ORIGINAL ARTICLE

Electroencephalographic Sleep Profiles Before and After Cognitive Behavior Therapy of Depression

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Background: Previous studies have not fully resolved the state-dependent vs traitlike behavior of the electroencephalographic sleep abnormalities associated with depression. We therefore examined the sleep profiles of depressed patients before and after 16 weeks of treatment with cognitive behavior therapy to determine the stability or reversibility of selected abnormalities.

Methods: Seventy-eight unmedicated patients with major depressive disorder were stratified into abnormal and normal subgroups on the basis of pretreatment sleep study results. Two prospectively defined types of sleep variables were studied: those expected to be traitlike or state independent (type 1) and those predicted to be reversible or state dependent (type 2).

Results: The type 1 sleep disturbances (reduced rapid eye movement latency, decreased delta sleep ratio, and decreased slow wave sleep [in percentage]) were stable, as predicted, across time. A composite measure of type 2 disturbances (based on rapid eye movement latency, sleep efficiency, and rapid eye movement density) improved significantly, although a minority of patients in remission had persistent abnormalities.

Conclusions: The electroencephalographic sleep correlates of depression can be disaggregated into state-independent and partially reversible subgroups. Persistent sleep disturbances in remitted patients may have ominous prognostic implications.

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LONGITUDINAL studies of electroencephalographic (EEG) sleep profiles in patients with depression suggest that some disturbances, such as increased rapid eye movement (REM) density and poor sleep efficiency, are reversible or state-dependent abnormalities.[1-3] Yet other features, notably decreased slow wave sleep, seem to be more persistent or traitlike.[1-3] One of the most widely replicated EEG sleep abnormalities, reduced REM latency, may exhibit both state-dependent and traitlike behaviors.[4] It is important to differentiate between state-dependent and traitlike abnormalities for several reasons.[2-4] State-dependent disturbances are more likely to reflect neurobiological processes underlying an acute episode of illness and, thus, may help identify target mechanisms for treatment. For example, the association of hypercortisolism, increased phasic REM sleep, and sleep continuity disturbances may identify a state of central nervous system hyperarousal that is more responsive to somatic than psychosocial therapies.[5-7] Conversely, state-independent "markers" are useful to study familial transmission of disorders and to identify patients at increased risk for relapse or recurrence.[3,4] The traitlike nature of reduced REM latency and decreased slow wave sleep is suggested by research using family studies,[8-11] longitudinal follow-up,[12-14] and other high-risk paradigms.[15,16]

Most previous follow-up studies of EEG sleep have focused on patients treated with pharmacotherapy.[12,13,17-23] Pharmacotherapy may introduce several potential confounds, however, including the distortion of sleep profiles by extraneous medication effects (eg, antihistaminic effects), "rebound" sleep disturbances triggered by drug discontinuation, and loss of informative cases due to rapid relapse after withdrawal of medication.[24-26] Nonpharmacological treatments such as interpersonal psychotherapy[27] or cognitive behavior therapy (CBT)[28] might obviate these confounds. However, this strategy has other potential shortcomings. Specifically, sample composition may be biased by the differential "sieve" effect, in which neurophysiologically disturbed patients may be less responsive to psychotherapy[5-7] or unavailable because of recurrence during longitudinal follow-up.[5,6] Such research is also hampered by the low prevalence of EEG sleep abnormalities typically seen in depressed outpatients.[5,6,14,21,24-26] Simply put, sleep pro-

