiatric Status Rating (PSR) component of the Longitudinal Interval Follow-up Evaluation (Shapiro and Keller 1979) and a HDRS score of <6 for a minimum period of 3 months prior to and following the second EEG sleep and HPA studies. Participants treated with psychotropic agents discontinued the medication for at least 3 months before the second EEG sleep and HPA studies.

Statistical analysis

For all summary variables, data were examined for normality using the Shapiro–Wilk W statistic (Shapiro and Wilk 1965). Cortisol measures were log-transformed prior to analysis. Student *t*-tests were employed for group comparisons on individual EEG sleep and HPA measures. The first night was considered as an adaptation night, and the mean values derived from night 2 and night 3 data were used. Paired *t*-tests were used for comparisons between the two clinical states. Correlation procedures were used for examining relationships between measures. Alpha was set at 0.05.

Results

Demographic and clinical characteristics of the adolescent samples

Demographic and clinical features of the two groups of adolescents at the time of recruitment are outlined in Table 1. The groups did not differ significantly with respect to age, gender, or ethnicity. As expected, the depressed group scored significantly higher on depressive symptoms and worse on psychosocial function measures than the controls.

The majority of depressed youth (14/16) were in their first episode of depression, and 6/16 (37.5%) patients received treatment with a psychotropic agent. The mean length of treatment in this group of patients was 13.6 weeks (standard deviation [SD] = 10.9, range 2–40 weeks). The mean length of the depressive episode was 27.9 weeks (SD = 18.3, range 9–72 weeks). Five subjects (31.3%) met criteria for anxiety disorder, 3 (18.8%) met criteria for disruptive disorder, and 5 (31.3%) had suicidal ideation.

EEG Sleep and HPA changes associated with depression in adolescents

Mean values for the major EEG sleep and HPA variables in controls and in actively ill depressed subjects are shown in Table 2. Compared with the controls, depressed adolescents had significantly reduced sleep efficiency, shorter REM latency, increased REM activity, higher REM density, and elevated NUFC excretion.

Effect of clinical state on EEG sleep and HPA measures in depressed adolescents

Mean values for EEG sleep and HPA measures during the depressive episode, and during remission, are outlined in Table 2. Length of the depressive episode or recurrent episode did not significantly affect any of the sleep or cortisol measures. Treatment with antidepressant drugs also did not influence sleep or cortisol measures. With the exception of sleep efficiency and REM episodes, sleep and HPA values during the depressive episode and remission correlated significantly. None of the EEG sleep variables changed significantly from episode to remission. NUFC excretion reduced significantly during remission. To better illustrate the effect of clinical state on EEG sleep and HPA measures, REM latency and NUFC values for individual subjects are depicted in Fig. 1. After controlling for the effects of age and gender, shorter REM latency values were associated with higher NUFC concentration levels during the depressive episode ($r_{12} = -0.57$, $p \leq 0.05$), but not during remission ($r_{12} = -0.14$, not significant [NS]).

Discussion

These results suggest that there are developmental continuities between adolescent and adult depression with respect to EEG sleep and HPA changes (specifically, sleep continuity disturbances, REM sleep changes, and elevated nocturnal cortisol secretion). Although data from other adolescent studies are highly variable, some of these studies also reported sleep continuity disturbances (Goetz et al. 1987; Goetz et al. 1991; Kutcher et al. 1992; Emslie et al. 1994; Dahl et al. 1996; McCracken et al. 1997; Armitage et al. 2000), short-

Table 1. Demographic and Clinical Characteristics (Mean ± SD) of the Sample at Recruitment

	Controls (n = *16*)	*Depressed* (n = *16*)	t	p
Age (years)	15.8 ± 1.9	15.6 ± 1.4	0.43	NS
Gender (male/female)	7/9	6/10	0.02	NS
Ethnicity (AA/AS/CC/HS)	2/4/7/3	3/4/5/4	0.68	NS
BDI score	1.9 ± 2.5	26.9 ± 7.9	12.05	0.0001
HDRS score	0.8 ± 1.4	22.6 ± 6.0	14.23	0.0001
CGAS score	84.3 ± 8.6	49.6 ± 5.2	13.79	0.0001

SD, standard deviation; NS, not significant; AA, African American; AS, Asian; CC, Caucasian; HS, Hispanic; BDI, Beck Depression Inventory; HDRS, Hamilton Depression Rating Scale; CGAS, Children's Global Assessment Scale.

