Which Depressive Symptoms Are Related to Which Sleep Electroencephalographic Variables?

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Sleep complaints and electroencephalographic (EEG) sleep abnormalities are associated with risk for new onset depression, illness severity, treatment outcome, and vulnerability for recurrence of depression. The aim of this study was to evaluate the strength of association between EEG sleep measures and depression symptoms, and to identify the variables that account for the majority of the association. Depression ratings from the Hamilton Rating Scale for Depression and the Beck Depression Inventory and polysomnographic measures were examined in 361 adult outpatients with major depressive disorder. Canonical correlation and serial multiple regression analyses were used to determine the associations between depressive symptoms and sleep measures. Canonical correlation showed a unidimensional relationship between depressive symptoms and sleep measures ($R = .55$, $p < .05$). Fifteen depression items and nine sleep measures accounted for 95% of the correlation. Depression variables encompassed a core set of mood, neurovegetative, and cognitive symptoms. Sleep variables were primarily related to delta EEG activity, and this may be reflective of impaired sleep "drive" or heightened arousal during sleep.

Key Words: Sleep, EEG sleep, depression, symptoms

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Introduction

Sleep and depression have complex interactions and associations. The delineation of which aspects of disturbed sleep are related to which depressive symptoms may lead to a clearer formulation of how these phenomena are interrelated.

Clinical formulations of depression have always included the complaint of disturbed sleep as a defining characteristic. Between 50 and 95% of depressed patients complain of severely disturbed sleep (Kupfer et al 1969; Ponnudurai et al 1981; Casper et al 1985; Hetta et al 1985), and a slightly smaller proportion of patients exhibit polysomnographic abnormalities (Benca et al 1992). Insomnia complaints that accompany depression include difficulties initiating and maintaining sleep as well as early morning awakenings. The constellation of electroencephalographic (EEG) sleep abnormalities in depression include increased sleep latency, REM sleep, and REM activity, and decreased sleep maintenance, slow-wave sleep, and REM latency (Benca et al 1992). In community samples and in first-degree relatives of affected probands, the complaint of insomnia (Ford and Kamerow 1989; Dryman and Eaton 1991) and sleep EEG abnormalities (Giles et al

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1988a, 1989b) have been associated with increased risk for the development of depression and appear to be related to the onset and expression of the illness.

Both sleep and depression are multidimensional phenomena. Sleep can be described in terms of its temporal, continuity, and architectural facets; depression can be described in terms of its affective, cognitive, and neurovegetative symptoms. The inherent multidimensionality of the two phenomena make it difficult to determine how the specific aspects of these two complex entities are related. One approach to addressing such complexity has been to conceive of depression in terms of overall severity and to evaluate the association of specific sleep variables with this factor. The EEG sleep variables that have been most intensively studied are REM latency, REM density, and slow-wave sleep time. Some studies using cross-sectional designs found that REM latency was correlated with severity of depression (for reviews see Thase and Kupfer 1987; Benca 1994). Longitudinal studies, however, have found that REM latency tends to be stable within individuals across time (Rush et al 1985a; Giles et al 1989a), and this runs counter to the argument of a direct REM latency–depression severity association. Cross-sectional and longitudinal studies have found that REM density tends to be correlated with severity of depression and that this measure varies with clinical state (Cartwright 1983; Zarcone and Benson 1983; Kerkhofs et al 1985; Buysse et al 1992; Nofzinger et al 1994). Finally, there is limited evidence that reduced slow-wave sleep is moderately correlated with illness severity (Simons and Thase 1992), but there is evidence from behavioral genetic studies that slow-wave sleep time is heritable and thus may have trait properties as well (Linkowski et al 1989).

A second strategy has been to conceive of depression in terms of symptom clusters and to evaluate the association of these clusters with selected sleep variables. For example, reduced REM latency is significantly correlated with the endogenous symptoms of terminal insomnia, appetite loss, distinct quality of mood, and unreactive mood (Giles et al 1986). Similarly, increased REM activity is correlated with a factor representing insomnia, gastrointestinal complaints, dry mouth, loss of appetite, decreased concentration, and suicidality (Kupfer et al 1984a).

