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All-Night Electroencephalographic Sleep and Cranial Computed Tomography in Depression

A Study of Unipolar and Bipolar Patients

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Summary. All-night electroencephalographic (EEG) sleep recording and cranial computed tomography were performed in 24 inpatients with major depression (14 unipolar, 10 bipolar). The patients showed the characteristic "depression-like" EEG sleep alterations and their ventricular brain ratio (VBR) was increased compared with the control subjects. No major differences were found between the unipolar and the bipolar groups. There was a close and positive association between the VBR values and several measures of slow wave sleep. It is hypothesized that this relationship is due to an altered function of the limbic-hypothalamic-pituitary-adrenocortical axis in depression that affects both EEG sleep and brain morphology.

Key words: Major depression – Unipolar disorder – Bipolar disorder – Sleep – Cranial computed tomography

Introduction

The electroencephalographic (EEG) sleep pattern in major depression is characterized by numerous alterations, including disturbed sleep continuity, changes in slow wave sleep (SWS), early onset of rapid eye movement (REM) sleep and increased density of rapid eye movements (REM density) during REM sleep (see: Gillin et al., 1984; Reynolds and Kupfer 1987). Most of these alterations occur for the first time around the fourth decade of life and then become progressively more pronounced with increasing age (Gillin et al., 1981; Knowles and McLean 1990; Lauer et al., 1991). The only exception is the REM density, which is consistently elevated in depressed patients of any age and, thus, is not affected by the process of aging (Lauer et al., 1991).

There are few studies comparing the EEG sleep of patients with unipolar and bipolar depression. A review of both the controlled and the uncontrolled investigations, however, reveals relatively consistent findings. The sleep continuity indices are reported to be either similar in the two subgroups of patients or slightly more disturbed in those with unipolar depression (Duncan et al., 1979; Feinberg et al., 1982; Giles et al., 1986; de Maertelaer et al., 1987; Kerkhofs et al., 1988). The sleep architecture appears to be similar in both subtypes, although the power of the whole EEG spectrum, in particular in the delta band, is described as being decreased in the unipolar group (Borbély et al., 1984) but normal in the bipolar group (Mendelson et al., 1987). Regarding REM sleep parameters, no differences between the two subtypes have been reported. The "depression-like" EEG sleep alterations have been found in both groups, although they appear to be somewhat more pronounced in the unipolar group (Duncan et al., 1979; de Maertelaer et al., 1987).

Compared with other psychiatric disorders (e.g., schizophrenia and eating disorders), investigations of brain morphology in affective illness are less frequent, perhaps because the affective disorders tend to have an episodic rather than a chronic, deteriorating course, where fixed lesions may play an important role. On the other hand, affective syndromes can often be observed in patients with neurological diseases, for example, neurodegenerative diseases (see: McNamara, 1991; Cummings, 1992), raising the question of whether structural brain alterations may be involved in the pathogenesis of affective disorders.

The majority of the computed tomography (CT) studies performed in depressed patients show an increase in the ventricular brain ratio (VBR) and in other CT indices (e.g., width of the cortical and cerebellar sulci; see: Jeste et al., 1988). In regard to the unipolar and bipolar subgroups several controlled studies yielded either an increase in ventricular size (e.g., Nasrallah et al., 1982; Targum et al., 1983; Luchins et al., 1984; Pearlson et al., 1984; Shima et al., 1984) or more or less normal VBR values (e.g., Scott et al., 1983; Rossi et al., 1987; Dewan et al., 1988; Iacono et al., 1988; van den Bossche et al., 1991). These inconsistencies may be partly related to

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methodological differences (e.g., equipment, scanning and measuring procedures, criteria for defining ventricular enlargement), making between-study comparisons difficult. To our knowledge, there have been only four studies with direct comparison of the VBR values of unipolar and bipolar patients (Dolan et al., 1985; Schlegel and Kretzschmar, 1987; Roy-Byrne et al., 1988; Andreasen et al., 1990) and none of these studies showed a difference. Furthermore, Dolan and co-workers (1985) found significantly larger ventricles in the two groups of patients than in the control subjects, whereas Andreasen et al. (1990) restricted this observation to men with bipolar depression. Schlegel and Kretzschmar (1987), on the other hand, found no differences in VBR values between unipolar, bipolar and control subjects. Thus, it is still a matter of debrate whether there is significant ventricular enlargement in unipolar or bipolar patients.

