Temporal Coherence in Ultradian Sleep EEG Rhythms in a Never-Depressed, High-Risk Cohort of Female Adolescents

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Background: *Previous work has indicated that low temporal coherence of ultradian sleep electroencephalographic rhythms is characteristic of depressed patients and of depressed women, in particular. It may also be evident in one quarter of those at high risk, based on a family history of depression.*

Methods: *The present study evaluated temporal coherence of sleep electroencephalographic rhythms in 41 adolescent girls with a maternal history of depression (high risk) and 40 healthy controls (low risk). The entire sample was followed clinically every 6 months for 2 years.*

Results: *Temporal coherence was significantly lower among the high-risk girls than in controls. Regression analyses predicted group from coherence values and correctly classified 70% of the high-risk group with a false-positive rate of 5% among controls. Moreover, 54% of the high-risk girls were identified with extreme low coherence. On clinical follow up, 14 girls showed depressive symptoms, 9 in the high-risk group (22.5%) and 5 controls (12.2%). Six met DSM-IV criteria for first-episode major depressive disorder, five high-risk and one control. Most importantly, 41% of those identified as having the most abnormal coherence values either showed symptoms of depression or met diagnostic criteria upon follow up.*

Conclusions: *Low temporal coherence is evident in adolescent girls at high risk for depression. The more abnormal the coherence, the greater the risk of a first episode of major depressive disorder within 2 years of sleep study, approximately 10 times greater than in controls.* Biol Psychiatry 2002;51:446–456 © *2002 Society of Biological Psychiatry*

Key Words: Adolescents, depression, risk factors, sleep, EEG coherence

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Introduction

Major depressive disorder (MDD) is recognized as a serious health problem throughout the world and as a leading cause of morbidity. As a leading cause of disability, depression also carries an economic cost to society (Murray and Lopez 1996). This is especially true for women, since there is a twofold greater prevalence of MDD in women than in men (Heller 1993; Kessler et al 1993). Female adolescents of depressed mothers may represent the group at greatest risk. Meta-analytic findings have also indicated that offspring of parents with MDD are four times more likely to develop an affective disorder than offspring with non-ill parents (Lavoie and Hodgins 1994; Speier et al 1995).

Although depression does not "breed true," and there will be some offspring who do not develop depression, the challenge is being able to identify, properly treat, and ultimately prevent the onset of this disease. As depression is recognized as a disorder that may begin at a young age, even in childhood (Fleming and Offord 1990), it is necessary to study and identify those groups at risk when they are young (adolescents or children), before they have become depressed. If a trait marker for MDD is discovered, the high-risk group could be further distilled such that preventive strategies for those at extreme risk could be initiated.

There is compelling evidence that sleep electroencephalographic (EEG) variables may represent a biological marker for depression. Sleep abnormalities first became associated with depression in 1976 when Kupfer reported the frequent occurrence of shortened latency to the first rapid eye movement (REM) sleep period in depressed patients (Kupfer 1976). Whereas REM latency was approximately 90 minutes in healthy adults, depressed patients showed significantly shorter mean REM latencies ($<$ 65 minutes). Although shortened REM latency has been consistently found in adults with MDD (Benca et al 1992; Kupfer and Reynolds 1992; Armitage 1995), there is an inconsistency in the literature concerning the sleep

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changes in children and adolescents with MDD (Birmaher et al 1996). Of four studies done in children (Dahl et al 1991; Emslie et al 1990; Puig-Antich et al 1982; Young et al 1982), only one, Emslie et al, showed shortened REM latency in inpatients. Of 11 studies in adolescents (Appelboom-Fondu et al 1988; Dahl et al 1990, 1996; Emslie et al 1994; Goetz et al 1987; Kahn and Todd 1990; Kutcher et al 1992; Lahmeyer et al 1983; McCracken et al 1997; Rao et al 1996, a reanalysis of Dahl et al 1990; Riemann et al 1995; Williamson et al 1995, a reanalysis of Goetz et al 1987), 5 showed reduced REM latency. Of these studies, the only one that examined premorbid REM latency in adolescent MDD was Rao et al. They reported that in a 7-year follow-up assessment of their control group, the adolescents who developed MDD had shown a trend for reduced REM latency compared with those who did not develop MDD. Studies of all age groups are difficult to interpret due to differences in sample populations and methodology, but they do suggest that shortened REM latency may be a marker for the first onset of MDD.