A third approach to examining the relationship between sleep and depression has been to evaluate the association between specific sleep variables and clinical outcome. For example, REM latency has been associated with responsiveness to pharmacotherapy (Kupfer et al 1981; Svendson and Christensen 1981; Rush et al 1985b, 1989), and reduced REM latency and decreased delta ratio have been associated with outcomes such as new onset of depression (Giles et al 1990), reduced time to recurrence, and/or increased likelihood of recurrence (Rush et al 1985b; Giles et al 1988b; Kupfer et al 1989; Thase et al 1996). Composite scores based on two or more sleep variables have also been used to predict clinical outcome as well as to distinguish depressed patients from other patient groups and/or from healthy controls (Thase et al in press). The composite scores typically were calculated using REM latency, REM density, and sleep maintenance variables.

Finally, the relationship between multiple sleep variables and multiple variables characterizing episode duration and depression history in an elderly depressed sample has been evaluated using canonical correlation analysis (Dew et al 1996). A single dimension yielded an overall canonical correlation of 0.60. The major contributing sleep variables were stage 1 sleep percent, REM density, and sleep efficiency. The clinical variables that contributed most substantially were duration of the index episode, number of hospitalizations, and endogenous subtype.

Common to all of these approaches is that the multivariate structure of depression was in some way simplified and only specific sleep variables were evaluated. Although these strategies have played substantial roles in describing the pathophysiology and clinical course of depression, the interrelations between a broad symptom profile and the range of EEG sleep measures most likely to be affected by depression have not been concurrently evaluated. Thus, the overall magnitude of association between depression and sleep is not clear, nor is it clear which specific aspects of the complex components of sleep and depression account for the association.

In the present study, we evaluated the relationship between a large set of sleep variables and a set of symptom items derived from both the Beck Depression Inventory (BDI) and the Hamilton Depression Rating Scale (HDRS) in a sample of 361 depressed patients. The sleep variables included visually scored parameters as well as period amplitude measures. Items from both the BDI and the HDRS were included because the two instruments assess different aspects of depression (Domken et al 1994; Brown et al 1995). The clinician-rated HDRS is more sensitive to neurovegetative symptoms, whereas the self-report BDI is more sensitive to cognitive and affective symptoms. By including both instruments, we were able to determine the depressive symptoms that were most strongly associated with sleep disturbance. The goals of the present study were to determine:

1. The overall strength of association between EEG sleep measures and depression symptoms;
2. The variables that account for the majority of the association; and
3. The sleep variables, and/or type of sleep variables, that were most associated with individual depressive symptoms.

Table 1. Patient Characteristics

Variable	Mean	SD
% female	62.3	—
Age	42.3	14.1
Beck Depression Inventory score	21.0	4.3
Hamilton Depression Rating Scale score	23.4	7.8
Age of onset (years)	30.8	13.8
Number of previous episodes	5.1	5.9
Duration of index episode (weeks)	29.0	27.0

Methods

Patients

Subjects were 361 patients identified from an archival database at Western Psychiatric Institute and Clinic, University of Pittsburgh, who met criteria for unipolar, nonpsychotic major depressive disorder by DSM-III-R and research diagnostic criteria (RDC), and scored ≥ 14 on the 17-item HDRS. Subjects were assessed using the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer 1978), had no psychotropic medication, no primary sleep disorders, and had a stable night–sleep/day–wake schedule. Patients were medically healthy, or were under treatment for conditions in which neither the illness nor the treatment altered sleep continuity or EEG activity (e.g., thyroid replacement hormones with normal thyroid tests; antibiotics for chronic conditions such as acne; atenolol for hypertension). Protocols for patient study routinely required a 14-day medication-free period prior to laboratory evaluation. Clinical criteria to rule out sleep disorders were implemented by research clinicians trained in research diagnostic assessment. Baseline sleep records were also reviewed by laboratory technologists for evidence of apnea and periodic limb movements, and the medical director of the sleep laboratory consulted on all records suggestive of a sleep disorder. Clinical and sleep data, inclusionary/exclusionary criteria, and specific laboratory methodology for subsets of this sample have been reported elsewhere (Elkin et al 1989; Frank et al 1990; Buysse et al 1992; Reynolds et al 1992; Simons and Thase 1992; Nofzinger et al 1993, 1995). Basic demographic and clinical information on the present sample is provided in Table 1.