PATIENTS AND METHODS

PATIENTS

The procedures used for recruitment, assessment, and treatment have been described in detail in earlier reports.[5,29] To summarize, outpatients meeting *DSM-III-R*[30] criteria for nonbipolar, nonpsychotic major depressive disorder were referred to our research team for a detailed secondary evaluation that included an independent research interview using both the Schedule for Affective Disorders and Schizophrenia[31] and the Hamilton Rating Scale for Depression (HRSD).[32] Patients were eligible for the study if they (1) met *Research Diagnostic Criteria*[33] for a diagnosis of primary (nonpsychotic) major depression, probable or definite endogenous subtype; (2) scored more than 14 on the 17-item HRSD; and (3) did not have untreated or poorly controlled general medical conditions that might cause depression (eg, hypothyroidism), confound EEG sleep studies (eg, sleep apnea), or require treatment with psychoactive agents (eg, corticosteroids or β-blockers). Exclusion criteria included *DSM-III-R* dysthymia, chronic (>18 months' duration) major depression, a history of substance abuse within the past 2 years, and well-established Axis II diagnoses of borderline or antisocial personality disorders. These criteria were chosen to maximize internal validity by reducing other known sources of outcome variance.[5]

Among the 90 outpatients who entered our treatment study,[5] 78 (87%) completed posttreatment (T_2) sleep studies. Twelve patients were not restudied: 1 remitted and relocated; 9 (6 nonresponders, 3 responders) declined to participate in T_2 studies; and 2 noncompliant patients were withdrawn from the protocol. Pretreatment characteristics of the study group are summarized in **Table 1**.

Healthy normal control subjects (n=44) were studied contemporaneously with identical assessment protocols.[29] Control subjects had no lifetime history of mental disorder (per the Schedule for Affective Disorders and Schizophrenia and Research Diagnostic Criteria). As it was not possible to age- and sex-match each depressed patient with a control, 2 overlapping age- and sex-equated control groups were formed for comparisons of traitlike (n=33, 14 men and 19 women; mean age, 32.8 years, SD=10.0) and state-dependent (n=27, 12 men and 15 women; mean age, 35.5 years, SD=8.9) variables.

EEG SLEEP STUDIES

All patients discontinued taking antidepressants for at least 2 weeks (6 weeks for fluoxetine hydrochloride) before baseline (T_1) sleep studies. All patients were monitored prospectively for at least 14 days to ensure abstinence from alcohol and other psychoactive substances. Patients kept daily logs of sleep-related activities and were instructed not to nap before sleep studies.

Posttreatment EEG sleep studies were typically performed 16 to 20 weeks after T_1. In 1 case, however, T_2 studies were completed after only 6 weeks of therapy because the patient required hospitalization after a suicide attempt.

Sleep was recorded using a routine polysomnographic montage. Paper speed was 10 mm/s, and sensitivity on the EEG channel was 7.5 μV/mm. High- and low-frequency filter settings were 30.0 and 0.3 Hz, respectively, for EEG and electrooculogram and 90 and 10 Hz, respectively, for electromyelogram. Sleep records were scored by certified polysomnographic technologists according to standard criteria.[34,35] Two night means were used to lessen the impact of night-to-night variability. Excellent interrater reliability of visual scoring (ie, intraclass correlation coefficients >0.85) was maintained in our laboratory by ongoing quality assurance procedures.

The automated methods used for period analysis of delta waves and REM counts have been described in detail elsewhere.[36] Four representative automated measures were used: the average delta count for the whole night, the delta ratio (a ratio of average delta counts from the first and second nonREM periods), the average REM counts for the whole night, and the average REM count for the first REM period. Four patients (2 at T_1 and 2 at T_2) had technically poor automated data that could not be used in the analyses.

SELECTION OF SLEEP VARIABLES

Although it is desirable to retain as much information as possible about the rich, multidimensional nature of sleep neurophysiology, univariate analyses of 20 different variables are unwieldy and increase the likelihood of false positive findings. We therefore selected a smaller number of representative sleep abnormalities, as described below.

Selection of Traitlike Variables

The typology of Kupfer and Ehlers[4] was used to select 3 presumed traitlike (type 1) abnormalities: reduced REM latency (≤65 minutes),[12] decreased slow wave sleep (≤8%),[24] and decreased delta sleep ratio (<1.1).[22] Because no single type 1 abnormality has high specificity for depression,[1,2] we defined an abnormal type 1 profile on the basis of at least 2 disturbances. Thirty-seven patients (41%) met this criterion at T_1. Compared with the remaining 53 patients, this subgroup had significantly reduced slow wave sleep (%) (t_{88}=–5.59, P=.0001), REM latency (t_{88}=–6.22, P=.0001), and delta ratio (t_{87}=–3.19, P=.002) values.