Ventricular enlargement reflects alterations in subcortical brain structures, including the basal ganglia, which are alleged to be involved in the regulation of sleep and arousal (see: McGinty, 1985; Jones, 1989). Consequently, such structural alterations could be accompanied by changes in the EEG sleep pattern. In support of this assumption is our recent finding in Huntington's disease of a close association between ventricular enlargement (as an experession of caudate atrophy) and an impairment of EEG sleep (Wiegand et al., 1991a). A close relationship between ventricular size and various sleep EEG parameters has also been demonstrated in several other neuropsychiatric disorders, for example, in human immunodeficiency virus (HIV) infection (Wiegand et al., 1991b), schizophrenia (van Kammen et al., 1988; Keshavan et al., 1991), anxiety disorders (Lauer and Krieg, 1992a), eating disorders (Lauer et al., 1989), post-traumatic stress disorders (Peters et al., 1990) and alcohol dependence (Ishibashi et al., 1987). Although not consistently across the studies, enlarged ventricles were found to be closely correlated with changes in the indices of sleep continuity, the amount of SWS, or the amount of REM sleep. All these observations emphasize the association of structural brain alterations and changes in EEG sleep pattern, at least during the acute state of illness. The current knowledge of whether or not the alterations of both brain morphology and EEG sleep persist during remission is extremely scanty and conflicting. In remitted patients with an affective disorder, both a normalization and a persistence of the EEG sleep alterations have been described (Knowles et al., 1986; Rush et al., 1986; Giles et al. 1987; Riemann and Berger, 1989; Steiger et al., 1989). In regard to brain morphology no follow-up investigations have so far been performed on depressed patients or on most of the neuropsychiatric disorders mentioned above. In eating disorder patients, however, an improvement of both the structural brain alterations (Krieg et al., 1988) and the sleep quality (Lauer and Krieg, 1992b) is reported after weight gain, further pointing towards an association of brain morphology and EEG sleep.

Although patients with affective disorders show clear changes in the nocturnal EEG sleep pattern and although alterations of brain morphology and metabolism have been described in such patients (see: McDonald and Krishnan, 1992), to our knowledge the present study is the first one to deal with the issue of whether there is a relation between ventricular size and EEG sleep parameters in affective disorders. To control for possible differences between unipolarity and bipolarity, this issue was further addressed in unipolar and bipolar disorders separately.

Methods

Subjects

The subjects were 24 inpatients with affective disorders (age range: 20–57 years; 12 women, 12 men). Fourteen patients suffered from a major depression, recurrent subtype, and the remaining 10 patients had a bipolar I disorder, depressed subtype. None of the patients fulfilled the criteria for a current/lifetime diagnosis of substance abuse. The patients' diagnoses were confirmed by the Structured Clinical Interview according to DSM-III-R (SCID; German version: Wittchen et al., 1990). Furthermore, the patients fulfilled the Research Diagnostic Criteria (RDC; German version: Klein, 1982) for either unipolar or bipolar disorder. According to these criteria, all patients suffered from a current major depressive episode, endogenous subtype. The severity of depressive symptomatology was assessed with the Inpatient Multidimensional Psychiatric Rating Scale (IMPS; German version: Hiller et al., 1986), second-order factor "depressive symptomatology (IMPS-D). The patients were off medication for at least 1 week prior to the investigation; we recently demonstrated that for all-night polysomnography this is a sufficient washout period to exclude possible effects of prior medication (Lauer and Pollmächer, 1992).

Twelve healthy subjects (age range: 23–60 years; 5 women, 7 men) with no personal or family history of psychiatric disorders served as a contol group for the polysomnographic investigation. As radiation rules prohibit CT examination on healthy volunteers, the control group for the CT measurements comprised 12 subjects (age range: 18–48 years; 8 women, 4 men) with minor health problems (e.g., headache, vertigo) on whom a CT examination was performed to exclude any cerebral process.

In all study participants physical illness was ruled out by a thorough physical examination and laboratory tests (e.g. ECG, blood analysis, and urinary drug screening). Subjects who complained of symptoms suggestive of narcolepsy, sleep apnoea, or restless legs syndrome were not included in the study protocol. Furthermore, none of the participants had been subjected to sleep deprivation, excessive alcohol or caffeine intake, shift work, or time shifts (≥ 3 h) during the 3 months preceding the study period.

Polysomnography

All subjects slept in our sleep research unit for two consecutive nights. After one night of habituation (including attachment of electrodes), the sleep of the second night was polygraphically recorded and visually scored according to standard procedure (Rechtschaffen and Kales, 1968); scoring was done by a trained technician who was blind to the clinical and CT data. The EEG sleep parameters routinely calculated have been defined elsewhere (Lauer et al., 1991). In addition, we computed the SWS latency (time from sleep onset till the first occurrence of stage-3 sleep) and the total and the relative amount of time awake and SWS during the individual non-REM periods.

Cranial CT

CT scans were obtained by a General Electric Scanner 9800, using the 256×256 matrix and a 10-mm slice thickness. Measurements

Table 1a. EEG sleep parameters (mean ± SD) in 24 inpatients with affective disorders and 12 healthy subjects