Recent work has indicated that composite or sleep profiles provide a stronger differentiation between subjects and controls than REM latency or other univariate approaches (Nofzinger et al 1999; Reynolds and Kupfer 1987). Moreover, those studies which include more precise computerized quantification of sleep EEG have shown even stronger between group differences. Such sleep microarchitectural techniques have shown increased incidence and/or amplitude of alpha and beta fast-frequency EEG activity and lower incidence and/or amplitude of slow-frequency delta activity during sleep in depressed adults (Borbély et al 1984; Armitage et al 1992; Armitage 1995; Armitage and Hoffmann 1997; Kupfer et al 1990, 1991; Reynolds et al 1990). Adults with depression also show evidence of sleep EEG dysregulation with a breakdown in the degree of synchronization between ultradian (90 min) sleep EEG rhythms (i.e., low temporal coherence) (Armitage 1995; Armitage et al 1992, 1993, 1999). Low temporal coherence is more strongly a characteristic of depressed women, whereas depressed men are more likely to show reduced slow-wave or delta activity, particularly in the first Non REM (NREM) sleep period (Armitage and Hoffman 1997, 2001; Armitage et al 1999, 2000a). Such findings provide preliminary evidence that the nature of the sleep EEG abnormality in depression is gender dependent. Low temporal coherence also appears to be characteristic of early onset depression, particularly among adolescents 13 to 16 years of age (Armitage et al 2000b). Adolescent girls show the lowest temporal coherence, providing additional support for a divergent pathophysiology of depression among males and females. Most importantly, low temporal coherence may be evident in those at risk for depression, based on family history (Fulton et al 2000). Of those with a positive family history of depression, but who had never experienced an episode of depression themselves, 23% had significantly lower coherence than healthy individuals with no personal or family history. These preliminary findings suggest that low temporal coherence may be a biological predictor of vulnerability to depression.

As part of a prospective longitudinal study examining potential pathoetiological factors associated with the onset of MDD in a high risk population, sleep macroarchitecture (including REM latency) and microarchitecture (temporal coherence) were examined. This report provides a detailed comparison of the differences in sleep variables between a high-risk cohort of adolescent females (a maternal history of MDD), as compared with a control group (no maternal history of depression). We hypothesized that REM latency would be significantly shorter and temporal coherence lower in the high-risk cohort when compared with controls.

Methods and Materials

Sample

There were 102 mother-daughter pairs screened for the study, of which 83 teenaged girls (age 12–15 years) and their mothers consented to participate. Recruits were identified either when their mothers responded to an advertisement placed in local newspapers or via contact through a local Psychiatry Outpatient Clinic. After an explanation of the purpose and details of the study, written informed consent (assent for minors) was obtained from all study participants (mothers and daughters). The protocol and consent forms were reviewed and approved by the Research Ethics Committee of the Queen Elizabeth II Health Science Centre in Halifax, Nova Scotia, Canada. Forty-three participants were identified as being in the high-risk group because their mother had a lifetime diagnosis of MDD. An age-matched group of 40 female teenagers, who had no maternal history of MDD or other Axis I disorders, comprised the control group. They were either friends of the at-risk teenager or were recruited through local schools. The sample sizes reported are 41 and 40 in the high-risk and control groups, respectively, because there were incomplete sleep data for two of the high-risk females.

Interviews

At the initial interview, all mothers were assessed using the Structured Clinical Interview for Diagnosis (SCID) (Spitzer et al 1986). The daughters of mothers presenting with a reported lifetime history of MDD according to DSM-IV criteria (APA 1994) were assigned to the high-risk group. All mothers also completed the Beck Depression Inventory (BDI) (Beck et al 1961) and were administered the 17-item Hamilton Rating Scale for Depression (HamD) (Hamilton 1960). Control group mothers were negative for a present or past history of major depressive disorder, but were not necessarily free of all psychopathology.

Two research nurses with extensive training in conducting psychiatric interviews completed the initial interview procedures. Another similarly trained research nurse, blind to group assignment, conducted follow-up interviews. Diagnoses were confirmed by two psychiatrists in case conference.

At baseline, all adolescents were interviewed with the Kiddie Structured Clinical Interview-Lifetime Version (K-SADS L, version 1982) (Orvaschel et al 1982) to ensure that they did not meet lifetime criteria for any mood, psychotic, or substance abuse disorders or other Axis I or II disorders (anxiety and externalizing disorder such as conduct disorder). No girls with current or past medical illnesses including that known to be associated with mood (e.g., endocrine disorders, epilepsy) were recruited. All teens also completed the BDI and were excluded from the study if they had a baseline score of nine or above. The interview of adolescents also included the HamD and Global Assessment of Functioning (GAF). To assess current level of pubertal development, teens completed the Tanner Self-Rating Questionnaire (Tanner 1992) to provide a categorical classification rating for pubertal status. The teens were given a sleep diary to be completed at home during the five "school nights" (Sunday to Thursday) immediately before the overnight sleep studies.

Sleep Laboratory Studies

Within 4 weeks of their interviews, all teenagers spent 2 consecutive weekend nights (Friday and Saturday) in the Sleep Disorders Laboratory at the Queen Elizabeth II Health Sciences Centre. Night one (Friday) served as a laboratory adaptation and screening night. All analyses were based on night-two (Saturday) data. The polysomnographic montage consisted of left and right central EEG (C3, C4) with a common linked reference (right and left ear lobe references passed through a 10 K ohm resistor), bilateral EOG, and EMG. In addition, for the first night, respiratory effort, airflow, and leg movements were recorded to ensure that there were no primary disorders of sleep (sleep apnea or periodic limb movement disorder).

