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# Sleep in Schizophrenia: A Polysomnographic Study on Drug-Naive Patients

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*A slow wave sleep (SWS) deficit and a shortened rapid eye movement (REM) sleep latency are commonly reported in schizophrenic patients. However, most of these patients have been off neuroleptic medication for only a short period of time. Therefore, the reported sleep alterations may be due to residual drug effects. We polysomnographically investigated 22 drug-naive patients with a schizophrenic disorder, paranoid type, and 20 normal controls. In addition, we assessed the ventricular brain ratio (VBR) by means of computed assisted tomography. Except for a prolonged sleep onset latency, increased wake time and decreased stage 2 sleep, the patients showed a sleep pattern, i.e., of SWS and REM sleep, comparable with that of controls. The VBR was increased in 71% of the patients but was not associated with the patients' clinical characteristics or their SWS and REM sleep patterns. Our results indicate that the commonly reported SWS and REM sleep changes in schizophrenia reflect the remnant of prior neuroleptic treatment rather than the pathophysiology of the disorder itself.* 
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KEY WORDS: *Schizophrenia; Drug-Naive; EEG sleep; Slow wave sleep; Rapid eye movement latency; Ventricular brain ratio*

The electroencephalographic (EEG) sleep profile in schizophrenia is often reported to be characterized by an impaired sleep continuity (prolonged time to fall asleep and frequent nocturnal awakenings), a decrease in slow wave sleep (SWS; particularly in stage 4 sleep), an early onset of the first rapid eye movement (REM) sleep period (shortened REM latency) and an increased density of rapid eye movements during REM sleep (REM density index) (reviews: Zarcone 1988; Keshavan et al. 1990a; Thaker et al. 1990; Tandon et al. 1992; Benson and Zarcone 1993).

However, most of the EEG sleep studies performed on patients with a schizophrenic disorder are limited by the fact that the patients were studied either during chronic neuroleptic treatment or after a short drug washout period. Regarding sleep, it is well known that acute and chronic treatment with neuroleptics as well as their discontinuation have profound effects on sleep regulation (Thaker et al. 1989; Taylor et al. 1991; Neylan et al. 1992; Tandon et al. 1992; Nofzinger et al. 1993; Wetter et al. in press). Moreover, there is a growing body of literature stating that butyrophenones (e.g., haloperidol) continue to act at central dopamine receptors even after they had been withdrawn for weeks or months and that cessation of phenothiazines (e.g., fluphenazine) induces a long-lasting dopaminergic supersensitivity (e.g., Korpi et al. 1984; Campbell and Baldessarini 1985; Sramek et al. 1987; Cohen et al. 1988, 1992; Baldessarini 1990). Therefore, it is questionable whether the sleep changes reported so far in schizophrenic patients who have been mostly drug-free for only 2 weeks prior to polysomnographic investigation indeed describe the genuine sleep pattern in this disor-

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der or simply reflect either drug withdrawal phenomena or residual drug effects.

A clarification of the authentic sleep pattern in schizophrenia can only be achieved by exclusively investigating patients who have never been treated with psychotropic drugs. To our knowledge, there are only four such studies that fulfill this requirement (Kupfer et al. 1970; Jus et al. 1973; Ganguli et al. 1987; Tandon et al. 1992). However, none of these studies indicate the patient's specific subtype of the schizophrenic disorder. Furthermore, two of these studies are limited by nonstandardized diagnostic procedures (Kupfer et al. 1970; Jus et al. 1973) or by sleep scoring methods that are no longer used (Kupfer et al. 1970; this study is not referred to again). In a third study, only a small sample of eight patients was investigated (Ganguli et al. 1987). The major findings of all these studies were a prolonged sleep onset latency and sleep fragmentation in patients compared with control subjects. No significant differences were observed either in sleep architecture (i.e., SWS and REM sleep) or in REM sleep measures (e.g., REM density). The only exception was that in two of these studies a shortened mean REM latency was found in schizophrenic patients (Jus et al. 1973; Tandon et al. 1992).

To detect changes in the sleep pattern of schizophrenic patients that are caused by the pathophysiology of the disorder and not by confounding influences (e.g., prior neuroleptic medication), we investigated a diagnostically homogenous group of 22 acutely paranoid schizophrenic patients who had never received any psychotropic medication. Because there have been reports of a close association between morphologic brain alterations and SWS deficit (van Kammen et al. 1988) or REM sleep measures (Keshavan et al. 1991) in schizophrenic patients, we additionally addressed this issue in a subgroup of 14 patients.