Measures

Clinical data included BDI responses (19 items) and HDRS responses (17 items) as well as age, sex, and clinical history of major depression. EEG sleep data included 19 variables from each patient's second night of baseline polysomnographic study (PSG). Each PSG included two electro-oculograms (EOG), one C3 or C4 electroencephalogram (EEG), and a submentalis or mentalis electromyogram (EMG). Total recording time required a minimum of 5 hours for all studies. In the evolution of laboratory procedures, protocols were such that 40% of subjects had fixed wake-up times at 6:30 AM. The remaining subjects were allowed to awaken according to their habitual wake-up time. The mean total recording periods were 430 min (7.2 hours: fixed wake-up time) and 451 min (7.5 hours: habitual wake-up time). This variability should not affect most of the variables in the present correlational analyses.

PSG records were acquired and scored according to Rechtschaffen and Kales criteria (Rechtschaffen and Kales 1968). Scorers met laboratory standards for interrater reliability (overall kappa ≥ .86). Each PSG was also digitized and subjected to period amplitude analysis to estimate delta and rapid eye movement activity (Doman et al 1995).

Visually scored PSG measures were selected to identify a range of continuity, sleep architecture, and REM measures. Specifically included were: sleep latency, total sleep time, sleep maintenance, amount of wakefulness during the last 2 hours of the night, stage 1 percent, delta sleep percent, REM sleep percent, REM latency, REM efficiency, and REM density. Sleep maintenance is defined as percent of non-REM (NREM) and REM sleep time after sleep onset and prior to wake-up time. REM efficiency is defined as the mean percent of REM sleep time averaged across REM periods. REM density is defined as a value from 0 to 8 for presence of eye movement activity as a proportion of a 1-min epoch. A score of 1 indicates that eye movements are present for 1/8 of a 1-min epoch, and so on.

The period amplitude measures included: average delta activity (counts/min) and rapid eye movement counts (counts/min) for the entire night and for the first, second, and third NREM and REM cycles. Delta ratio (delta counts/min from NREM-1 divided by NREM-2) was also included. This variable measures the decline in delta EEG intensity over the first two NREM sleep cycles.

Analyses

A preliminary analysis was conducted to evaluate the effects of age and sex on EEG sleep measures (Reynolds et al 1990). Significant age effects were found for the following variables: REM latency, sleep maintenance, stage 1 percent slow-wave sleep percent (SWS%), early morning wakefulness, delta counts NREM-1, REM counts REM-1, and delta ratio. Sex effects were found for REM latency and SWS%. All sleep variables were adjusted for age and sex effects. Following the preliminary analysis, a hierarchical statistical approach, consisting of three steps,

was used to analyze the relationship between the depressive symptom items and the adjusted sleep measures.

First, the overall relationship between the 36 individual BDI and HDRS items, and the 19 sleep variables was determined using a canonical correlation analysis. This statistical method provides a means of assessing two sets of variables concurrently to determine if factors exist within each variable set, and to evaluate the correlation between the factors from the two variable sets.

Following the initial canonical correlation analysis, we performed a series of hierarchical canonical correlations to identify the variables within each data set that accounted for the majority of the overall correlation. BDI and HDRS items with low standardized canonical coefficients were eliminated first. Sleep variables with low standardized canonical coefficients were eliminated second. In both cases, an item was deleted from either data set only if its removal caused less than a 1.0% drop in the overall canonical correlation. The elimination process for each data set was terminated after a 2.5% cumulative reduction in the canonical correlation. Thus, the process of iteratively removing symptom and sleep variables with low canonical coefficients was terminated after the overall correlation was reduced by 5.0%. The cutoff value of 5% was adopted to ensure that the overall correlation was not substantially attenuated by the deletion process.

In the third step, the sleep variables that accounted for the majority of the canonical correlation were regressed onto each of the BDI and HDRS items that remained after the reduction process. This procedure identified the sleep variables that correlated most strongly with the specific depressive symptoms. Stepwise regressions were used for these analyses.

Variables in these analyses were not transformed. Although several variables were nonnormally distributed, the degree of skew and kurtosis does not affect parameter estimates within the canonical correlation analyses (Seber 1984). Moreover, since the hierarchical canonical correlation analyses did not rely on probability estimates to determine the contribution of each variable to the overall model, the nonnormal distribution of several variables will not affect the results of these analyses. For the regression analyses, inference on the parameter estimates can be based on the normality assumption given the large sample size in our application (Serfling 1980).