	Patients with affective disorder ($n = 24$)	Healthy subjects ($n = 12$)	Ancova	
			Group effects F(1)	Age effects F(1)
Age (years)	39.0 ± 11.3	36.4 ± 12.6	0.40	–
IMPS-D (% max. value)	39.5 ± 7.9	–	–	–
Sleep period time (SPT; min)	416.6 ± 64.2	433.5 ± 34.3	0.44	4.32[a]
Sleep efficiency index (%)	78.4 ± 17.6	91.1 ± 7.4	5.45[a]	12.43[b]
Sleep onset latency (min)	21.7 ± 13.4	17.1 ± 8.1	1.25	0.24
SWS latency (min)	42.0 ± 36.0	18.1 ± 9.1	4.21[a]	2.82
Number of awakenings	16.1 ± 15.1	7.5 ± 5.6	3.62	2.94
Intermittent time awake (min)	49.7 ± 45.1	23.9 ± 28.5	3.35	8.09[b]
REM latency (min)	53.2 ± 36.8	80.8 ± 19.5	6.02[a]	17.98[c]
Mean REM density index	3.7 ± 1.1	2.4 ± 1.1	11.07[b]	0.68
Stage-3 sleep (%SPT)	6.2 ± 4.5	8.0 ± 5.5	0.72	7.11[a]
Stage-4 sleep (%SPT)	4.2 ± 5.7	4.2 ± 4.6	0.20	16.42[c]
SWS (%SPT)	10.4 ± 9.2	12.2 ± 8.7	0.06	15.90[c]
REM sleep (%SPT)	20.2 ± 6.0	16.8 ± 4.7	2.95	1.23
Movement time (%SPT)	0.5 ± 0.5	0.7 ± 0.5	1.34	6.87[a]
First sleep cycle				
Cycle duration (min)	79.1 ± 39.3	98.7 ± 17.3	2.21	8.44[b]
REM period (min)	25.9 ± 19.7	17.9 ± 9.3	1.44	2.15
Time awake (% non-REMP)	4.7 ± 14.2	2.9 ± 2.4	0.35	2.12
SWS (% non-REMP)	21.4 ± 27.9	29.0 ± 23.4	0.28	19.80[c]
REM density index	3.3 ± 1.5	1.9 ± 1.0	8.73[b]	0.21
Second sleep cycle				
Cycle duration (min)	101.5 ± 32.6	103.8 ± 26.9	0.06	0.12
non-REM period (min)	77.9 ± 24.2	86.6 ± 23.6	0.97	0.04
REM period (min)	23.6 ± 13.3	17.3 ± 11.1	1.68	1.54
Time awake (% non-REMP)	7.0 ± 11.0	5.0 ± 11.2	0.12	2.81
SWS (% non-REMP)	22.8 ± 19.2	24.4 ± 23.4	0.01	1.50
REM density index	3.6 ± 1.3	2.3 ± 1.6	6.62[a]	0.42
Third sleep cycle				
Cycle duration (min)	111.3 ± 39.3	93.4 ± 27.3	1.88	0.07
non-REM period (min)	84.1 ± 36.4	67.8 ± 22.1	1.88	0.10
REM period (min)	27.3 ± 13.4	25.6 ± 10.6	0.14	0.00
Time awake (% non-REMP)	11.2 ± 18.4	4.7 ± 9.2	1.15	2.42
SWS (% non-REMP)	8.7 ± 15.8	8.5 ± 10.0	0.00	0.21
REM density index	3.6 ± 1.3	2.7 ± 1.4	4.33[a]	2.68

IMPS-D, Inpatient Multidimensional Psychiatric Scale, factor "depressive symptomatology"; SWS, slow wave sleep; REM, rapid eye movement sleep; non-REMP, non-REM period; –, not tested; [a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$

Table 1b. Ventricular brain ratio in 24 inpatients with affective disorders and 12 control subjects

	Patients with affective disorders ($n = 24$)	Control subjects ($n = 12$)	Ancova	
			Group effects F(1)	Age effects F(1)
Age (years)	39.0 ± 11.3	32.7 ± 9.7	4.39[a]	–
Ventricular brain ratio (%)	4.92 ± 3.28	3.13 ± 0.39	7.12[a]	0.09

–, not tested; [a] $P < 0.05$

for assessing the ventricular brain ratio (VBR) were performed on a scan through the region of the cella media of the lateral ventricles. The VBR was calculated with a pixel-density method on the computer console as previously described in detail (Krieg et al., 1988, 1989). With this method, inaccuracies resulting from visual tracing of the ventricles or from a possible bias of the examiner can be ruled out. With reference to our large normative data base (Krieg et al., 1988), we consider a VBR value less than 4.7% to be "normal". Owing to unreliable results, linear measurements for evaluating the width of cortical sulci were not carried out.

Table 2. EEG sleep parameters (mean ± SD) in 14 depressed inpatients with "normal" VBR values and 10 depressed inpatients with elevated VBR values