Polysomnographic data were recorded on a Melville Diagnostics "Sandman" System using either Nicolet amplifiers (high-frequency filters 30 Hz, low-frequency filter at 0.5 Hz) or Grass amplifiers (35 Hz and 0.3 Hz filter settings) with a sensitivity setting of 7 μV/mm. For night-two data, EEG was digitized online at 250 Hz through a 12-bit analog to digital converter integral to the Sandman System. Raw digitized data were stored on optical diskettes for offline period amplitude analysis (PAA). Sleep records were scored according to standard criteria (Rechtschaffen and Kales 1968) by trained research personnel who have demonstrated a greater than 90% agreement on an epoch-by-epoch basis. Although the key focus of this paper was on temporal coherence of ultradian rhythms, macroarchitecture sleep-stage variables were also included for comparative and interpretative purposes. These included: total time in bed (TIB), total sleep time (TST), sleep onset (from "lights out" to either first epoch of three consecutive epochs of stage 1 or a single epoch of any other stage), REM latency (sleep onset to REM onset), sleep efficiency (TST/TIB $\times$ 100), and the percentage of different sleep stages as a function of TST.

The signal-processing PAA algorithm used here has been described in detail elsewhere (Armitage et al 1992, 1999; Hoffmann et al 1979). Briefly, incidence and amplitude are evaluated in delta (0.5 to $<$4 Hz), theta (4 to $<$8 Hz), alpha (8 to $<$12 Hz), sigma (12–16 Hz), and beta (16 to $<$32 Hz) frequency bands. The complete algorithm includes half-wave zero-cross and a full-wave first-derivative analysis reflecting wave incidence and an amplitude analysis in all five-frequency bands. The zero-cross analysis computes the time between successive zero-voltage crossings in each second, thereby determining the underlying frequency of each wave and is preferentially sensitive to slow-frequency EEG activity. The first-derivative analysis computes the time between successive negative voltage inflections in each second, thereby determining the underlying frequency of each wave, and is preferentially sensitive to fast-frequency EEG activity. At the end of each 30-sec epoch, the percentage of first-derivative time and zero-cross time spent in each frequency band is computed. Following PAA, separate time series are constructed and averaged across 1-min epochs, in preparation for cross-spectral analysis.

Cross-spectral analysis is used to determine the periodicity and coherence of ultradian rhythms in period-analyzed sleep EEG using BMDP-IT routines (Dixon 1983). Cross-spectral analysis is part of a larger class of time series analyses developed to detect hidden cycles in a string of recurrent events (Gottman 1981). The techniques have been applied to population growth trends in wildlife, cognitive performance, moment-to-moment EEG, and a variety of physiologic measures including temperature, heart rate, and gastric motility (Klein and Armitage 1979; Dixon 1983; Armitage 1986; Armitage et al 1992). In the present study, we focused exclusively on ultradian rhythms in the 80 to 120 min range, that of the REM-NREM sleep cycle and of the basic rest-activity cycle.

Cross-spectral analysis is based on a fast-Fourier transform (FFT) that decomposes time series of complex events into multiple sine and cosine components reiteratively, until all variance in the times series is captured. A power or amplitude value (area under the curve) is derived for each sine/cosine fit, reflecting the goodness of fit and the strength of ultradian rhythms. The period at which power is maximal (i.e., accounts for the largest portion of variance) reflects the dominant rhythm (Dixon 1983; Gottmann 1981). This analysis is bivariate, determining periodicity in each of two-time series and peak periodicity between the two.

Coherence, like a squared coefficient, reflects the degree of synchrony between two time series at each detectable period. Coherence at the period of maximal cross-spectral power reflects the degree of synchrony between the two dominant rhythms (Dixon 1983; Gottmann 1981). In keeping with reported methodology and findings (Armitage 1995; Armitage et al 1993, 1999; Armitage and Hoffmann 1997), we evaluated *interhemispheric* coherence between left and right beta (BCOH), and between left and right theta (TCOH) rhythms. *Intrahemispheric* coherence was evaluated between beta and delta rhythms in the right (BDRCOH) and in the left (BDLCOH) hemispheres, and between theta and delta rhythms in the right (TDRCOH) and left (TDLCOH) hemispheres. Thus, six amplitude coherence and periodicity measures were computed for each subject.

Follow-Up Assessments

Every 6 months, for a period that will eventually extend to 5 years following baseline assessment, each adolescent in the study was and will be interviewed by a trained research nurse blind to their group status or previous assessment findings. Each interview consists of the KSADs, HamD, and the GAS. Youths also have completed the same questionnaires as completed at baseline, including the BDI, SSS, DEQ, and Pubertal Development Scale. Youths are also asked to complete a mini version of the Life Stressor and Social Resources Inventory (LISRES), which assesses whether a number of life stressors had occurred during the previous 6-month period since the time of the last assessment.