## METHODS

### Subjects

The initial study sample, which was recruited over a 5-year period, consisted of 48 consecutively admitted inpatients with a first episode or an acute exacerbation of a schizophrenic disorder, paranoid type, who at the time of admission were reported to be drug naive. During the study enrollment, however, a history of psychotropic drug treatment (between 3 months to 5 years before assessment) or of psychoactive drug abuse/dependence was confirmed in 13 (27%) of these patients. After assessment with the Structured Clinical Interview according to DSM-III-R [SCID, German version, Wittchen et al. 1990], the diagnosis of four (8%) patients had to be changed to schizophreniform disorder, provisional, because the duration of illness was less than 6 months. Nine patients either refused to participate in the study ($n$ = 6 or 13%) or were not willing to continue the investigation after having spent the habituation night in the sleep laboratory ($n$ = 3 or 6%). Thus, the final study sample consisted of 22 drug-naive inpatients with a first episode or an acute exacerbation of a schizophrenic disorder, paranoid type (diagnosed according to DSM-III-R [APA 1987] as assessed by the SCID; subchronic: $n$ = 13, chronic: $n$ = 9; eight women, 14 men; age range: 21 to 55 years). None of the patients fulfilled the current or lifetime diagnostic criteria for any other psychiatric disorder. The mean duration of illness was 34 ± 41 months (range: 7 to 164 months). On average, the patients scored 54.5 ± 11.2 points on the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962). According to the proposal of Benson and Zarcone (1993), we assessed the positive symptomatology by the BPRS factor "thought disturbance" (sum score of the items "conceptual disorganization," "grandiosity," "hallucinatory behavior," and "unusual thought content"/4) and the negative symptomatology by the BPRS factor "anergia" (sum score of the items "emotional withdrawal," "motor retardation," "blunted affect," "disorientation"/4). The patients scored 18.1 ± 3.5 points on "positive" symptoms and 3.3 ± 1.4 points on "negative" symptoms. All patients gave written informed consent to participate.

To determine whether a family history of affective disorders (i.e., of first-degree relatives with the diagnosis of a bipolar disorder, major depression, and depression not otherwise specified) had a significant influence on the sleep pattern in schizophrenia, the patients and their relatives were interviewed. The diagnosis of the patients' first-degree relatives was achieved using the SCID or the Munich Diagnostic Checklist for DSM-III-R (MDCL; Hiller et al. 1990). A parental major depression was verified in six patients. In two of these patients, one of their siblings fulfilled diagnostic criteria for a schizophrenic disorder. The first-degree relatives of the remaining 16 patients had no current or lifetime history of psychiatric disorders.

Sleep recordings were performed during the first week after hospital admission. In 14 patients, cranial computed tomography (CCT) was performed within 2 to 4 days after sleep recordings (three women, 11 men; age range: 21 to 43 years; subchronic: $n$ = 9; chronic: $n$ = 5; duration of illness: 26.3 ± 36.8 months; BPRS score: 54.6 ± 11.1 points). The remaining eight patients either refused to participate in this part of the study ($n$ = 7 or 32%) or were not able to complete the CCT investigation ($n$ = 1 or 5%).

Twenty normal controls (seven women, 13 men; age range: 23 to 44 years) with no personal and family history of psychiatric disorders served as a control group for the polysomnographic investigation. Because German radiation rules prohibit x-ray examinations of healthy volunteers, the control group for the CT measurements consisted of 14 subjects (nine women, five men; age range: 18 to 48 years) with minor health problems (e.g.,

vertigo, headache) on whom a CT examination had been performed to exclude any cerebral processes. This control group was selected from our large normative data base (Krieg et al. 1988). The normal controls and the CT control subjects were matched as closely as possible to the patients' age and gender.

In all study participants the absence of primary sleep disorders such as sleep apnea or "periodic movements in sleep" syndrome was confirmed by clinical exploration and by visual inspection of the polysomnograms. In case of doubt, the protocol required exclusion from the study. Possible concurrent medical disorders and drug abuse were ruled out by a thorough medical examination and laboratory tests including ECG, blood analysis, and urinary drug screening (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates). Furthermore, none of the participants were reported to be a habitual napper or had been subjected to sleep deprivation, excessive alcohol (>25 g/day) or coffee intake (>500 ml/day), shift work, or time shifts (≥3 hours) during the 3 months prior to the study period. Participants were not allowed to take a nap on polysomnographic investigation days. This was monitored for the patients by the staff and was ascertained by direct personal interviews in the evenings before sleep recordings for the normal controls. Ten patients participated in a second protocol in which cerebrospinal fluid was sampled in the morning after the last night of sleep recording to determine concentrations of amino acids (Do et al. 1995).