Continued on next page

files that are undisturbed at pretreatment will not "normalize" further after recovery.

In this study, the sleep profiles of 78 depressed outpatients are examined before and after treatment with CBT. Changes in sleep profiles are studied with respect to the level of pretreatment abnormality and the predicted behavior of selected sleep disturbances (ie, traitlike vs reversible). We hypothesize that the sleep disturbances proposed to be traitlike will persist into remission, whereas the presumed state-dependent disturbances will normalize after effective nonpharmacological treatment.

RESULTS

SLEEP DISTURBANCES PREDICTED TO BE STABLE (TYPE 1 ABNORMALITIES)

Consistent with the prediction of state independence, only the MANCOVA main effect for the sleep group was significant (**Table 3**). Univariate sleep group effects were significant on REM latency ($F_{1,70}$=20.01, P<.001) and slow wave sleep (%) ($F_{1,70}$=20.96, P<.001), but not delta sleep ratio ($F_{1,70}$=3.48, P=.07).

Selection of State-Dependent Variables

Thase et al[29] developed a discriminant index score based on 3 sleep measures—REM latency, REM density, and sleep efficiency—to characterize the state-dependent (type 2) sleep profiles of Kupfer and Ehlers.[4] It was previously reported that patients with abnormal index scores were significantly less responsive to CBT[5] and interpersonal psychotherapy,[6] but not antidepressant therapy,[6] compared with patients with normal profiles. The validation and psychometric characteristics of this variable are described in a separate publication.[29] An optimal "cutting score" was calculated using the following simplified equation: $-20.5 + (0.0519 \times \text{REM latency}) - (1.61 \times \text{REM density}) + (0.22 \times \text{sleep efficiency})$. Scores of 0 or lower identified patients with abnormal type 2 profiles; higher scores were considered normal. Forty (44%) of the 90 patients had an abnormal type 2 profile at T_1. These patients differed significantly from the remainder (n=50) on 9 of 17 standard sleep measures (**Table 2**). Each of the differences could be attributed to either poor sleep efficiency or increased phasic REM sleep.

As noted earlier, reduced REM latency is considered to be both a type 1 and a type 2 variable in the model proposed by Kupfer and Ehlers.[4] For example, a traitlike reduced REM latency value (eg, 55 minutes) may decrease even further (eg, 20 minutes) during a severe depressive episode. However, because few outpatients have such markedly reduced values, we predicted that REM latency would be relatively stable even when grouped with the other type 2 abnormalities. The classifications did not overlap significantly despite sharing reduced REM latency as a common disturbance: normal type 1 and normal type 2, n=32 (36%); normal type 1 and abnormal type 2, n=21 (23%); abnormal type 1 and normal type 2, n=18 (20%); and abnormal type 1 and abnormal type 2, n=19 (21%) (χ^2=1.2, *df*=1, *P*=.27).

TREATMENT AND OUTCOME

The 16-week, 20-session individual therapy protocol[28] began immediately after T_1 sleep studies. No psychotropic medications were permitted during therapy in the acute phase. All therapists had completed 2 years or more of supervised training, and their competency was "certified" by accepted standards.[37,38] Symptoms were assessed every other week by independent clinical evaluators and patient self-reporting. Remission was defined by at least 2 consecutive HRSD scores of 6 or less sustained to the end of the protocol.[39] At T_2, the remitted group of patients (n=43, 55%) had significantly lower scores on the HRSD (mean=2.1, SD=2.4) than the remainder (n=35; mean=9.7, SD=4.8, t_{76}=8.47, *P*<.0001). The remitted group also experienced significantly greater improvement on the Beck Depression Inventory[40] (t_{76}=7.57, *P*<.0001) and the Global Assessment Scale[41] (t_{76}=–6.97, *P*<.0001).