Those subjects who demonstrate psychopathology based on the KSADS at any follow-up interview are offered a clinic appointment at a relevant mental health program for further assessment and/or treatment. If youths are diagnosed with MDD, all further follow-up data are obtained through a phone interview completed at the 6-month time points.

Statistical Procedures

The primary analysis compared the high-risk and control group with respect to demographics, sleep laboratory data, and each of the assessment instruments. For the baseline scales, univariate analysis included *t* tests for the paired samples and Chi-square tests, where appropriate. Sleep EEG temporal coherence was compared in a split-plot factorial multivariate analysis of variance (MANOVA). Least-squares multiple comparisons tested individual mean differences for significant effects. Split-plot MANOVA was also computed on the sleep macroarchitectural variables following statistical procedures outlined above.

Results

At baseline, the high-risk ($n = 41$) and control group ($n = 40$) did not differ in main demographic variables or global functioning. The girls were not significantly different in age, being on average 13.56 ± 1.36 and 13.73 ± 1.06 years of age, in the high-risk and control groups.

There were no significant differences in level of functioning of the two groups as measured by the GAF with values of 86.1 in the group deemed to be at risk and 86.4 in the control group. Socioeconomic status was not measured. Ethnic/racial distribution was predominantly Caucasian, except for one subject in the high-risk group of mixed parentage (Caucasian/Hispanic), and three control subjects (one East Indian, two black). Physically, the two groups were not significantly different with average body mass index (BMI) of 21.37 ± 4.37 in the high-risk group and 21.04 ± 3.28 in the control subjects. Both groups did not express clinically significant depressive symptoms, as demonstrated by mean scores for both groups being < 5 on the BDI and < 2 on the HamD. As identified through the Tanner questionnaire, 92.7% of the girls (38/41) in the high-risk group had started menses, which is marginally different than the low risk group (80% or 32/40) (Chi-square 2.755, $p = .096$). Sleep diaries were deemed unreliable for data analysis as they had a variable completion rate with many missing data points.

Table 1. Means and Standard Deviations (in Brackets) of Age and Rating Scale Scores of Mother-Daughter Pairs by Group

MOTHERS		
	Depressed ($n = 34$)	Control ($n = 38$)
Age (years)	40.8 (5.0)	43 (4.2)
BDI Score	11.6 (12.0)	3.8 (3.7) $p = 0.02$
HamD Score	7.9 (6.8)	.9 (1.4) $p = 0.09$
DAUGHTERS		
	High Risk ($n = 41$)	Controls ($n = 40$)
Age (years)	13.54 (1.36)	13.73 (1.06)
Tanner Score	15.5 (1.5)	15.1 (2.1)
BDI Score	4.80 (3.85)	3.78 (3.99) $p = .24$
HamD Score	1.93 (2.37)	1.20 (2.0) $p = .14$

BDI, Beck Depression Inventory; HamD, Hamilton Rating Scale for Depression.

Mothers in the high-risk group were of a similar age (mean = 40.8 ± 5.0) when compared with the mothers in the control group (mean = 43.0 ± 4.2). As expected, based on their lifetime diagnosis for depression, mothers in the high-risk group, on average, scored higher in the BDI (mean = 11.6 ± 12.0) and HamD (mean = 7.9 ± 6.8) when compared with mothers in the control group BDI (mean = 3.8 ± 3.7) and HamD (mean = .9 ± 1.4) (BDI, $t = -3.6$, df = 70, $p < .001$) (HamD, $t = -6.19$, df = 703, $p < .001$). (See Table 1.) Twenty-three percent of the mothers in the high-risk group met current criteria for MDD. The mean age of onset of depression for the mothers was 24.1 ± 9.0 years. Forty-four percent of the mothers had experienced their first onset of depression before the age of 20. Twenty-six percent of the sample had experienced only one episode of depression.

Demographic information and rating-scale scores on mothers and daughters are shown in Table 1.

Sleep Macroarchitecture

The means and standard deviations for the macroarchitectural variables are shown in Table 2. There were no significant differences between the two groups on any macroarchitectural sleep variable, including REM latency.