## Polysomnography

All subjects slept in our sleep research unit for two consecutive nights. In the habituation night the electrodes were attached to the scalp, but sleep was not recorded. The sleep of the second night was recorded between 2300 hours and 0700 hours, using standard procedures (electroencephalogram: $C_3$-$A_2$, $C_4$-$A_1$ [time constant: 0.3 sec; low-pass filtering: 70 Hz]; horizontal electrooculogram; submental electromyogram). The sleep records were scored visually according to standard criteria (Rechtschaffen and Kales 1968) by trained technicians who were blind to the clinical and CCT data. The sleep scorings are routinely monitored by one of the authors (T.P.) and the interrater reliability, which is calculated bimonthly, ranges between $r = 0.88$ to $r = 0.92$. The definition of the EEG sleep parameters calculated has recently been described in full detail (Lauer et al. 1995). In addition, data transformation (natural logarithm, basis 10 logarithm) was performed to normalize the distributions of SWS data.

## Cranial CT

CT scans were performed on a General Electric Scanner 9800, using the 256 × 256 matrix and a 10-mm slice thickness. Measurements 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 by one of the authors (J.C.K.) with a pixel-density method on the computer console as previously described in full detail (Krieg et al. 1988). Using this method, inaccuracies that result from visual tracing of the ventricles or from a possible bias of the examiner can be ruled out. According to our large normative data base (Krieg et al. 1988), we consider a VBR value of less than 4.7% as "normal."

## Statistics

In addition to descriptive statistics, an analysis of variance (ANOVA) was computed. If the variance was proven to

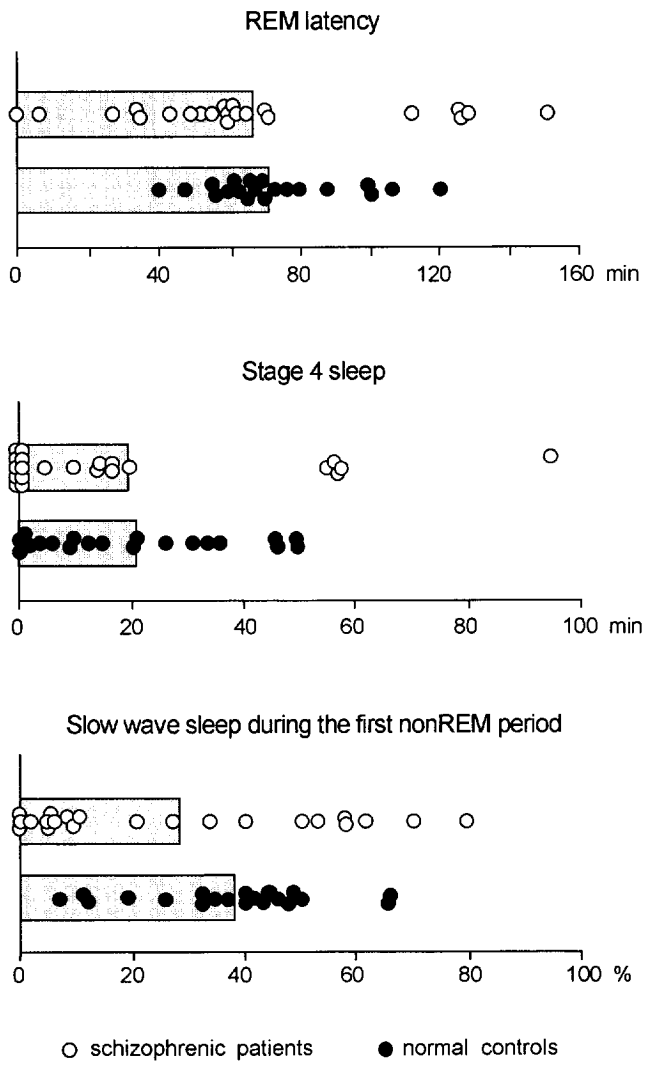


**Figure 1.** REM latency (*upper panel*), absolute amount of stage 4 sleep (*middle panel*), and relative amount of slow wave sleep during the first nonREM period (*lower panel*) in 22 drug-naive schizophrenic patients (*open circles*) and 20 normal controls (*closed circles*). Bars represent mean values.