HYPOTHESES AND STATISTICAL TESTS

Three hypotheses were tested: (1) type 1 abnormalities will persist despite remission; (2) the abnormal type 2 profile and 2 of its component variables (increased REM density and poor sleep efficiency) will normalize after treatment; and (3) remission will be associated with greater improvements of type 2 (state-dependent), but not type 1 (state-independent), sleep disturbances.

The primary analyses used a mixed-model design of nonorthogonal (correlated) main effects.[42] Nonorthogonality resulted from unequal cell sizes and the fact that the abnormal type 2 profile was associated with a lower remission rate.[5] A multivariate analysis of covariance (MANCOVA) was performed on the type 1 variables and an analysis of covariance (ANCOVA) was performed using the discriminant index score as a composite measure of type 2 disturbance. Age was covaried in each analysis. These analyses yielded 2 between-subject effects—remission group (remitted vs unremitted) and sleep group (abnormal at T_1 vs normal at T_1)— with time (T_1 vs T_2) as the within-subject effect. The method described by Maxwell and Delaney[42] was used to interpret the potentially correlated effects. All F ratios were calculated using type III sums of squares. The 3-way interaction terms (remission group, sleep group, and time) were interpreted first. If significant, analyses would be limited to explication of the 3-way interaction, using either paired or between-group *t* tests. If not significant, the 2-way interactions (remission group and sleep group, remission group and time, and sleep group and time) were examined next. Main effects were interpreted only if relevant interactions were definitely not significant (*P*>.10).[42] With harmonic mean cell sizes of 37 subjects, main effect sizes (f) of 0.33 or more were detectable with statistical power of 80% or greater (α=.05, β=.20).[43]

A second analysis compared the T_2 sleep of the patients who remitted (normal vs abnormal profiles at T_1) with that of the control groups. Again, a MANCOVA (type 1 variables) and an ANCOVA (type 2 composite score) were performed. Normalization of sleep abnormalities would result in no differences across groups at T_2.

In the third analysis, the stability of the abnormal/normal classifications (from T_1 to T_2) were examined using Mantel-Haenszel χ^2 tests. Whereas type 1 profiles were predicted to be stable, the abnormal type 2 classification was predicted to normalize at T_2.

When the T_2 sleep of the patients who remitted (abnormal, n=16; normal, n=27) was compared with that of the control group (n=33), a significant MANCOVA group effect was again observed ($F_{6,138}$=3.54, *P*<.003). Univariate analyses confirmed this effect on all 3 variables at T_2 (REM latency: $F_{2,71}$=3.19, *P*=.05; slow wave sleep: $F_{2,71}$=4.44, *P*=.02; delta sleep ratio: $F_{2,71}$=3.11, *P*=.05). In each case the group with type 1 abnormalities had significantly lower values than the other 2 groups, which were indistinguishable.

The proportion of patients with abnormal type 1 profiles was almost identical at T_1 (30 of 78) and T_2 (29 of 78). There was highly significant concordance (ie, stability) of these classifications between time points (78% agreement; Mantel-Haenszel χ^2=22.2, *df*=1, *P*<.0001).

SLEEP DISTURBANCES PREDICTED TO BE STATE-DEPENDENT (TYPE 2 ABNORMALITIES)

The ANCOVA 3-way interaction term, the time and remission group and the sleep group and remission group 2-way interactions, and the main effect for remission status were not statistically significant. There was, how-