	Ventricular brain ratio		Ancova		Tukey's test	
	≤4.70% ($n = 14$)	>4.70% ($n = 10$)	Group effects F(1)	Age effects F(1)	VBR ≤4.7% vs healthy subjects	VBR >4.7% vs healthy subjects
Age (years)	38.9 ± 11.8	39.3 ± 11.2	0.01	–	–	–
Duration of illness (years)	4.8 ± 5.1	5.3 ± 5.7	0.10	–	–	–
Number of episodes	2.7 ± 3.2	3.1 ± 4.1	0.15	–	–	–
IMPS-D (% max. value)	40.9 ± 8.0	41.3 ± 5.4	0.07	0.13	–	–
VBR (%)	2.61 ± 1.18	8.16 ± 2.33	–	–		*
Sleep period time (SPT; min)	408.1 ± 80.1	428.6 ± 31.2	0.70	3.37		
Sleep efficiency index (%)	77.4 ± 20.0	78.9 ± 14.5	0.20	8.54[b]	*	*
Sleep onset latency (min)	21.7 ± 15.2	21.6 ± 11.2	0.00	0.01		
SWS latency (min)	41.1 ± 34.7	43.0 ± 39.4	0.00	0.88	*	*
Number of awakenings	16.9 ± 14.7	15.1 ± 16.3	0.09	1.54		
Intermittent time awake (min)	48.0 ± 45.0	52.2 ± 47.7	0.04	3.59		
REM latency (min)	52.5 ± 34.8	54.2 ± 41.4	0.05	15.78[b]	*	*
Mean REM density index	3.5 ± 0.7	3.9 ± 1.5	0.55	0.67	*	*
Stage-3 sleep (%SPT)	4.6 ± 3.6	8.3 ± 5.0	5.51[a]	4.87[a]	*	
Stage-4 sleep (%SPT)	3.3 ± 5.2	5.5 ± 6.5	1.35	10.78[b]		
SWS (%SPT)	7.9 ± 7.3	13.8 ± 10.7	4.22[a]	10.90[b]	*	
REM sleep (%SPT)	20.0 ± 6.6	20.4 ± 5.4	0.02	0.16		
First sleep cycle						
Time awake (% non-REMP)	5.1 ± 17.2	4.0 ± 9.2	0.02	2.96		
SWS (% non-REMP)	18.0 ± 27.7	26.1 ± 29.0	0.74	8.58[b]		
Second sleep cycle						
Time awake (% non-REMP)	8.2 ± 13.3	5.3 ± 7.0	0.47	2.80		
SWS (% non-REMP)	16.8 ± 14.4	31.2 ± 22.5	4.35[a]	2.14	*	
Third sleep cycle						
Time awake (% non-REMP)	9.8 ± 14.8	13.3 ± 23.4	0.21	0.86		
SWS (% non-REMP)	2.3 ± 2.9	17.9 ± 22.0	6.24[a]	0.27	*	

IMPS-D, Inpatient Multidimensional Psychiatric Scale, factor "depressive symptomatology"; VBR, ventricular brain ratio; SWS, slow wave sleep; REM, rapid eye movement sleep; non-REMP, non-REM period. ANCOVA, –, not tested; [a] $P < 0.05$, [b] $P < 0.01$; Tukey's test, *significant

Statistical Evaluation

Besides descriptive statistics (mean ± SD), a one-way analysis of covariance (ANCOVA) with age as the covariate was used to test for differences among the groups. In the case of comparisons of three samples, *a posteriori* group-by-group comparisons were calculated using Tukey's test to control for the increased Type-I error rate. In addition, Pearson correlation coefficients were calculated to assess associations among patient characteristics, EEG sleep parameters, and VBR values.

Results

Polysomnography

The patients and the healthy volunteers did not differ in age or gender (Table 1a).

The sleep efficiency index was significantly lower in the patients. This was mainly due to an increased intermittent time awake together with more frequent nocturnal awakenings; the latter differences, however, approximated the level of significance ($P = 0.07$ and $P = 0.06$, respectively). Regarding sleep architecture, only the relative amount of REM sleep tended to be increased in the patients ($P = 0.09$); further parameters, i.e. the relative and absolute amounts of slow wave sleep, did not differ between the patients and the control subjects. However, the patients did show a significantly prolonged SWS latency. The mean REM latency was shortened and the mean REM density index was increased in the patients. Analysis of the first three sleep cycles showed that the REM density indices for the respective REM periods were significantly increased. All other parameters calculated (duration of the cycles and of the respective non-REM and REM periods, and the absolute and relative amount of time awake and slow wave sleep) did not differ significantly between the patients and the controls.

There were significant age effects on nearly all sleep continuity parameters (sleep period time, sleep efficiency index, intermittent time awake, movement time), on REM latency, and on the SWS parameters for the total night as well as for the first sleep cycle; during the second sleep cycle, the effects of age on SWS were close to significance ($P = 0.06$).

Cranial CT

The gender distribution was similar in the patients and the control subjects. The mean age in the patient group