Table 1. EEG Sleep Measurements (mean ± SD) in Drug-Naive Patients with a Schizophrenic Disorder, Paranoid Type, and in Normal Controls

| | Schizophrenic Patients (n = 22) | Normal Controls (n = 22) | ANOVA F(1,40) | ANOVA *p*-value |
|---|---|---|---|---|
| Age (years) | 32.7 ± 8.6 | 30.7 ± 6.7 | 0.75 | 0.39 |
| Women/Men | 8 / 14 | 7 / 13 | 0.01[a] | 0.92 |
| Sleep period time (min) | 397.3 ± 66.7 | 442.8 ± 26.4 | 8.11 | 0.006 |
| Total sleep time (min) | 366.1 ± 60.9 | 435.1 ± 28.3 | 21.44 | < 0.001 |
| Sleep efficiency index (%) | 77.8 ± 12.2 | 93.8 ± 3.6 | 31.71 | < 0.001 |
| Sleep onset latency (min) | 57.6 ± 53.1 | 20.2 ± 11.0 | 9.58 | 0.003 |
| Slow wave sleep latency (min) | 19.8 ± 11.9 | 16.6 ± 7.5 | 1.08 | 0.30 |
| Number of awakenings | 13.9 ± 7.2 | 7.4 ± 5.4 | 11.06 | 0.001 |
| Wake after sleep onset (%SPT) | 8.3 ± 7.6 | 2.7 ± 2.4 | 10.02 | 0.003 |
| REM latency (min) | 66.5 ± 40.2 | 73.7 ± 20.8 | 0.52 | 0.47 |
| REM latency (-wake time; min) | 62.5 ± 36.7 | 72.8 ± 20.7 | 1.20 | 0.27 |
| Mean REM density index | 1.82 ± 0.56 | 2.1 ± 1.07 | 0.98 | 0.32 |
| Stage 1 sleep (%SPT) | 7.5 ± 4.0 | 6.6 ± 3.6 | 0.59 | 0.44 |
| Stage 2 sleep (%SPT) | 50.6 ± 9.2 | 57.0 ± 7.4 | 6.14 | 0.02 |
| Stage 3 sleep (% SPT) | 7.5 ± 5.9 | 8.8 ± 3.8 | 0.72 | 0.40 |
| Stage 4 sleep (%SPT) | 5.0 ± 7.7 | 4.5 ± 3.9 | 0.05 | 0.82 |
| Slow wave sleep (%SPT) | 12.5 ± 10.6 | 13.4 ± 5.8 | 0.11 | 0.74 |
| REM sleep (TSPT) | 19.4 ± 6.4 | 19.4 ± 4.5 | 0.00 | 0.97 |
| **First Sleep Cycle** | | | | |
| REM period duration (min) | 13.9 ± 8.4 | 15.4 ± 10.9 | 0.24 | 0.62 |
| Wake time (% NREMP) | 6.7 ± 9.4 | 2.5 ± 1.6 | 3.86 | 0.05 |
| Slow wave sleep (%NREMP) | 28.9 ± 26.8 | 38.5 ± 16.3 | 1.92 | 0.17 |
| REM density index | 1.31 ± 0.87 | 1.33 ± 0.84 | 0.01 | 0.94 |
| **Second Sleep Cycle** | | | | |
| NonREM period duration (min) | 73.4 ± 23.6 | 79.2 ± 19.3 | 0.76 | 0.39 |
| REM period duration (min) | 24.6 ± 19.0 | 21.4 ± 11.4 | 0.43 | 0.51 |
| Wake time (%NREMP) | 5.2 ± 6.8 | 3.5 ± 8.1 | 0.57 | 0.45 |
| Slow wave sleep (%NREMP) | 17.9 ± 19.8 | 29.0 ± 20.5 | 3.19 | 0.08 |
| REM density index | 1.56 ± 0.91 | 2.06 ± 1.60 | 1.62 | 0.21 |

[a] $X^2$ test.
SPT = sleep period time; NREMP = NonREM period.

be inhomogenous, the data were reanalyzed using nonparametric tests (Mann-Whitney U test). Intercorrelations among variables were analyzed by computing Pearson correlation coefficients and by stepwise multiple linear regression procedures. The level of significance was set at 5% (two-tailed).