Sleep Microarchitecture

Table 3 shows the microarchitecture analysis of the amplitude (strength) and periodicity (length) of EEG rhythms. No significant group effects were evident in the

Table 2. Means and Standard Deviations (in Brackets) of Select Sleep Macroarchitectural Variables by Group

Sleep Variable	High Risk (n = 41)	Controls (n = 40)
TST (min)	461 (29.5)	453.6 (25.3)
TIB (min)	488.5 (22.9)	482.7 (25.0)
Sleep efficiency (TST/TIB × 100)	94.4 (4.3)	94.0 (3.3)
Sleep latency (min)	14.5 (14.4)	18.7 (15.1)
REM latency (min)	101.3 (46.4)	106.9 (61.6)
% Stage 1	5.8 (3.5)	5.0 (2.5)
% Stage 2	53.3 (7.1)	56.7 (5.7)
% Stages 3 and 4	19.0 (5.7)	17.6 (6.8)
% Stage REM	21.5 (4.9)	20.4 (5.0)

REM, rapid eye movement; TIB, total time in bed; TST, total sleep time.

amplitude of ultradian rhythms for either inter- or intrahemispheric measures by MANOVA test criteria ($F_{1,77}$ = 1.6; 1.5 respectively, $p < .22$). Thus, there was no evidence of dampened or phase-shifted rhythms in the high-risk group. Although the mean period of ultradian rhythms was shorter in controls, the group effect was not significant for either inter- or intrahemispheric measures, by MANOVA test criteria ($F_{1,77}$ = 2.2; 2.7; respectively, $p < .15$). As a result, no further analyses were conducted on these data.

Temporal Coherence

Means and standard deviations of the six coherence measures are shown in Table 4. Intrahemispheric coherence showed a significant overall group effect ($F_{1,77}$ = 7.5, $p < .007$) and a group by hemisphere interaction ($F_{1,77}$ = 5.8, $p < .02$) from MANOVA. Univariate analyses confirmed significantly lower intrahemispheric coherence in the high-risk group for BDRCOH, ($F_{1,77}$ = 8.8, $p < .004$); BDLCOH ($F_{1,77}$ = 3.9, $p < .05$) and TDLCOH ($F_{1,77}$ = 6.4, $p < .01$). The three other coherence measures did not differentiate between groups ($F < 1$). See Table 4.

Sensitivity and Specificity

As an alternative way to highlight the between-group differences, we established a cut-point that maximally differentiated those at high risk from controls (.70 for each coherence measure). This analysis, equivalent to a receiver operator characteristics (ROC) analysis, determines the sensitivity and specificity of a group identification. The majority of the at-risk group fell below the .70 cut point, and the majority of the control group were well above it. Of the high-risk group, 20% (8/41) showed low coherence on *all* six measures, compared with only 2.5% of controls (1/40). With regard to the intrahemispheric measures alone, 40% to 60% of those at high risk for MDD were identified as abnormal, compared with 10% of controls. A scatter plot of the average coherence (mean of all six measures) in each participant is shown, by group, in Figure 1. Note that only two subjects in the no-risk group fell below the cut-point, as compared with the majority of those at high risk (32/41).

Stepwise multiple regression analyses were also computed, predicting group membership (high risk, controls) from BDRCOH, BDLCOH, TDRCOH—the three coherence measures—which were significantly lower in the high-risk group. The overall regression analysis was significant, as would be expected ($F_{1,77}$ = 8.8, $p < .004$).

Table 3. Means and Standard Deviations (in Parentheses) of the Average Amplitude (Strength) and Period (Length) for Inter- and Intrahemispheric Coherence Measures by Group

	High Risk	Control
Interhemispheric		
Amplitude (power)	988.0 (693.2)	1021.0 (474.9)
Period (min)	177.7 (110.7)	140.3 (86.3)
Intrahemispheric		
Amplitude (power)	1522.5 (974.9)	1843.7 (674.1)
Period (min)	167.5 (93.9)	137.9 (61.9)

Table 4. Means and Standard Deviations (in Brackets) of All Inter- and Intrahemispheric Temporal Coherence Measures by Group

Coherence Means	High Risk (n = 41)	Control (n = 40)
Interhemispheric		
BCOH	.92 (.12)	.94 (.10)
TCOH	.88 (.13)	.85 (.13)
Intrahemispheric		
BDRCOH*	.78 (.16)	.85 (.12)
BDLCOH*	.75 (.20)	.86 (.10)
TDRCOH	.71 (.16)	.75 (.22)
TDLCOH*	.62 (.23)	.82 (.10)

BCOH, beta coherence; BDLCOH, beta and delta left coherence; BDRCOH, beta and delta right coherence; TCOH, theta coherence; TDLCOH, theta and delta left coherence; TDRCOH, theta and delta right coherence.
*$p < .05$.

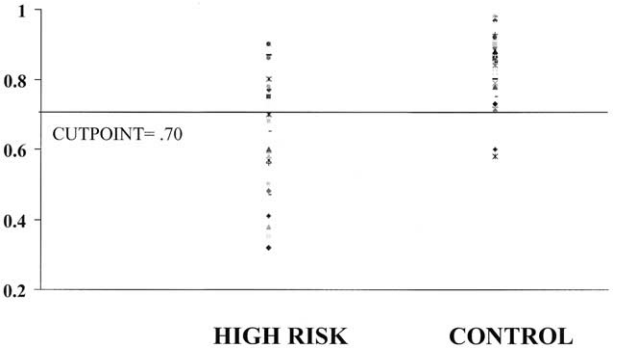

Figure 1. Scatterplot of right hemisphere coherence values (averaged across measures) for each subject in each group.