Results

Sleep Profile of Sample

To ensure that this sample was representative of patients typically described in the literature, we evaluated the incidence of sleep complaints and sleep EEG abnormalities measures. The three sleep symptom items on the HDRS were used to identify frequency of sleep complaints, and the mean values for the EEG sleep variables were used to evaluate degree of polysomnographic sleep disturbance. Sixty-five percent of the patients had one or more severe sleep complaints (defined as a sleep item score of 2). This includes 38% with initial insomnia, 39% with middle insomnia, and 41% with delayed insomnia (early morning awakening). As seen in Table 2, the sample exhibited a mean EEG sleep profile that is consistent with that typically observed in depressed outpatients. REM latency was reduced (mean = 62.6 ± 24.3 min), and REM sleep percent was moderately elevated (mean = 24% ± 5.3%).

Canonical Correlation Analysis

The overall canonical correlation between the 19 Beck items, the 17 HDRS items, and the 19 sleep variables was 0.55 ($p < .05$). The analysis yielded only one significant dimension, indicating that sleep and depression variables are related to a single, underlying construct.

Hierarchical Canonical Correlations

Variables were iteratively deleted until the overall canonical correlation was reduced by 5% (i.e., from 0.55 to 0.52). Fifteen of the original 36 symptom variables and nine of the original 19 sleep variables were retained in the reduced model.

Eight HDRS items and seven BDI items were retained in the hierarchical analyses. The mean canonical coefficient values for each instrument were comparable (HDRS mean = 0.25, BDI mean = 0.22). Nine of the 15 symptom variables had canonical coefficients above 0.20; canonical coefficients equal to, or greater than, 0.20 are generally considered to be significant contributors to the dimensional factors. The nine symptom items were depressed mood (BDI), weight loss (BDI), diminished libido (HDRS), sleep disturbance (BDI), psychic anxiety (HDRS), self blame (BDI), somatic anxiety (HDRS), initial insomnia (HDRS), and work ability (BDI). It should be noted that only two of the retained symptom variables were related to sleep disturbance. Canonical coefficients for the 15 symptom variables are presented in Table 3.

Both visually scored and automated EEG sleep variables, as well as NREM and REM variables, were retained after the hierarchical analyses. The sleep variables were average delta activity (counts/min) for entire night, delta activity for the first, second, and third NREM cycles, average REM counts for the first REM period, stage 1 percent, REM efficiency, sleep latency, and delta ratio. All nine of the EEG sleep variables that remained after the

Table 2. EEG Sleep Means

Variable	Mean	Standard deviation	Minimum	Maximum
Sleep latency (min)	21.7	21.7	0	225.0
Total sleep (min)	421.4	50.4	289.0	585.0
Sleep maintenance (%)	92.7	8.1	51.2	100.0
Early morning wakefulness (min)	16.5	21.6	0.0	120.0
Stage 1 percent	5.3	3.7	0.0	24.3
Delta Sleep percent	9.3	8.4	0.0	3.7
REM percent	24.0	5.3	8.6	42.1
REM latency (min)	62.6	24.3	6.0	188.0
REM density (visually scored)	1.4	0.5	0.4	4.0
REM efficiency	89.2	9.1	40.4	100.0
Delta counts—NREM-1	25.7	15.9	0.2	74.3
Delta counts—NREM-2	21.0	13.2	0.4	58.0
Delta counts—NREM-3	13.2	10.5	0.3	59.3
REM counts—REM-1	5.6	4.5	0.1	27.8
REM counts—REM-2	7.1	4.7	0.0	27.6
REM counts—REM-3	7.4	4.8	0.0	27.8
Whole night delta counts	16.5	9.9	0.5	50.9
Whole night REM counts	7.4	3.9	0.4	24.2

iterative analyses had canonical coefficients above 0.20. Delta counts for NREM-2 had a disproportionately large canonical coefficient of 1.06. A larger proportion of the NREM measures, as compared to REM measures, remained in the model (86% vs. 29%, $p < .05$), and the NREM variables appeared to have larger canonical coefficient values (NREM mean = 0.49 vs. REM mean = 0.26). More period amplitude variables than visually scored variables were retained in the final model (66% vs. 33%, $p < .05$). Canonical coefficients for all the EEG sleep variables are presented in Table 3.

To ascertain what proportion of the residual canonical correlation corresponded to the relationship between subjective and objective sleep measures, disturbed sleep and initial insomnia were deleted from the final model. The correlation was reduced from 0.52 to 0.49. The remaining correlation was significant ($p < .0001$).