Table 1. Demographic and Pretreatment Clinical Characteristics*

Characteristic	Total (N=90)	Completers (n=78)	Noncompleters (n=12)	*t* or χ^2
Sex, No. (%)				
Male	**40** (44)	33 (42)	7 (58)	1.08†
Female	**50** (56)	45 (58)	5 (42)	
Age, y	38.4 (9.7)	38.0 (10.0)	41.0 (8.0)	0.98‡
Education, y	14.6 (2.5)	14.5 (2.6)	15.2 (2.4)	−0.88‡
No. of previous episodes	1.5 (2.2)	1.5 (2.3)	1.0 (1.5)	−0.80‡
Age at onset of first episode, y	31.7 (11.0)	31.3 (10.6)	34.9 (13.5)	1.07‡
Recurrent subtype, No. (%)				
No	46 (51)	38 (49)	8 (67)	1.34†
Yes	44 (49)	40 (51)	4 (33)	
Pretreatment ratings				
Hamilton Rating Scale for Depression	20.2 (4.4)	20.5 (4.1)	18.2 (6.0)	−1.71‡
Global Assessment Scale	53.5 (8.8)	53.2 (7.4)	55.7 (15.1)	0.55‡§
Beck Depression Inventory	25.9 (8.0)	26.0 (7.7)	24.8 (10.1)	−0.49‡
Posttreatment ratings				
Hamilton Rating Scale for Depression	5.7 (5.6)	5.5 (5.3)	6.6 (7.9)	0.44‡℠§
Global Assessment Scale	81.7 (14.3)	82.0 (13.5)	79.7 (19.2)	−0.52‡§
Beck Depression Inventory	8.2 (8.7)	8.0 (8.5)	9.6 (10.4)	0.59‡§

*Data are given as mean (±SD) unless otherwise noted.
†df=1.
‡df=88.
§Significant heterogeneity of variance (noncompleters>completers).

Table 2. Pretreatment Electroencephalographic Sleep Variables in Abnormal and Normal Type 2 Groups*

	Abnormal (n=40)	Normal (n=50)	*t* (*df*=88)
Composite score variables			
Sleep efficiency, %†	82.2 (8.4)	93.0 (3.6)	−9.07‖
REM latency, min‡	63.4 (17.2)	75.4 (22.4)	−2.81¶
REM density, min/units‡	1.69 (0.48)	1.31 (0.32)	4.25‖
Sleep continuity			
Time asleep, min	355.5 (51.6)	402.8 (41.1)	−4.84‖
Sleep latency, min†	26.4 (18.3)	14.3 (8.6)	4.04‖
Time awake, min‡	51.4 (37.4)	16.3 (13.9)	6.76‖
No. of awakenings	6.8 (2.8)	5.2 (3.0)	2.63¶
Time awake in last 2 h, min‡	25.1 (17.4)	8.0 (6.6)	6.58‖
Non-REM sleep			
Stage 1, %‡	5.0 (2.1)	4.3 (2.9)	1.92
Stage 2, %	61.4 (8.3)	58.9 (9.0)	1.36
Slow wave sleep, %‡	10.5 (7.1)	13.8 (9.3)	−1.46
Automated average delta counts‡§	18.8 (8.3)	21.1 (10.4)	−1.04
Automated delta sleep ratio†§	1.54 (0.76)	1.32 (0.55)	1.37
REM measures			
REM, %	23.2 (5.5)	22.8 (5.2)	0.31
REM, min	83.6 (25.6)	92.4 (24.1)	−1.68
REM activity, units‡	145.4 (79.5)	123.2 (47.0)	1.53
No. of REM periods	3.5 (0.8)	3.9 (0.8)	−2.69¶
REM intensity	0.40 (0.18)	0.30 (0.10)	2.98¶
Automated average REM counts (whole night)‡§	7.64 (2.90)	6.04 (2.67)	2.82¶
Automated average REM counts (first REM period)‡§	6.02 (3.62)	4.51 (3.18)	2.37#

*Data are given as mean (SD). REM indicates rapid eye movement.
†Log transformation used in statistical test.
‡Square root transformation used in statistical test.
§Cell sizes are 40 and 49, respectively; df=87.
‖P≤.001.
¶P≤.01.
#P≤.05.