Table 2. Selected EEG Sleep and Cortisol Variables (Mean ± SD) in Controls and Depressed Adolescents (during MDE and Remission)

	Control subjects (n = 16)	*Depressed (MDE) (n = 16)*	*Depressed (remission) (n = 16)*	*Controls versus MDE*	*MDE versus remission*
Sleep architecture					
Stage 1 sleep (%)	6.2 ± 1.7	6.0 ± 2.1	6.2 ± 2.5	0.19	0.50
Stage 2 sleep (%)	50.6 ± 6.0	50.3 ± 5.2	51.2 ± 4.5	0.17	0.85
Stage 3 sleep (%)	8.0 ± 2.6	8.4 ± 4.0	9.0 ± 2.7	0.31	0.86
Stage 4 sleep (%)	15.5 ± 3.8	14.7 ± 4.0	13.5 ± 3.9	0.57	1.49
REM sleep (%)	19.6 ± 2.8	20.6 ± 2.5	20.2 ± 3.5	1.03	0.42
Sleep continuity					
Sleep latency (minutes)[a]	16.0 ± 7.2	25.8 ± 20.5	21.5 ± 11.0	1.24	0.36
Total sleep time (minutes)	464.1 ± 28.9	464.5 ± 28.4	469.2 ± 22.4	0.04	1.40
Sleep efficiency (%)	93.5 ± 3.2	90.9 ± 3.1	92.6 ± 2.3	2.38*	2.07
Awake time (minutes)	9.3 ± 5.5	11.3 ± 5.2	10.0 ± 5.5	1.08	0.99
REM measures					
REM latency (minutes)	109.1 ± 39.0	84.8 ± 26.6	88.4 ± 25.3	2.06*	1.76
REM activity (units)	115.7 ± 30.5	148.2 ± 38.5	145.8 ± 39.0	2.65*	0.61
REM density (units/minute)	1.1 ± 0.3	1.6 ± 0.4	1.7 ± 0.4	3.99***	1.44
REM duration (minutes)	90.2 ± 14.8	96.2 ± 15.0	96.0 ± 17.9	1.90	0.71
Number of REM episodes	3.8 ± 0.4	4.0 ± 0.5	3.8 ± 0.5	1.46	1.38
Cortisol variables					
NUFC concentration (ng/mL)[a]	14.7 ± 7.7	25.7 ± 13.2	15.1 ± 6.9	2.75**	5.97***

[a]Analyses were performed on the logarithm.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.0001$.
MDE, major depressive episode; REM, rapid eye movement; NUFC, nocturnal urinary free cortisol.

ened REM latency (Lahmeyer et al. 1983; Dahl et al. 1990; Goetz et al. 1991; Kutcher et al. 1992; Emslie et al. 1994; Dahl et al. 1996), increased phasic REM sleep (Lahmeyer et al. 1983; Dahl et al. 1990; Goetz et al. 1991; Emslie et al. 1994; McCracken et al. 1997), and elevated nocturnal cortisol secretion (Dahl et al. 1991; Kutcher et al. 1991; Goodyer et al. 1996). Despite these similarities, developmental differences also are evident. For instance, none of the studies, including this one, reported a slow-wave sleep deficit in depressed youth, with the exception of one study that used microarchitectural analysis (Armitage et al. 2001).

The results of the present study, together with a previous pilot investigation in adolescents with depression (Rao et al. 1997), provide further evidence for the relative stability of EEG sleep measures observed in adult depressed patients during remission (Rush et al. 1986; Kupfer et al. 1988; Steiger et al. 1989; Steiger et al. 1991; Buysse et al. 1992; Giles et al. 1993; Kupfer et al. 1993; Lee et al. 1993; Thase et al. 1994; Jindal et al. 2002). It is not clear whether the EEG sleep variables will continue to remain stable with subsequent depressive episodes or more severe changes occur with progression of the illness. Some studies with adult depressed patients revealed more abnormal EEG sleep changes in cases with multiple episodes (Thase et al. 1995; Jindal et al. 2002), whereas other investigations did not find significant differences between patients with sin-