Multiple Regression Analyses

EEG sleep correlates of depressive symptom items are presented in Table 4. Symptom items, the overall multiple correlation (MR), the direction of the association (±), partial correlation values (R^2), and the probability values are also presented.

Ten of the 15 symptoms were associated with one or more EEG sleep variables. When a symptom had multiple sleep correlates, the correlates in all but one case (initial insomnia) included both NREM and REM sleep variables. In most cases, however, NREM variables were the first to be entered into the regression models and captured the largest proportion of variance.

The general relationship between the depression symptom items and EEG sleep variables was such that greater symptom severity correlated with more abnormal sleep for all symptom items except depressed mood. In this case, two of the three sleep correlates were in the expected direction. Ability to work, self-blame, loss of social interests, guilt, and somatic anxiety did not, as independent items, have significant EEG sleep correlates.

Discussion

We have taken advantage of a large data set of carefully diagnosed patients with nonpsychotic, unipolar major depression to evaluate the specific association between clinical symptoms of depression and EEG sleep measures using multivariate statistical methods. The overall association between a broad range of sleep measures and clinical symptoms was moderately high ($r = .55$) and the relationship was unidimensional. Of the 36 depression symptoms items and 19 EEG sleep measures considered, a subset of 15 depression items and nine sleep measures accounted for 95% of the correlation. The association was largely independent of the relationship between subjective sleep complaints and polysomnographically measured sleep. The sleep variables included diminished delta activity,

Table 3. Residual Canonical Correlation Model

	Canonical coefficients
Depression symptoms	
Depressed mood (H)	0.46
Weight loss (B)	0.33
Loss of libido (H)	0.28
Disturbed sleep (B)	0.28
Psychic anxiety (H)	0.27
Self-blame (B)	0.26
Somatic anxiety (H)	0.23
Initial insomnia (H)	0.21
Work ability (B)	0.20
Loss of appetite (H)	0.19
Guilt (H)	0.18
Social interest (B)	0.18
Loss of insight (H)	0.17
Indecision (B)	0.16
Failure (B)	0.14
Sleep variables	
Delta counts—NREM-2	1.06
Delta counts—NREM-3	0.52
Stage 1 percent	0.47
Whole night delta counts	0.32
Delta counts—NREM-1	0.38
REM counts—REM-1	0.29
REM efficiency	0.23
Sleep latency	0.23
Delta ratio	0.20

H, Hamilton Depression Rating Scale; B, Beck Depression Inventory.

increased stage 1 percent, increased REM activity, increased sleep latency, and increased REM efficiency. The depression variables included weight/appetite loss, dysphoria, sleep problems, decreased libido, feelings of failure, and indecision.

The depressive symptoms accounting for the majority of the variance were derived from both the HDRS and the BDI and incorporate domains that have been traditionally considered separate. Neurovegetative, cognitive, and affective domains are represented. Specific symptoms are related to the extent that they are the most salient features of the construct of depression. Of the nine criteria used to diagnose depression, six are represented. The symptoms not accounted for are fatigue, suicidality, and psychomotor abnormalities. This finding underscores the essential relationship between sleep and depression, i.e., that EEG sleep disturbance is related to most of the core features of depression and not just to a subset of symptoms or to the subjective complaints of disturbed sleep.

The EEG sleep variables accounting for the majority of variance included both NREM and REM measures derived from both visual and period amplitude scoring procedures. NREM variables, however, captured the largest proportion of variance, and one particular NREM variable accounted for a disproportionate amount of depressive symptom variance in the canonical correlation analyses: delta counts for NREM-2. Thus the association between sleep disturbance and depression primarily derives from an inverse association between delta intensity and severity of depression, and secondarily derives from a positive association between REM activity and severity of depression. Diminished delta intensity and increased REM activity may be related phenomena to the extent that they represent increased arousal during sleep or impaired sleep "drive" (Borbely 1992).

Increased arousal and impaired sleep drive, although related, are not necessarily the same phenomenon. On the one hand, arousal dysregulation may be a primary feature of depression, and sleep initiation and maintenance problems are a consequence (i.e., hyperarousal promotes shallower sleep). On the other hand, impaired sleep drive may be a primary feature of depression, and increased arousal is a consequence (i.e., shallower sleep allows for nocturnal hyperarousal). The distinction, though subtle, may implicate different neurobiologic substrates.