Table 3. Multivariate Analysis of Type 1 (Traitlike) Sleep Abnormalities*

	Abnormal Group				Normal Group				Univariate ANCOVAs (F Ratios)	
	Remitted (n=16)		Unremitted (n=12)		Remitted (n=27)		Unremitted (n=20)			
Sleep Variables	T_1	T_2	T_1	T_2	T_1	T_2	T_1	T_2	Age (*df*=1,70)	Sleep (*df*=1,70)
REM latency†	52.2 (9.68)	62.7 (14.5)	56.8 (13.2)	61.3 (13.5)	80.3 (19.9)	75.8 (27.0)	80.7 (22.9)	81.7 (50.7)	0.47	20.01‡
Slow wave sleep, %†	7.95 (6.88)	7.33 (5.07)	9.07 (9.64)	6.14 (6.70)	15.8 (7.8)	13.9 (6.18)	15.0 (7.09)	13.8 (7.36)	3.06	20.96‡
Delta sleep ratio§	1.25 (0.71)	1.22 (0.47)	1.38 (0.83)	1.31 (0.39)	1.44 (0.48)	1.54 (0.51)	1.76 (0.69)	1.55 (0.77)	2.40	3.48

*Data are given as mean (±SD). MANCOVA indicates multivariate analysis of covariance; ANOVA, analysis of covariance; T_1, baseline, and T_2, posttreatment. MANCOVA: age, $F=2.70$, P≤.05; time, sleep, and remission, $F_{3,69}=0.80$; time and remission, $F_{3,69}=0.67$; sleep and remission, $F_{3,68}=0.01$; time and sleep, $F_{3,69}=1.17$; remission, $F_{3,68}=0.68$; sleep, $F_{3,68}=16.61$, P≤.01; time, $F_{3,69}=1.36$.
†Square root transformation used for statistical test.
‡P≤.001.
§Log transformation used for statistical test.

ever, the predicted interaction of time and sleep group (**Table 4**). Whereas normal scores did not change significantly ($t_{43}=-1.48$, $P=.16$), the abnormal type 2 scores increased (ie, improved) significantly ($t_{33}=5.13$, $P<.0001$). This resulted in a highly significant between-group difference in change scores from T_1 to T_2 (normal group: mean=−0.37, SD=1.66; abnormal group: mean=2.02, SD=2.30; $t_{76}=5.34$, $P=.001$).

A MANCOVA was next performed on the individual type 2 variables (**Table 5**). The overall results were identical to those using the composite score. Univariate tests revealed that the significant time and sleep group interaction was largely due to improved sleep efficiency, although there was also a trend for REM density to decrease.

At T_2, the composite scores of the patients who remitted (abnormal type 2, n=16; normal type 2, n=27)

Table 4. Analysis of the Effects of Time, Remission Group, and Sleep Group on the Type 2 Composite Variable*

Pretreatment Classification	Remitted (n=43) T_1	Remitted (n=43) T_2	Unremitted (n=35) T_1	Unremitted (n=35) T_2		ANCOVA Summary (F Ratios, *df*, and *P*) Age	Time, Remission, and Sleep	Time and Remission	Remission and Sleep	Time and Sleep	Remission	Sleep†	Time†
Abnormal‡ (n=34)	−1.38 (1.24)	0.27 (1.91)	−2.26 (2.78)	0.93 (1.47)	F	9.61	2.03	0.02	2.05	28.9§	0.09	51.1	11.9
Normal§ (n=44)	1.59 (1.33)	1.44 (1.40)	2.11 (1.39)	1.38 (1.40)	*df*	1,73	1,74	1,74	1,73	1,74	1,73	1,73	1,74
					P	.003	.16	.89	.16	<.001	.77	<.001	<.001

*Data are given as mean (SD). T_1 indicates baseline; T_2, posttreatment.
†Main effects are not interpreted because of significant interaction.
‡Cell sizes: remitted, n=16; unremitted, n=18.
§Cell sizes: remitted, n=27; unremitted, n=17.