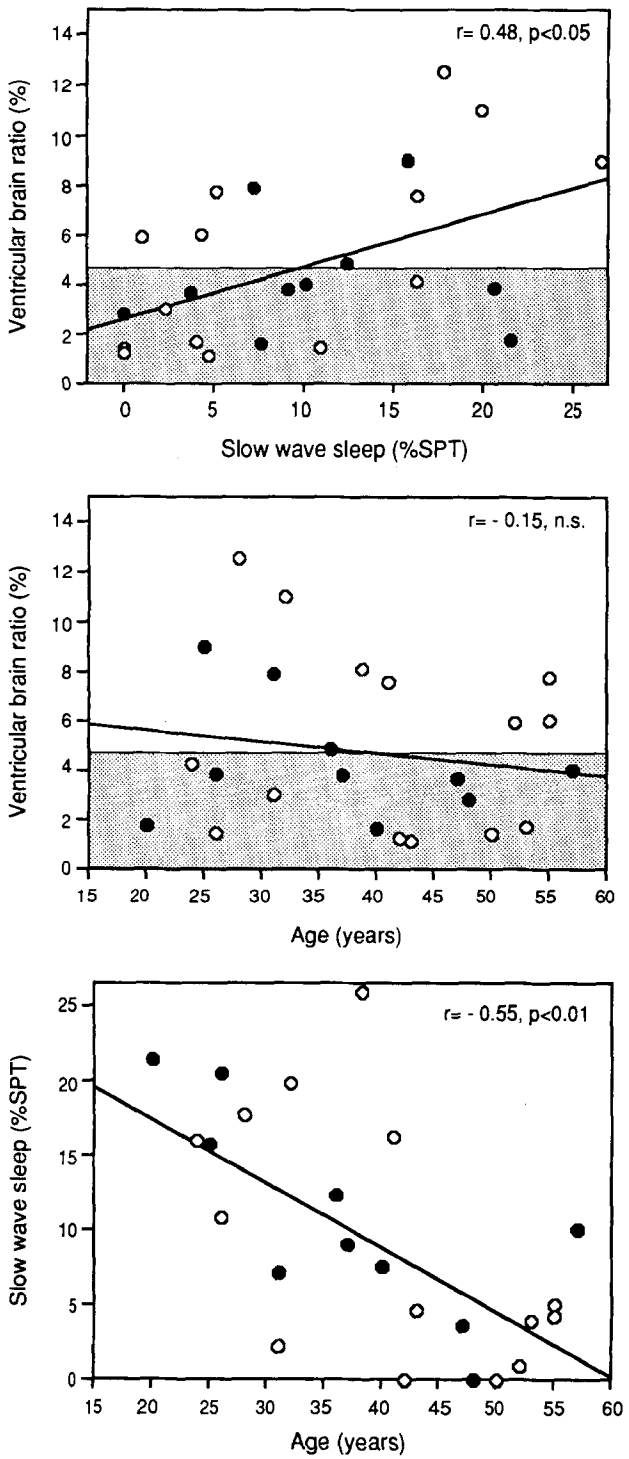

Fig. 1. Associations between ventricular size (VBR), slow wave sleep (% sleep period time), and age in 24 inpatients with major depressive disorder (*open circles:* patients with unipolar depression, $n = 14$; *closed circles:* patients with bipolar depression, $n = 10$; *shaded area:* normal range of the VBR values). The graphs clearly indicate that the observed association between ventricular size and slow wave sleep is not an indirect effect of age

was 6 years above that in the control group. This difference was significant (Table 1b). Therefore, the VBRs of the two groups were compared by performing an analysis of covariance to parcel out possible age effects. The VBR values of the patients were found to be significantly higher than those of the controls, and age was found to have almost no effect. More specifically, in 10 (42%) patients, but in none of the control subjects, the VBR values measured exceeded the cutoff point for a "normal" VBR value (4.7%). In the group of patients, low correlations were obtained between the VBR values and the variables age ($r = 0.15$), duration of illness ($r = 0.12$), number of episodes (Spearman rank correlation coefficient: $r = 0.17$), or severity of depressive symptomatology ($r = 0.01$). Regarding the control subjects, there was also no correlation between VBR values and age ($r = 0.31$).

EEG Sleep and VBR Measurements

Splitting the patient sample at the cutoff point of a "normal" VBR value (4.7%) resulted in two subsamples that were similar in age and gender [Yates corrected chi-square (1) $= 0.17$, n.s.], distribution of unipolarity and bipolarity [Yates corrected chi-square (1) $= 0.31$, n.s.], duration of illness, number of episodes, and severity of depressive symptomatology (Table 2).

Regarding EEG sleep parameters, the patients with an "abnormal" ventricular size showed a significantly greater amount of stage-3 sleep than those patients with a "normal" VBR value. Furthermore, the amount of SWS of the total night as well as of the second and third non-REM periods were significantly increased in those patients with VBR values higher than 4.7%. EEG sleep parameters related to either sleep continuity or REM sleep did not differ between the two subsamples. The only exception was a trend to a prolonged second REM period in the patients with enlarged ventricles ($P = 0.06$).

Each of the two subsamples differed from the healthy subjects in the same manner as reported above for the total sample of patients. In addition, the patients with "normal" VBR values had less stage-3 sleep and less SWS both during the total night and during the second and third sleep cycles than the control subjects. In the patients with "enlarged" ventricles, these SWS parameters did not differ from those of the healthy subjects.

Finally, the EEG sleep parameters affected by age were identical to those mentioned for the total sample.

Calculation of Pearson correlation coefficients yielded significant positive correlations between the VBR values and most of the SWS parameters, i.e., the amount of stage-3 sleep ($r = 0.60$, $P < 0.01$), the amount of SWS of the total night ($r = 0.48$, $P < 0.05$; see Fig. 1), and the amount of SWS during the second ($r = 0.54$, $P < 0.01$) and third ($r = 0.42$, $P < 0.05$) non-REM periods. The correlation coefficients between VBR values and the remaining EEG sleep parameters were far from significance.

Unipolarity Versus Bipolarity

The patient characteristics were similar in the unipolar and bipolar subgroups (Table 3).