The observed association between the clinical and sleep domains, as with any correlational analysis, can be interpreted in several ways: arousal during sleep or impaired sleep drive may predispose patients to the observed core depressive symptoms, the core symptoms may predispose patients to aroused sleep or impaired sleep drive, or the two phenomenon may be related to a third variable, e.g., common neurobiologic dysregulation.

With respect to the possibility that disturbed sleep may lead to core depressive symptoms, it is possible that diminished slow-wave sleep and intensified REM sleep correspond to processes that interfere with the putative functions of sleep; several scenarios are possible. A number of functions have been ascribed to sleep, including NREM-related energy conservation (Walker and Breger 1980) and tissue restoration (Adam and Oswald 1977), as well as REM-related mood regulation (Perlis et al 1993, 1995) and memory consolidation (Winson 1990). Interference with the normal coordination of one or more of these functions may predispose individuals to such symptoms as weight loss, depressed mood, and/or memory and concentration problems. Very few studies, however, examine the linkage between specific sleep abnormalities, specific depressive symptoms, and putative sleep functions. A recent study by Perlis and colleagues attempted to create such a link by suggesting that the mood regulatory function of REM sleep is related to the dampening of sympathetic and somatic arousal during REM sleep, and that this function is compromised and results in mood disturbance when REM sleep is excessively activated (Perlis et al 1995).

With respect to the possibility that observed core

Table 4. Multiple Regression Analyses for Individual Depression Symptoms

Variable	Direction	Full model R^2	Partial model R^2	Probability > F
Weight loss (B) (multiple regression = 0.34)				
Stage 1 percent	(+)	.04	.04	0.000
REM counts—REM-1	(+)	.02	.06	0.007
REM efficiency	(+)	.01	.07	0.027
Sleep latency	(+)	.01	.08	0.038
Mean whole night delta	(−)	.03	.12	0.002
Depressed mood (H) (multiple regression = 0.26)				
Delta counts—NREM-2	(−)	.04	.04	0.000
Delta counts—NREM-3	(+)	.02	.06	0.005
REM counts—REM-1	(+)	.01	.07	0.029
Loss of appetite (H) (multiple regression = 0.24)				
Delta counts—NREM-1	(−)	.03	.03	0.001
REM counts—REM-1	(+)	.02	.05	0.021
Stage 1 percent	(+)	.01	.06	0.039
Psychic anxiety (H) (multiple regression = 0.20)				
Delta counts—NREM-2	(−)	.02	.02	0.004
REM counts—REM-1	(+)	.02	.04	0.009
Sleep disturbance (B) (multiple regression = 0.19)				
Delta counts—NREM-1	(−)	.04	.04	0.000
Decreased libido (H) (multiple regression = 0.19)				
Delta counts—NREM-2	(−)	.04	.04	0.000
Initial insomnia (H) (multiple regression = 0.18)				
Delta counts—NREM-2	(−)	.01	.02	0.024
Delta ratio	(−)	.01	.03	0.041
Failure (B) (multiple regression = 0.13)				
Delta counts—NREM-2	(−)	.01	.02	0.011
Indecision (B) (multiple regression = 0.13)				
Delta counts—NREM-2	(−)	.02	.02	0.016
Loss of insight (H) (multiple regression = 0.10)				
Sleep latency	(+)	.01	.01	0.046

H, Hamilton Depression Rating Scale; B, Beck Depression Inventory.

symptoms may lead to increased arousal during sleep or to impaired sleep drive, several scenarios are possible. Let us consider two. First, it may be that symptoms such as depressed mood, psychological anxiety, and self-blame *directly* lead to increased arousal during sleep and interfere with the maintenance of deep sleep (i.e., cognitive arousal → somatic arousal). In support of this possibility, there is preliminary evidence that stress-induced ruminative type worry diminishes slow-wave sleep intensity in the first sleep cycle of normal subjects (Hall et al 1996). Second, it may be that symptoms such as depressed mood, psychological anxiety, and self-blame *indirectly* lead to impaired sleep drive (mood disturbance → maladaptive behaviors → impaired sleep drive). If depressed individuals spend excessive amounts of time in bed and/or are more sedentary, because of mood symptoms, these behaviors may lead to difficulties with initiating and maintaining deep sleep. Although excessive amounts of time in bed is associated with poor sleep maintenance (Spielman 1987), it is not clear that depressed patients spend excessive amounts of time in bed and/or whether sedentary behavior alone is associated with diminished delta activity, reduced REM latency, and increased REM density (Feinberg et al 1992).