## RESULTS

### Polysomnography

The ANOVA revealed that sleep period time, total sleep time, sleep efficiency index, and the relative amount of stage 2 sleep were significantly decreased in the schizophrenic patients (SP) compared with the normal controls (NC). The sleep onset latency, number of awakenings and relative amount of wake time after sleep onset were significantly increased in the SP. The wake time during the first nonREM period was increased in the SP and the amount of SWS during the second nonREM period tended to be decreased compared with the NC. The remaining EEG sleep parameters (including SWS latency, the absolute and the relative amounts [according to sleep period time] of stage 3 and stage 4 sleep, SWS, and all REM sleep measurements) were similar in SP and NC (see Table 1). Regarding REM latency, which on average was quite similar in patients and normal controls, 22.7% (5/22) of the SP and 5% (1/20) of the NC had a REM latency shorter than 40 minutes (with two patients showing values shorter than 10 minutes; Figure 1). However, these frequencies did not differ significantly ($\chi^2[1] = 2.68$, $p = .101$). Furthermore, the comparison of the log-transformed values of the SWS parameters revealed no significant differences between the SP and the NC ($F[1,40] < 1.67$, $p > .20$).

By computing multiple linear regression equations using age, gender, duration of illness, BPRS sum score, and positive and negative symptomatology as independent variables, strong linear associations were found between positive symptom ratings and REM latency ($\beta = -0.56$, $p = .01$; adjusted $R^2 = 0.28$; on a single item level this was due mainly to "conceptual disorganiza-

tion"; $\beta = -0.51$, $p = .02$; adjusted $R^2 = .22$) and REM latency minus wake time during the first nonREM period, respectively ($\beta = -0.61$, $p = .004$; adjusted $R^2 = .34$; this was due mainly to "conceptual disorganization"; $\beta = -0.50$, $p = .02$; adjusted $R^2 = .20$). The remaining independent variables, including negative symptom ratings, were not associated with any EEG sleep parameter, particularly those describing SWS.

### Cranial CT

Because there were significant differences between SP and the control subjects (CS) regarding age and gender distributions, the VBR values of both groups were compared using a two-factor analysis of covariance (factors: groups, gender; covariate: age). With this procedure, the VBR values of the SP were found to be significantly increased compared with those of the CS (see Table 2). In detail, the VBR values that were measured exceeded our cutoff point for a "normal" VBR value in 10 (71%) of 14 SP, but in none of the 14 CS. This distribution differed significantly ($\chi^2$ [1] = 15.56, $p < .001$).

In the schizophrenic patients, no associations were found between VBR values and age ($r = 0.00$, $p = .99$), duration of illness ($r = 0.08$, $p = .77$) or severity of symptomatology (BPRS sum score; $r = 0.29$, $p = 0.30$). Furthermore, neither the positive nor the negative symptom scores (BPRS) were correlated with the VBR values (positive symptoms: $r = .08$, $p = 0.78$; negative symptoms $r = 0.30$, $p = .29$). There was no association between VBR values and age ($r = -0.07$, $p = .80$) in the control subjects.

### EEG Sleep and VBR Measurements

Because of the low number of schizophrenic patients displaying a "normal" ventricular size (VBR < 4.7%; $n = 4$), a correlational analysis was performed in the patient sample instead of a group statistical approach.

The VBR values were significantly and positively associated with the number of awakenings ($r = 0.64$, $p = .01$) and the amount of wake time during the second nonREM period ($r = 0.72$, $p = .003$). Close associations could not be confirmed between VBR values and SWS measurements (SWS latency, amounts of stage 3 and stage 4 sleep, SWS of the total night, and also of the first and second nonREM period and the log-transformed SWS values) or the REM sleep parameters (REM latency, REM density, and the amount of REM sleep).

### Subchronic (n = 13) versus Chronic Schizophrenic Patients (n = 9)

The chronic SP had a significantly shorter sleep period time than the subchronic SP (357.9 ± 85.1 minutes and 424.5 ± 31.6 minutes, respectively; F[1,20] = 6.74, $p = .017$) and a longer sleep onset latency (83.9 ± 66.2 minutes, and 39.4 ± 33.6 minutes, respectively; F[1,20] = 4.32, $p = .050$). All other parameters investigated (including age, severity of symptomatology, all parameters of SWS, REM latency, REM sleep, REM density indices and VBR) did not differ significantly between the two subgroups ($F < 2.30$, $p > 0.15$).