Only two subjects in the control group had extreme predicted values that identified them as high risk (false positive rate 5%). Twelve subjects in the high-risk group (29%) were incorrectly classified as within normal values (miss rate). The hit rate, therefore, was 71% correct identification of the at-risk group. Further, the regression analysis identified extreme values (i.e., maximally distinct from the no-risk group) in 22/41 (54%) girls at high risk.

To further illustrate the between-group differences in the relationship between beta, theta, and delta rhythms, a representative subject from each group is presented in Figure 2. Note that the phase relationship between beta and delta activity is more fixed and regular in the control. The high-risk girl, however, shows less consistent change in delta through the night with elevated beta activity. The phase relationship between beta and delta is more erratic, sometimes in phase (see epoch 500), sometimes out of phase (epochs 250–300), and occasionally unrelated (epochs 650–675). Theta rhythms in this girl at risk are dampened and less regular. Thus, it is not surprising that average coherence was .58 in the girl at risk and .90 in the control subject.

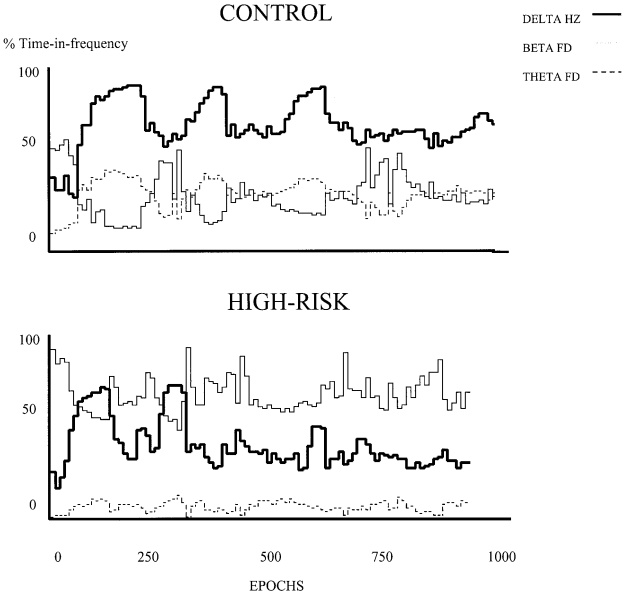

Figure 2. All-night delta, beta, and theta incidence from the left central recording site (C4) in representative control (top) and high-risk (bottom) subjects. Epoch duration = 30 sec.

Sample Follow Up

There is now a significant burden of illness in the high-risk adolescent females. Fourteen adolescents either have been diagnosed with a psychiatric illness or have shown depressive symptoms that do not meet DSM-IV criteria in severity and/or duration. Nine of these girls were in the high-risk group (22%). Only five of these girls were in the no-risk group (12.5%). Six subjects were diagnosed with first episode unipolar MDD, five in the group at risk (12.2%) and one in the no-risk group (2.5%). Data from one of those high-risk girls is shown in Figure 2 above. Six additional girls showed depressive symptoms at follow-up but did not meet criteria, four of whom were in the high-risk group. Of the two other girls not at risk, one was diagnosed with attention deficit disorder (ADD) and the other as oppositional defiant disorder plus dysthymia.

Perhaps most striking, almost all of the girls who showed symptoms at follow up had extreme values from the regression analysis. For example, of the no-risk girls with symptoms at follow up, two had been classified as high risk by regression (i.e., false positives) and had coherence values that were well below the group mean. Further, all nine of the high-risk girls with symptoms or an MDD diagnosis at follow up were correctly classified as high risk by regression analysis (hits). More importantly, however, these nine girls were all contained in the 22 cases identified with the most extreme values in the at-risk group from the regression analysis. Thus, 41% of those identified as having the most abnormal coherence values either showed symptoms or met diagnostic criteria within 2 years of the sleep study. The average of all coherence measures was 0.67 ± .22 (range .19–.82) in the nine girls who showed depressive symptoms or had a first episode of MDD at follow-up. This value is significantly lower than the control group (.88 ± .11, $p < .01$) and substantially lower than the mean of the entire at-risk group (.75 ± .16).

Discussion

The present study demonstrated significantly lower temporal coherence in a group of 41 adolescent girls at risk for depression, compared with 40 girls at no risk. Of the six coherence measures included, temporal coherence between beta and delta rhythms in both hemispheres and between theta and delta in the left hemisphere maximally discriminated between groups. Multiple regression analyses accurately predicted group membership, with a hit rate of 71% in the high-risk group and a false positive rate of 5%. At clinical follow-up, 11 girls had developed depressed symptoms, including the 2 false positives. Of those 22 girls at risk for depression with extreme low coherence, 9 in total (41%) had either depressive symptoms or a diagnosis of MDD. Focusing on only those who met diagnostic criteria, 1/40 girls at no risk (2.5%) versus 5/41 at-risk girls (12%) met criteria for MDD within 2 years. The incidence of MDD was four to five times greater in the girls at risk for MDD, in line with previous reports (Lavoie and Hodgins 1994), but was 10 times greater in those with lowest coherence (5/22). Thus, low

coherence was a better predictor of subsequent onset of depression than maternal family history alone, and suggests that low coherence confers a high risk for depression, even in the absence of family history. It is, however, entirely possible that maternal history and temporal coherence covary. The mothers of those girls who developed depressive symptoms may very well have extreme low values of coherence themselves. Unfortunately, the mothers did not participate in sleep study and, thus, this suggestion awaits confirmation.