With regard to the possibility that an underlying neurobiological dysfunction may be responsible for the association observed in the present study, there is emerging evidence that prefrontal and limbic system abnormalities exist in depression, and that such abnormalities may be related to both the symptoms of depression and to sleep abnormalities. Waking studies using positron emission tomography (PET) have demonstrated hypometabolism in anterolateral prefrontal cortex, particularly in the left hemisphere, in depressed patients (reviewed in George et al 1994). Sleep studies have shown that depressed patients have *higher* cortical and limbic metabolic rates during

early NREM sleep (Gillin et al 1994; Ho et al 1996) and during REM sleep (Maquet and Franck 1989; Nofzinger et al 1996). From these pieces of evidence, we can speculate that depression includes a consistent pattern of frontal and limbic system dysfunction, and that these neurobiological abnormalities may give rise to some of the cardinal symptoms of depression and to some of the sleep EEG stigmata typically observed in depression. For example, attention deficits, persistent dysphoria, and delta activity abnormalities may all stem from frontolimbic dysregulation. If this is the case, the correlation observed in the present study would be due not to the direct relationship between affective disorder and sleep disturbance, but to a common underlying neurobiologic abnormality.

Leaving aside the issue of how the two phenomena evaluated in this study are related, there are three remaining issues that should be highlighted. First, in our sample of patients with depression, terminal insomnia was not the most frequent sleep complaint. Our depressed patients reported all three forms of insomnia with about equal frequency. Thus it is probably not the case that early morning awakening (terminal insomnia) is the cardinal form of insomnia in outpatient depression. Second, both NREM or REM sleep variables were associated with individual depressive symptoms. In all but one case (initial insomnia), the correlates comprised sleep variables from both the NREM and REM sleep domains. This suggests that theories which posit that abnormal sleep may be depressogenic must take into account the reciprocal relationship between NREM and REM sleep. It is also clear, however, that the NREM measures, particularly those relating to delta intensity, are more primarily associated with the six core depressive symptoms noted in this study. This emphasis is consistent with the perspective that diminished NREM sleep, or processes associated with NREM sleep, may be depressogenic (Beersma and Hoofdakker 1992).

Third, the EEG sleep correlates of the subjective measures of sleep disturbance *were not* objective measures of sleep initiation or maintenance, but rather measures of diminished delta intensity. This implies that perception of the ability to fall asleep and stay asleep is more powerfully associated with absence of delta activity during sleep than by the apparent recognition of how much time is spent initiating sleep or sleeping. This finding is initially counterintuitive; it suggests that slow-wave sleep deficits influence patient assessment of the ability to fall asleep and stay asleep more directly than actual time awake. One possible explanation is that delta activity may be related to other EEG activities that were not measured in this study, such as beta activity. Delta and beta activity during sleep are likely to be inversely correlated. Beta activity has been associated with insomnia (Freedman 1986; Mercia and Gaillard 1991), and there is preliminary evidence that beta activity is associated with enhanced memory processing during sleep onset (Wyatt et al 1994). Accordingly, beta activity may correspond to a level of brain activity that makes it difficult for the patient to discriminate sleep from wakefulness. Since beta activity was not measured in the studies reported here, measures of diminished delta activity may have simply assumed the variance that otherwise would have been taken by measures of beta activity.

Conclusions

The present study lends support to the proposition that sleep and depression are intimately related phenomena. The relationship is mediated by a select group of variables, and the relationship is not founded upon the association between subjective and objective measures of sleep disturbance. The relevant depression variables are not limited to the neurovegetative aspects of depression but rather clearly encompass most of the core symptoms of depression. The relevant sleep variables appear to be primarily related to NREM variables, but REM measures are represented. The combination of the sleep EEG variables appear to be related to degree of arousal during sleep or to impaired sleep drive.

Finally, given the overall canonical correlation of 0.55, it is clear that factors unrelated to those measured in this study are accounting for a great deal of either sleep disturbance and/or depressive symptom variance. Future statistical modeling may benefit from incorporating measures from other relevant dimensions, e.g., measures of life stress, coping ability, access to resources, etc.

Addendum

Some of the data presented here have been published as abstracts. In the first publication (*Sleep Research,* 24, p 175) only BDI data were evaluated. In the second publication [*Sleep Research,* 24(A), p 275] both HDRS and BDI data were evaluated, but the effects of age and gender were not taken into account.

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