### Patients with (n = 6) and Patients Without (n = 16) a Family History of Major Depression

Division of the total sample based on a family history of major depression resulted in two subgroups that did not differ with regard to any of the parameters investigated (clinical characteristics, EEG sleep parameters, and VBR). For example, in the patients with a family history of major depression mean REM latency was 57.6 ± 41.2 minutes compared to 64.3 ± 36.1 minutes in the patients without a family history (F[1,20] = 0.14, $p = .71$). One of the two patients showing a so-called sleep onset REM latency (REM latency < 10 minutes; Figure 1) had a parent with major depression, the other did not.

## DISCUSSION

The major findings of the present polysomnographic study on 22 drug-naive patients with a schizophrenic disorder, paranoid type, were profound difficulties in sleep initiation and maintenance (e.g., a threefold

Table 2. Ventricular Brain Ratio (mean ± SD) in Drug–Naive Patients with a Schizophrenic Disorder, Paranoid Type, and in Control Subjects

| | Schizophrenic patients (n = 14) | Control subject (n = 14) | | | p-value |
|---|---|---|---|---|---|
| Age (years) | 31.4 ± 7.5 | 25.3 ± 3.7 | ANOVA: | F = 7.44 | 0.01 |
| Women/Men | 3 / 11 | 9 / 5 | | $\chi^2(1) = 5.25$ | 0.02 |
| Ventricular brain ratio (%) | 6.33 ± 2.53 | 2.38 ± 0.90 | ANCOVA: | F = 13.81 | <0.001 |

ANCOVA with age and gender being covariates.

lengthening of sleep onset latency and an increased wake time after sleep onset, particularly during the first nonREM period, compared to normal controls) as well as a decrease in stage 2 sleep. On the other hand, no systematic changes were found in regard to any slow wave sleep or REM sleep measurements. CCT revealed an elevated VBR in 71% (10/14) of the schizophrenic patients. A close and negative association was observed between severity of positive symptoms (as assessed by the BPRS factor "thought disturbance") and REM latency. No associations, however, were obvious among negative symptomatology, VBR, and SWS and REM sleep parameters.

An impairment of sleep initiation and maintenance in schizophrenia, including a decreased amount of stage 2 sleep, has been documented in nearly all sleep studies regardless of the patients' drug status (Zarcone 1988; Keshavan et al. 1990a; Thaker et al. 1990; Tandon et al. 1992). Furthermore, our findings indicate that the sleep initiation is more disturbed in chronic versus subchronic schizophrenic patients. However, these observations are not unique to schizophrenia because they are frequently found in other psychiatric disorders as well as in primary sleep disorders (Kales and Kales 1984; Lauer et al. 1991, 1992; Benca et al. 1992).

On the other hand, an SWS deficit, a shortened REM latency and, more recently, an increased REM density have been claimed to be EEG sleep features typical for schizophrenia (Feinberg and Hiatt 1978; Benson and Zarcone 1989, 1993; Keshavan and Tandon 1993). In our study on drug-naive schizophrenic patients, however, we failed to find any such systematic changes. Although these "negative" findings are in contrast to those reported in almost all other polysomnographic studies (review: Zarcone 1988; Thaker et al. 1990; Tandon et al. 1992), they are in line with observations from the few studies in drug-naive schizophrenic patients (Jus et al. 1973; Ganguli et al. 1987; Tandon et al. 1992) and in patients off neuroleptic drugs for more than 2 months (Van Cauter et al. 1991). The only exception is REM latency, which in two investigations was found to be significantly shorter in drug-naive schizophrenic patients than in control subjects (Jus et al. 1973; Tandon et al. 1992). However, in both studies this difference was probably not due to shortened values in the schizophrenic patients but rather to prolonged values in the control subjects. In more detail, Jus et al. (1973) and Tandon et al. (1992) reported mean REM latencies in schizophrenic patients that are similar to that of the present study (Jus et al / Tandon et al./present study: REM latency: *53 minutes/65 minutes/66 minutes* [the somewhat shorter REM latency found by Jus et al. can be best explained by the well-known effect of age on REM latency, because their patients had a mean age of 71 years]; REM latency minus wake time: *not indicated/60 minutes/62 minutes*). On the other hand, in both studies the mean REM latency of the controls has to be considered as prolonged: Jus and colleagues reported a mean value of 93 minutes in their controls aged 66 to 80 years, but the REM latency usually reported in that age range is about 50 to 60 minutes (e.g., Miles and Dement 1980; Lauer et al. 1991; Reynolds et al. 1991; Bliwise 1993).Tandon and co-workers observed a mean value of 97 minutes in their controls, with two of them having an unusually long REM latency of >220 minutes forcing the mean value up. Moreover, although a certain number of schizophrenic patients show REM latencies below 40 minutes, one has to be aware that this is the case in less than one-fifth of the drug-naive patients (Ganguli et al. 1987: 1 of 8; Tandon et al. 1992: 3 of 20; Riemann et al. 1994 [R.D., personal communication]: 3 of 10; present study: 5 of 22). Therefore, little evidence emerges from polysomnographic studies on drug-naive patients that REM latency is indeed shortened in schizophrenia.