Table 5. Multivariate Analysis of Type 2 (State-Dependent) Sleep Variables*

Sleep Variables	Abnormal Group: Remitted (n=16) T_1	Abnormal Group: Remitted (n=16) T_2	Abnormal Group: Unremitted (n=18) T_1	Abnormal Group: Unremitted (n=18) T_2	Normal Group: Remitted (n=27) T_1	Normal Group: Remitted (n=27) T_2	Normal Group: Unremitted (n=17) T_1	Normal Group: Unremitted (n=17) T_2	Univariate ANCOVAs (F Ratios): Age (*df*=1,73)	Univariate ANCOVAs (F Ratios): Time and Sleep (*df*=1,74)
Sleep Efficiency†	83.6 (7.48)	88.9 (7.06)	81.0 (9.89)	88.8 (4.89)	92.8 (3.72)	92.3 (4.15)	94.0 (3.52)	93.3 (4.74)	7.53‡	14.97§
REM Latency‖	63.4 (20.2)	69.1 (30.6)	62.5 (16.1)	67.8 (19.0)	73.2 (21.9)	72.0 (19.3)	78.8 (25.2)	80.9 (57.7)	0.56	1.22
REM Density‖	1.59 (0.34)	1.48 (0.44)	1.75 (0.60)	1.52 (0.42)	1.33 (0.26)	1.31 (0.37)	1.35 (0.37)	1.34 (0.35)	0.66	2.87

*Data are given as mean (SD). MANCOVA indicates multivariate analysis of covariance; ANCOVA, analysis of covariance; T_1, baseline; T_2, posttreatment; and REM, rapid eye movement. MANCOVA: age, $F_{3,71}=4.30$, P<.01; time, sleep, and remission, $F_{3,72}=0.23$; time and remission; $F_{3,72}=0.02$; sleep and remission, $F_{3,71}=1.57$; time and sleep, $F_{3,72}=6.17$, P<.001; remission, $F_{3,71}=0.86$; sleep (main effects not interpreted because of significant interaction), $F_{3,71}=19.23$; time (main effects not interpreted because of significant interaction), $F_{3,72}=5.75$.
†Log transformation used in statistical test.
‡P<.01.
§P<.001.
‖Square root transformation used in statistical test.

and the controls (n=27) did not differ significantly ($F_{2,65}=2.38$, $P=.10$). However, the patients with abnormal type 2 profiles who remitted had significantly lower scores than the control group (mean=0.27, SD=1.91 vs mean=1.58, SD=2.00; $t_{41}=2.12$, $P=.04$).

Consistent with the results described above, the proportion of patients with abnormal type 2 profiles decreased significantly from T_1 (34 of 78) to T_2 (22 of 78) (Mantel-Haenszel $\chi^2=4.00$, $df=1$, $P=.05$). Concordance was high (84% [37/44]) among patients with normal T_1 profiles, whereas 56% (19/34) of those with abnormal scores at T_1 were reclassified as normal at T_2. This difference in stability was highly significant (Mantel-Haenszel $\chi^2=7.44$, $df=1$, $P=.006$).

COMMENT

Our study is the first prospective test of the model by Kupfer and Ehlers[4] of EEG sleep disturbance in patients with depression. We found that the proposed type 1 variables—reduced REM latency, decreased delta sleep ratio, and decreased slow wave sleep (%)—were stable or traitlike. Our research design does not, of course, permit differentiation between true traits and abnormalities that may have developed as "scars" or sequelae of depressive episodes.[2-4] However, other groups have found evidence of traitlike behavior using family studies[8-11] and high-risk paradigms.[12-16] Moreover, no evidence of progressive worsening or "scarring" of type 1 variables was found in a recent study comparing first-episode and highly recurrent depressions.[44]