Regarding the EEG sleep parameters, the unipolar patients had a lower sleep efficiency index. The two sub-

Table 3. EEG sleep parameters and VBR values (mean ± SD) in 14 inpatients with unipolar depression and 10 inpatients with bipolar depression

	Unipolar depression (UP) ($n = 14$)	Bipolar depression (BP) ($n = 10$)	Ancova			Tukey's tests	
			Group effects F(1)	Age effects F(1)	VBR effects F(1)	UP vs healthy subjects	BP
Age (years)	40.7 ± 11.2	36.7 ± 11.6	0.73	–	–	–	–
Duration of illness (years)	5.1 ± 5.4	4.7 ± 5.3	0.09	–	–	–	–
Number of episodes	2.5 ± 3.2	3.2 ± 4.1	0.43	–	–	–	–
IMPS-D (% max. value)	40.3 ± 4.1	41.6 ± 9.1	0.15	0.13	0.01	–	–
Ventricular brain ratio (%)	5.3 ± 3.8	4.4 ± 2.4	0.64	0.60	–	*	*
Sleep period time (SPT; min)	401.5 ± 78.1	437.7 ± 29.4	1.76	2.87	0.98		
Sleep efficiency index (%)	72.2 ± 19.4	87.2 ± 9.9	5.21[a]	9.23[b]	1.16	*	
Sleep onset latency (min)	24.8 ± 14.7	17.3 ± 10.7	2.01	0.10	0.00		
SWS latency (min)	37.7 ± 29.6	47.7 ± 44.4	0.76	0.90	0.04	*	*
Number of awakenings	17.3 ± 14.7	14.5 ± 16.3	0.10	1.24	0.31		
Intermittent time awake (min)	63.7 ± 48.7	30.1 ± 32.4	2.80	3.67	0.04	*	
REM latency (min)	55.4 ± 41.8	50.1 ± 30.4	1.16	14.34[b]	0.40	*	*
Mean REM density index	3.7 ± 1.4	3.6 ± 0.5	0.01	0.41	0.86	*	*
Stage-3 sleep (%SPT)	6.3 ± 5.4	6.0 ± 3.2	0.00	3.26	10.60[b]		
Stage-4 sleep (%SPT)	3.8 ± 5.9	4.8 ± 5.7	0.01	8.85[b]	1.14		
SWS (%SPT)	10.1 ± 10.7	10.8 ± 6.9	0.00	8.45[b]	5.47[a]		
REM sleep (%SPT)	19.2 ± 6.5	21.6 ± 5.2	1.29	0.22	0.23		
First sleep cycle							
Time awake (% non-REMP)	5.3 ± 17.2	3.7 ± 9.1	0.32	2.71	0.02		
SWS (% non-REMP)	18.3 ± 23.1	25.8 ± 34.5	0.10	7.34[b]	0.31		
Second sleep cycle							
Time awake (% non-REMP)	7.8 ± 7.7	5.8 ± 14.9	0.09	2.23	0.63		
SWS (% non-REMP)	20.8 ± 22.1	26.8 ± 14.2	1.55	1.22	7.91[b]		
Third sleep cycle							
Time awake (% non-REMP)	15.8 ± 22.2	5.7 ± 11.0	1.21	1.06	0.32		
SWS (% non-REMP)	10.8 ± 20.4	6.1 ± 7.9	0.18	0.01	4.27[a]		

IMPS-D, Inpatient Multidimensional Psychiatric Scale, factor "depressive symptomatology"; SWS, slow wave sleep; REM, rapid eye movement sleep; non-REMP, non-REM period. Ancova, –, not tested; [a] $P < 0.05$, [b] $P < 0.01$; Tukey's test, *significant

groups did not differ on any of the other parameters. In comparison with the control subjects, both subgroups showed a prolonged SWS latency, a reduced REM latency, and increased REM density indices during the total night as well as during the first and second REM periods. In addition, the unipolar patients had a lower sleep efficiency index and more intermittent time awake than the healthy volunteers.

Each of the two subsamples had significantly higher VBR values than the control subjects [$F(2) = 3.95$, $P < 0.05$]. The *a posteriori* Tukey's test revealed a significant difference between each patient sample and the control subjects.

ANCOVA with age and VBR values as covariates revealed the same group differences as mentioned earlier. Age had a significant effect on sleep efficiency, REM latency, the amount of stage-3 sleep, and the amount of SWS during the total night as well as during the first sleep cycle. Significant effects of the VBR values were observed on the amount of stage-3 sleep and on the amount of SWS during the total night as well as during the second and third sleep cycles.

Discussion

The present polysomnographic investigation of patients with affective disorders showed the EEG sleep pattern commonly reported in such samples with a broad age range: disturbed sleep maintenance, delayed onset of SWS, shortened REM latency and increased REM density. These changes in EEG sleep were similar in the unipolar and bipolar patients, with the exception that the former had more difficulties in maintaining sleep. The CT examination of the patients revealed a significantly increased mean VBR, a 42% rate of "abnormally" high VBR values and no differences between the unipolar and bipolar subtypes. The main finding of the study, however, was a close and positive association between the VBR values and most of the SWS parameters: the

patients with "enlarged" ventricles (VBR > 4.7%) spent more time in SWS than those with "normal" ventricles, whereby the latter group showed an altered pattern of SWS in comparison with the control subjects.