Somewhat surprising, the mean values of temporal coherence in the at-risk sample reported in this study were comparable to recent findings in symptomatic depressed adults (Armitage et al 1999) and adolescents (Armitage et al 2000b) with MDD, most of whom had more than one episode of depression. One might have expected higher coherence in those at risk; however, it has been suggested previously that temporal coherence is a trait like feature of depression, evident even in those in clinical remission (Armitage et al 1993). The change in coherence with clinical state may be more subtle or may be evident within an individual, but not in group data. Understanding the factors that influence temporal coherence and the mechanisms that underlie these measures will shed light on the relationship between coherence and depression.

Low temporal coherence has been interpreted to reflect a breakdown in the organization and synchronization of sleep EEG rhythms in those with depression and, more globally, the basic rest activity cycle (Armitage et al 1999, 2000b). Placed in the context of previous work on depression, there are a number of neurophysiological factors that could produce or contribute to both low temporal coherence and risk for depression. Since the increased risk for depression in females occurs during the reproductive years, gender steroids may well contribute to risk (Halbreich and Lumley 1993; Parry 2000). Moreover, estrogen and progesterone alter neuronal firing rates (Majewska 1992), the sleep cycle, and EEG frequencies (Driver et al 1996; Manber and Armitage, 1999). Low temporal coherence is most evident in depressed females after puberty (Armitage et al 2000b) and in adulthood before menopause (Armitage et al 1999; Armitage and Hoffmann 1997, 2001). It is quite possible that gender steroids alter temporal coherence (Armitage et al 1999). For example, estrogen would be expected to preferentially increase fast frequency activity during sleep and, thus, in turn would increase arousal and activation and could alter the phase relationship between beta, delta, and theta activity (Driver et al 1996; Manber and Armitage 1999). Because coherence, but not periodicity or amplitude, was impaired in those with MDD and those at risk, it seems plausible that it is an inconsistent, erratic phase relationship between EEG rhythms that produces low coherence.

In addition, both very fast (>40 Hz) beta and very slow delta (<1 Hz) activity play a role in synchronizing neural discharge and its propagation across the scalp (Amzica and Steriade 1995a, b; 1998a, b; Steriade 1993; Steriade et al 1993). It is conceivable that a disruption in neural synchronization would also contribute to erratic phase relationships among fast- and slow-frequency EEG activity and ultimately would lower temporal coherence.

Dysregulation of numerous neurotransmitter systems including acetylcholine, GABA, and serotonin have been thought to underlie MDD, although it continues to be debated whether it is sub- or suprathreshold or sensitivity (Janowsky et al 1996). Others have suggested that it is an imbalance in cholinergic/aminergic neurotransmission that underlies depression (McCarley 1982). Such an imbalance alters the REM/NREM sleep cycle. If those with MDD and those at risk have impaired neurotransmitter regulation, they may also be differentially sensitive to changes in gonadal hormones and ultimately show extreme low coherence even early in adolescence.

Alternatively, there is ample evidence of functional deficits in the right hemisphere in depression (Goldstein et al 1977; Liotti et al 1991; Emslie et al 1998). These findings resonate with our suggestion that the regulation of EEG activity within and between the two hemispheres is impaired in depression. The present study indicates that low temporal coherence and its potential underpinnings are also evident in adolescent girls at risk for depression who have no past or current depressive symptomology. Thus, low temporal coherence appears to be an antecedent of the illness, evident *before* symptoms of depression are revealed. These findings also support a recent paper identifying low coherence in 20% to 30% of those at risk for mood disorders based on either maternal or paternal history (Fulton et al 2000). The present study, however, offers a number of design improvements over earlier reports, by excluding a maternal history of bipolar illness and restricting the sample to adolescent girls. We speculate that those at greatest biological risk will show an earlier age of onset and that those with a first episode later in adulthood will be less likely to show premorbid extreme low values of temporal coherence. Certainly, if our hypothesis is correct, those additional 11/22 girls with extreme low coherence values in the at-risk group should be more likely to experience an episode of depression in the next few years. Such speculation, however, awaits confirmation as we follow this sample.