Similarly, an SWS deficit, which is claimed to be typical for schizophrenia, can be occasionally observed in drug-naive patients. The respective mean values of visually scored stage 3 sleep, stage 4 sleep, and SWS, however, were found in the present study and by others to be either comparable in patients and controls (Jus et al. 1973, Tandon et al. 1992) or to be increased rather than decreased in the patients (Ganguli et al. 1987). A possible bias of our findings caused by a far too low amount of SWS in the normal controls can be excluded, because 12% to 14% SWS in samples of healthy subjects 20 to 45 years of age are commonly reported in the literature (see Miles and Dement 1980; Lauer et al. 1991; Bliwise 1993). One might criticize that visual scoring of SWS is not as sensitive as computer analysis. In line with this argument would be the finding of Ganguli et al. (1987) that after data were adjusted for age, schizophrenic patients had a significantly lower *total* count of delta-waves than the control subjects. However, this difference disappeared when the counts were analyzed as *averaged per minute.* Moreover, several studies have demonstrated that there is a large overlap between visually scored and computer analyzed SWS (Hoffman et al. 1984; Armitage 1995), which is further increased when 30-second sleep epochs are analyzed (as in the present study) instead of 60-second epochs (e.g., Ganguli et al. 1987; Tandon et al. 1992). These findings further limit the argument that the failure to observe any SWS deficit in drug-naive schizophrenic patients is caused by scoring methods that are not sensitive enough. In regard to frequency band analyses, one might speculate that the power in the delta-band is decreased in schizophrenia. Today, however, such data are not available for drug-naive patients. Thus, systematic changes in parameters describing the pattern of SWS are not obvious in drug-naive patients with a schizophrenic disorder.

Finally, the REM density indices previously claimed to be increased in schizophrenia (Benson and Zarcone

1993) were found by us and others to be normal or decreased rather than increased (Ganguli et al. 1987; Tandon et al. 1992).

In summary, the present findings in a diagnostically homogenous sample of drug-naive paranoid schizophrenic patients as well as the observations of other authors (although obtained in diagnostically heterogeneous but also drug-naive patient samples) provide very little evidence for the common opinion that schizophrenia is characterized by a polysomnographic profile of a shortened REM latency, a reduced amount of slow wave sleep, and increased REM density indices.

In our view, the discrepancies in polysomnographic findings between drug-naive and often so-called "drug-free" schizophrenic patients have to be related primarily to prior neuroleptic medication, the effects of which are still present in the latter group at the time of investigation. It has been clearly demonstrated in a number of studies that after cessation of butyrophenones, such as haloperidol and bromperidol, these drugs continue to act significantly on central dopaminergic neurons for at least 7 weeks or more in animals (e.g., Campbell and Baldessarini 1985; Cohen et al. 1988, 1992) as well as in humans (e.g., Korpi et al. 1984; Hubbard et al. 1987; Sramek et al. 1987; Cambon et al. 1987; Farde et al. 1988; Baldessarini 1990). These prolonged antidopaminergic effects are closely associated with small amounts of the residual drug that are concentrated near sites of action in the brain and, thus, may mask supersensitivity (Cohen et al. 1992). Likewise, withdrawal of phenotiazines (e.g., fluphenazine, thioridazine, chlorpromazine) induces a dopaminergic supersensitivity that lasts for more than 3 weeks (e.g., Cohen et al. 1988, 1992) and plasma levels of thioridazine are detectable up to at least 7 weeks after withdrawal (Sramek et al. 1987). In addition, symptoms consistent with cholinergic rebound can be observed frequently in patients withdrawn from neuroleptics for several weeks (for review, see Gilbert et al. 1995). Therefore, patients exposed to antipsychotic drugs cannot be considered to be free of residual drug effects for weeks after its discontinuation even when the drug is below detectable levels in blood or tissue (Cohen et al. 1988, p. 342).