Our polysomnographic findings in affectively ill patients, including the effects of age on sleep, closely resemble those reported by numerous other authors (see: Gillin et al., 1981, 1984; Reynolds and Kupfer, 1987; Knowles and Mc Lean, 1990; Lauer et al., 1991) and, therefore, require less comment. A comparison of the unipolar and bipolar patients yielded a lower sleep efficiency index in the unipolar patients. Further indices of disturbed sleep continuity (sleep onset latency, intermittent wake time), however, were similar in the two subgroups, as were the measures of sleep architecture, REM latency and REM density. Compared with the healthy subjects, both subgroups of patients had EEG sleep alterations resembling those found in the total sample, with the exception that the decreased sleep efficiency index and the increased wake time were found only in the unipolar patients. These findings are in line with those reported in other controlled and uncontrolled studies (Duncan et al., 1979; Feinberg et al., 1982; Giles et al., 1986; de Maertelaer et al., 1987; Kerkhofs et al., 1988; Thase et al., 1989). It should be mentioned, however, that in one study (Jernajczyk, 1986) the REM latency was reported to be similar in bipolar patients and in healthy subjects; the author himself, however, claimed that this finding might be due to the rather mild depressive symptomatology of the patients studied. In accordance with the literature, our depressed patients displayed the commonly reported "depression-like" EEG sleep pattern. Furthermore, the changes were similar in the unipolar and bipolar patients, the only exception being a slightly more disturbed sleep efficiency in the unipolar depressives.

In 42% of the patients investigated, we observed VBR values that, according to our normative data base (Krieg et al., 1988), exceeded the cutoff point for a normal VBR. Furthermore, the mean VBR values of the patients were significantly higher than those of the control subjects. Both observations are in line with a recent review of the literature by Jeste et al. (1988), in which the authors state that about 30% of the patients with affective disorders had abnormally large ventricles and that the mean VBR of these patients was 1.5 times that of control subjects from the same studies. In respect to unipolarity and bipolarity, we found similar mean VBR values and an identical frequency of "enlarged" ventricles in the two subtypes of the disorder, which is consistent with the observations of other authors (Dolan et al., 1985; Schlegel and Kretzschmar, 1987; Roy-Byrne et al., 1988; Andreasen et al., 1990). In addition, both the unipolar and bipolar patients had higher mean VBR values than the control subjects. Dolan and co-workers (1985) reported similar findings; their study sample, however, consisted of mainly late middle-aged patients, in whom effects of age on ventricular size become obvious (Baron et al., 1976; Zatz et al., 1982). On the other hand, Schlegel and Kretzschmar (1987) observed VBR values in unipolar and bipolar patients that were similar to those of control subjects. Finally, Andreasen et al. (1990) reported the ventricular size to be enlarged only in bipolar (manic) men. In the present investigation, the three bipolar patients with "abnormally" high VBR values were indeed men; the remaining five bipolar men, however, had normal values, a finding that limits the observation of Andreasen et al. (1990) of a significant gender effect on the VBR of bipolar patients. Therefore, although the finding of enlarged ventricles in depression is not as unequivocal as are the EEG sleep abnormalities, the question arises of what factors cause or contribute to the development of the structural brain alterations in depression. Several studies, including the present one, report no evidence that the ventricular size in *affective disorders* is associated with duration or severity of illness, family history of psychiatric disorders, kind of prior medication, or history of alcohol or drug abuse (e.g., Dolan et al., 1985; Roy-Byrne et al., 1988; Schlegel et al., 1989a; Andreasen et al., 1990), although enlarged ventricles have been reported in chronic alcoholics (Ishibashi et al., 1987) and in chronic benzodiazepine abusers (Schmauss and Krieg, 1987).

A promising line of inquiry is the search for neurochemical correlates of ventricular enlargement. The main candidates are the hormones of the limbic-hypothalamic-pituitary-adrenocortical (LHPA) axis, the dysfunction of which is well documented in major depression (see: Holsboer, 1992). Although comparisons of the VBR values in DST-nonsuppressors and DST-suppressors yielded contradictory results (Targum et al., 1983; Rothschild et al., 1989; Schlegel et al., 1989b), a number of studies revealed evidence for a close and positive association between ventricular size and urinary/plasma concentration of cortisol in depressed patients (Kellner et al., 1983; Rothschild et al., 1989; Schlegel et al., 1989b) as well as in eating disorder patients (Krieg et al., 1988, 1989; Lauer et al., 1989). In addition, a close inverse association between ventricular size and the concentration of dopamine-beta-hydroxylase (which catalyzes the formation of noradrenaline from dopamine and the concentration of which is influenced by glucocorticoids; Rothschild et al., 1984) was also reported in depressed patients by Meltzer et al. (1984) and in schizophrenic patients by van Kammen et al. (1983). Therefore, in contrast to the clinical characteristics, which appear to add little information to the explanation of ventricular enlargement at least in affective disorders, biochemical correlates, i.e., the hormones of the LHPA axis, have to be considered to exert a significant influence on brain morphology (i.e., ventricular size) in individuals with affective disorders, as is also the case in those with Cushing's disease (Momose et al., 1971) and in steroid-treated patients (Bentson et al., 1978; Okuno et al., 1980).