Previous work, most notably by Giles and colleagues, has indicated that short REM latency may be a marker for depression, present in the unaffected but at-risk siblings and children of depressed probands (Giles et al 1998). Low temporal coherence also appears to be such a marker, although the two groups of adolescent girls in the present

study did not differ on REM latency; however, the sleep macroarchitectural characteristics reported here, and including REM latency, are well in line with other studies (McCracken et al 1997; Emslie et al 2001; Goetz et al 1987; Khan and Todd 1990; Armitage et al 2000b). Either temporal coherence reflects a different biological risk factor or process than REM latency and perhaps identified a different group of individuals at risk, or the temporal coherence measures are more sensitive. A number of previous studies in both adults and children with MDD have indicated very low correlations between temporal coherence and REM latency. Additionally, symptomatic patients differ from controls on coherence measures even in the absence of between-group differences on REM latency (Armitage and Hoffmann 1997, 2001; Armitage et al 1999, 2000b). Regardless, both types of measures have shown clinical utility in characterizing those with depression and those at risk. As suggested by Rao et al (1996), REM latency may be most useful in predicting clinical course. Continuing follow-up of the present sample may well identify a relationship between REM latency and clinical course.

The findings from the present study, however, need to be interpreted with some caution due to a number of limitations. Sleep diaries were completed for five nights (Sunday through Thursday), but sleep at home was not monitored. Sleep studies occurred after five school nights when more regular bed times and wake times might be expected. "Lights out" and "lights on" times in the laboratory were chosen to approximate, within 1 hour, subjects' reported bed times and wake times at home during school nights/days. Nevertheless, the accuracy of the diary data cannot be verified. It would have been more rigorous to include actigraphy data to verify sleep habits at home (Sadeh et al 1994). Although it is reasonable to include only females because of their increased risk of depression, much explanatory information is lost in the process. We also cannot determine whether low temporal coherence is due to the environment that results from growing up with a depressed parent, genetic factors, or the interaction between the two. The stressors at home or at school were not recorded or examined. Furthermore, since this study included only those girls with a maternal history of depression, we cannot address whether our findings are also applicable to girls with a depressed father or if the results generalize to adolescent boys. The argument has been made previously that low temporal coherence is more characteristic of depression in women during the reproductive years (Armitage and Hoffmann 1997, 2001; Armitage et al 1999). Coupled with the findings here, boys with depressed mothers might be expected to show higher coherence and/or less extreme values than their female counterparts. To explore these relationships further, it would be necessary to study girls with paternal history of depression, boys with depressed fathers, and those with depressed mothers.

There is additional evidence to suggest that having depression in both parents confers a greater risk for offspring than having only one parent with the illness (Merikangas et al 1988). To our knowledge, epidemiologic data that address potential gender linkage have yet to be collected. Although recent work by Kendler et al (2001) strongly suggest that depression is more heritable in females, we did not inquire into the full genetic loading for affective disorder in all first- and second-degree relatives in the present study.

In addition, we are unable to comment definitively on the correlation between genetic load and coherence or on pubertal stage and coherence. Also, it is possible that low coherence in the high-risk group may emerge at a specific pubertal stage (or worsen developmentally). According to the Tanner Self-Rating Scale, which had been shown to be an accurate assessment of pubertal stage as compared with a physical examination (Morris and Udry 1980), most of our subjects were in Tanner stages 4 to 5. Of those at Tanner stage 5, we failed to record menstrual phase at the time of the sleep study, thus no hypothesis can be advanced with respect to the menstrual phase and coherence values.

This study asks the question, "Why does having a depressed mother place a girl at risk for developing depression?" In an attempt to answer this question, Goodman and Gotlib (1999) postulate four potential mechanisms, suggesting that having a mother with depression may: 1) confer a genetic predisposition; 2) confer dysfunctional neuroregulatory mechanisms that interfere with emotional regulation processes and consequently increase vulnerability to depression; 3) expose children to negative or maladaptive cognitions, behaviors, and affect which places them at high risk; 4) within the context of the lives of children with depressed mothers, particularly the stressors, confers an increased risk. We postulate that temporal coherence (or any potential biological marker) does not increase risk due exclusively to one mechanism, rather it is an amalgam of genetic (mechanism #1), neuroregulatory dysfunction (mechanism #2), and psychosocial stressors (mechanism #4).

Why are these findings important? The reality of limited healthcare resources dictates that it is appropriate to employ strategic prophylactic measures for groups at risk. The results of this study suggest that female adolescents with a maternal history of affective illness might benefit from specific investigative measures. If it is discerned that in addition to their family history they have low temporal coherence on their sleep investigations, careful monitoring and/or early intervention can be advocated. There is ample

evidence of the benefit of biological measures in early detection of disease throughout medicine. To give just one example, relatives of patients with familial gastrointestinal polyposis are regularly examined for the potential development of carcinoma. Patients with a family history of depression and low temporal coherence may also need to be screened and regularly monitored.

The development of effective intervention and early treatment strategies directed by this research remains one of our long-range goals. Such goals depend on longer-term, prospective, longitudinal follow-up data, and a complete evaluation of the clinical correlates of low temporal coherence in those already ill with depression.

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