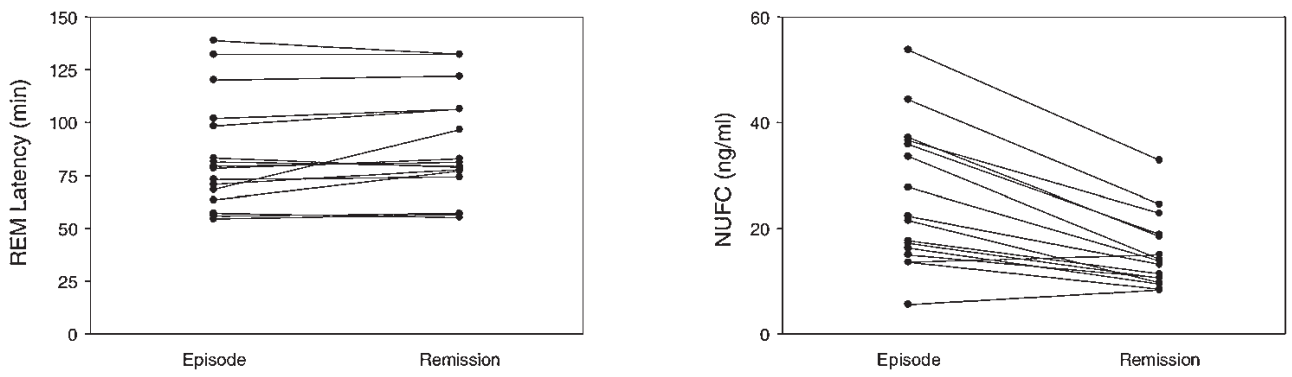

FIG. 1. REM latency nocturnal urinary free cortisol (NUFC) values during the major depressive episode and in remission.

gle and multiple episodes (Giles et al. 1989; Poland et al. 1997). Longitudinal studies of patients with early stage of illness are necessary to confirm the evolution of such changes prospectively.

HPA activity, as reflected by NUFC concentration, was higher during the depressive episode than during remission. In contrast to the state-independent EEG sleep profile observed in depression, elevated HPA activity appears to be more state-dependent (Carroll et al. 1976; Holsboer et al. 1982; Greden et al. 1983; Gerken et al. 1985; Steiger et al. 1989; Steiger et al. 1991; Rao et al. 1997). Increased HPA activity occurs in approximately 40% of depressed patients, with normalization occurring during remission. Nonnormalization of the HPA activity might be associated with an early relapse of depressive episode (Targum 1983; Holsboer et al. 1987; Charles et al. 1989; Cosgriff et al. 1990). Congruent with these reports, all of the participants in the current study continued to remain in remission for at least 3 months following participation in the sleep and neuroendocrine protocol in the remitted state.

The association between reduced REM latency and elevated cortisol secretion in major depressive disorder was reported by some other studies (Rush et al. 1982; Asnis et al. 1983; Annseau et al. 1984; Feinberg and Carroll 1984; Mendlewicz et al. 1984; Kerkhofs et al. 1986; Giles et al. 1987; Shipley et al. 1989; Poland et al. 1992; Rao et al. 1996), suggesting that dysregulation of mood, sleep, and HPA axis may be linked, at least in part, by common neuronal systems. However, the strength of association between REM latency and cortisol values in depressed adolescents was diminished during remission, as was noted in a study of adult depressed patients (Rao et al. 2004). It is possible that pharmacological or psychosocial interventions might target the regulatory mechanisms of these two physiological systems to different degrees, thus weakening their link at least temporarily. Longitudinal assessment of these measures at baseline and during the course of treatment will be helpful in determining the progression, or lack, of changes in response to treatment (Schüle 2007).

These results should be interpreted in the context of methodological limitations, The sample was modest in size. In addition, stringent criteria were established for EEG sleep and HPA studies both at baseline and during remission (specifically medication-free period). Therefore, the findings will not be generalized to patients with severe depressive symptoms and/or active suicidal behavior requiring hospitalization or continued treatment with antidepressant drugs.

Conclusion

Combining the studies of adolescent and adult patients with depression, the findings that sleep measures are independent of clinical state, whereas HPA abnormalities are state dependent, suggest that EEG sleep and HPA measures make differential contributions to our understanding of the pathophysiology and prognosis of mood disorders.

Disclosures

Drs. Rao and Poland have no financial ties or conflicts of interest to report.

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