In the present study, a close and positive association was found between VBR values and parameters of SWS (stage-3 sleep and SWS during the total night as well as during the second and third non-REM periods). The absence of a correlation between VBR values and the amount of SWS during the first non-REM period is not entirely unexpected. In depressed patients, this period especially is of short duration (= shortened REM latency)

and is often disturbed by interspersed awakenings and a late onset of SWS (which may, but does not necessarily cause a reduced amount of SWS). Thus, it seems likely that these changes mask possible associations between morphological brain alterations and SWS during the first non-REM period. At first glance it seems hardly intelligible that ventricular "enlargement" was associated with an *undisturbed* amount of SWS during the total night and during the second and third non-REM periods. As mentioned earlier, several investigations have shown evidence of a close and positive association between ventricular enlargement and an elevated free urinary/plasma concentration of cortisol. Given the findings that the administration of cortisol in healthy subjects results in elevated plasma cortisol levels and an increase in SWS (von Bardeleben et al., 1988; Born et al., 1989), hypercortisolism in depression should be accompanied by an increased rather than an unchanged amount of SWS. On the other hand, the pulsed administration of CRH causes a decrease in SWS (Holsboer et al., 1988). Thus, it seems likely that the amount of SWS reflects the "ratio" of CRH and cortisol effects. In other words, in most patients increased CRH release causes (via ACTH release) elevated cortisol secretion with its impact on brain morphology, i.e., ventricular enlargement; the amount of SWS may remain undisturbed, however, because both CRH and cortisol are elevated, keeping the ratio of their effects on SWS constant. On the other hand, in some subjects an increase in CRH secretion may cause a blunted ACTH release with almost undisturbed cortisol secretion; in this case, ventricular size is not affected, but the amount of SWS may be reduced due to the predominance of CRH effects. For the following reasons, this explanation has to be considered strictly speculative: no neuroendocrine data were available in the present investigation and, as ethical objections and radiation protection rules prohibit X-ray CT examination in healthy volunteers, no direct control group could be established on whom both a CT and polysomnographic investigation could be performed. But a possible testing of the hypothesis is provided by the performance of a combined dexamethasone (DEX)/CRH challenge test in parallel with a computed tomographic and polysomnographic investigation in depressed patients. Briefly, the administration of a single bolus of CRH in DEX-pretreated depressed patients frequently results in elevated secretion of ACTH and cortisol, while control subjects do not show this response (see: Holsboer, 1992). There are, however, a number of patients in whom the administration of CRH fails to induce an activation of the LHPA axis (unpublished observations). Perhaps these patients are the subjects with normal ventricular size and a disturbed pattern of SWS.

Our CT findings also have to be discussed in terms of the anatomical structures involved in sleep regulation and modulation. Ventricular enlargement in depression may reflect structural changes in the surrounding ganglia and there are indeed a number of imaging studies on depressed patients showing structural and functional alterations in the basal ganglia (Baxter et al., 1985; Buchsbaum et al., 1986; McDonald and Krishnan, 1992). Adjacent to the ventricles are also the thalamic nuclei, which were termed the "head ganglia" of sleep by Koella (1967). In essence, the current knowledge about the involvement of the thalamus in sleep regulation/modulation evidences a thalamic pacemaker driving cortical synchronization during non-REM sleep (see: Parkes, 1985; Jones, 1989). Thus, structural changes in the thalamus may result in a disturbance of synchronized EEG pattern. The observation of reduced sleep spindle activity in depressed patients (de Maertelaer et al., 1987) supports this view, whereas the present finding of undisturbed, synchronized cortical activity (SWS) in parallel with ventricular enlargement does not. Therefore, our findings are hard to fit in with the current knowledge about the role of subcortical structures in the synchronization of cortical activity. However, since these brain areas are assumed to *modulate* rather than to regulate sleep, it may well be that possible influences on SWS are counterbalanced or compensated for by the "forebrain system" (constituted by the orbitofrontal cortex and the basal forebrain), another loop important in cortical synchronization (see: Jones, 1989). In the case of general cerebral atrophy, ventricular dilatation is usually associated with a widening of the sulci, which, on the other hand, is known to diminish EEG amplitude. This may result in an artificially reduced amount of visually scored SWS. However, we observed a low amount of SWS, not in the patients with enlarged ventricles but in those in whom the VBR values were rated as normal. Thus, a possible influence of cortical atrophy on our results is rather unlikely.

In conclusion, we are aware that the attempt to explain the association between ventricular size and changes in SWS in depressed patients on the basis of a disturbed function of the LHPA axis is rather speculative and needs experimental confirmation. At a minimum, our findings of no major differences in polysomnographic and CT measurements in unipolar and bipolar patients fit the hypothesis of similar pathogenetic mechanisms in the two disorders. Finally, the observation of no change in the amount of SWS in a considerable portion of our depressed patients clearly has implications for the widely held view that depressive disorders are related to disturbed SWS and, therefore, that these disorders may provide a model for SWS regulation (e.g., Beersma and Van den Hoofdakker, 1992; Borbély, 1987).

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