Although reduced REM latency and decreased slow wave sleep (%) were stable in this study, they are not necessarily static phenomena. For example, an age-dependent decline of both measures is well documented.[45-48] Reductions of REM latency and slow wave sleep (%) also can be induced by environmental[49] and pharmacological[50] manipulations. Therefore, multiple mechanisms are probably involved in the genesis of these sleep abnormalities. What role, then, might type 1 disturbances play in depressive vulnerability? Several lines of research document the importance of the first non-REM period for the restorative quality of sleep, processing affectively charged memories, and maintaining optimal neuropsychological performance (see, eg, Horne[51]). The type 1 profile also is associated with blunted nocturnal growth hormone secretion, another state-independent correlate of depression.[4,52] Decreased slow

wave activity during the first non-REM period also could serve as a faulty "barrier" against intrusion of the more neurophysiologically arousing REM sleep.[2] Thus, people with type 1 sleep disturbances may have increased vulnerability to depression because of persistent information processing deficits or difficulties modulating affect in response to significant stressors.[5,51]

The incomplete normalization of the type 2 variables is not fully consistent with the predictions of the Kupfer-Ehlers model.[4] Only a "thin" majority of the abnormal type 2 profiles had normalized at T_2, and the remitted and unremitted groups had comparable improvements. Demonstration of a close relationship between improvement in sleep profiles and quality of remission would have been stronger evidence of state dependence. Perhaps the unremitted patients were not symptomatic enough to permit differentiation of neurophysiological parameters. Specifically, the 8-point HRSD difference between the remitted and unremitted groups at T_2 is only about 40% of the magnitude that typically separates controls and untreated depressed patients. Conversely, the time between T_1 and T_2 studies may have been too short to permit full recovery. Differential attrition of unremitted patients with abnormal T_1 studies also may have compromised the power to detect between-group differences,[5] although the similarity of cell means is inconsistent with a type II error. Kraemer et al[20] suggest that multiple studies across several clinical states may be necessary to completely disentangle state-dependent and traitlike abnormalities.

Is the partial normalization of type 2 disturbances clinically significant? The observed improvement in sleep efficiency has obvious beneficial effects. Most effective antidepressant therapies also suppress REM sleep,[1,2] although the physiological benefit of this effect is less immediately obvious. Some evidence links increased phasic REM sleep to intensity of dysphoric affects, perhaps resulting from an imbalance of serotoninergic and cholinergic neurotransmission.[2] Consistent with this notion, an earlier study showed that the reduction in phasic REM sleep following CBT was correlated with improvements in affective and cognitive symptoms.[53] Buysse et al[14] similarly observed a small reduction in phasic REM sleep in their study of 42 depressed patients treated with interpersonal psychotherapy. The reduction of REM sleep observed after psychotherapy, however, is much smaller than that observed with use of most antidepressant medications.[1,2]

Two limitations of this study warrant comment. First, the results observed in this relatively uncomplicated group of outpatients may not be fully generalizable to unselected populations. Second, without parallel pharmacotherapy or placebo groups, it is possible that the observed changes in sleep resulted from spontaneous remission or repeated testing. However, we found no effect for repeated testing in an earlier study of controls,[26] and it is unlikely that a 55% remission rate is attributable to spontaneous remission.[54] The predicted stability of the type 1 sleep disturbances also is not consistent with regression to the mean.

Although improvements in clinical ratings of neurovegetative symptoms are well documented, evidence that psychotherapy exerts comparable effects on more direct measures of brain function has been slow to emerge. When our current results are added to those of Baker and colleagues[55,56] (ie, normalization of cerebral glucose metabolism after behavioral treatment of obsessive-compulsive disorder), Shear et al[57] (ie, reduced vulnerability to lactate-induced panic attacks after CBT), and Joffe et al[58] (ie, decreased thyroid hormone levels after CBT for depression), it seems probable that modern forms of psychotherapy do have significant neurobiological effects. Nevertheless, the persistence of sleep abnormalities in remitted, but unmedicated, patients may have worrisome prognostic implications.[5,12-14,21] In future studies we will examine whether residual sleep abnormalities convey a greater risk of relapse during naturalistic follow-up and, among patients who remain well, whether sleep profiles eventually will normalize.

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