Because the central dopaminergic and cholinergic systems are significantly involved in sleep regulation (see: Stock 1980; Gillin et al 1981; Hilakivi 1987; Steriade and McCarley 1990), alterations in these systems induced by cessation of neuroleptic treatment should result in certain changes in sleep pattern. And indeed, studies in which schizophrenic patients were polysomnographically investigated before and after neuroleptic withdrawal indicate (although not unequivocally) that after drug cessation SWS is decreased, REM latency is shortened, and REM density is increased (Thaker et al. 1989; Neylan et al. 1992; Nofzinger et al. 1993), but all the measurements tend to "normalize" after more than 4 weeks (Tandon et al. 1992). These immediate changes in sleep *after* drug cessation correspond with the sleep pattern commonly reported as typical for schizophrenia. On the other hand, they also coincide well with the long-lasting changes induced in the central dopaminergic and cholinergic systems by cessation of neuroleptics. Therefore, it is plausible that the discrepancies in polysomnographic findings between drug-naive and so-called "drug-free" schizophrenic patients are due to pharmacologic residual and/or drug cessation effects that are still present in the latter group.

One major characteristic of the sleep pattern observed in the present study was the high interindividual variability in the patients. To some extent, this was unexpected, because we investigated a *diagnostically homogenous* patient sample. This raises the question of whether there still may be a certain subtype of this diagnostic group that goes along with alterations in either SWS or REM sleep. In the original version of the hypercholinergic-hyperdopaminergic model of schizophrenia (Tandon and Greden 1989), these EEG sleep alterations were related to the negative type of the disorder. However, in the present study as well as in the study by Tandon et al. (1992), no close associations were found between the severity of negative symptomatology and any of the EEG sleep parameters investigated. Although Ganguli et al. (1987) observed a significant and negative correlation between negative symptoms and the log-transformed values of the absolute amount of SWS in eight patients, this association could not be replicated in our larger sample of 22 patients. In addition, we and others (Ganguli et al. 1987; Tandon et al. 1992) were not able to replicate any relationships between SWS and REM sleep measures and the duration of illness or the subchronic and chronic course of the disorder. Recently, Keshavan et al. (1990b) speculated that a short REM latency and a decreased SWS may be present particularly in patients with a family history of affective disorders. This assumption, however, is not supported by the present investigation or that of Tandon et al. (1992). Finally, some studies in "drug-free" patients indicate a positive association between neuroradiologic alterations (e.g., enlarged ventricular size) and either an SWS deficit (van Kammen et al. 1988) or a lengthened REM latency (Keshavan et al. 1991). In the present study, 71% (10 of 14) of the patients exhibited elevated VBR. Although this proportion is relatively high, it does not contradict other findings in the literature (for review, see Van Horn and McManus 1992; Sharif et al. 1993). Furthermore, the lack of correlations between VBR values and the patients' characteristics (e.g., age, positive and negative symptom ratings, course of illness) observed in the present study concur with the conclusion of Lewis (1990), that the patients' age, duration of illness and hospitalization, severity of negative and positive symptomatology as well as other parameters (for example, responsiveness to neuroleptic

treatment, cognitive impairment) were not associated closely enough with ventricular enlargement to be regarded as important causative candidates. In regard to EEG sleep parameters, we obtained close associations between VBR values and indices of arousals (e.g., number of awakenings) but failed to replicate relationships between VBR values and SWS (van Kammen et al. 1988) or REM sleep measures (Keshavan et al. 1991).

Thus, there is little evidence that severity of negative and positive symptomatology, the duration of illness, the subchronic or chronic course of illness, the presence/absence of a family history of affective disorders or neuroradiologic alterations (e.g., ventricular enlargement) sufficiently explain the high interindividual variability in SWS and REM sleep in drug-naive schizophrenic patients. The only association close enough to be considered here was found between REM latency and severity of positive symptoms, i.e., of conceptual disorganization. Recently, Keshavan et al. (1995) found conceptual disorganization to be closely and negatively associated with SWS (total delta count) in schizophrenic patients. Under the preposition that REM latency and SWS, i.e., of the first nonREM period, are strongly interrelated, our observation and that of Keshavan et al. (1995) would point in the same direction. However, we failed to find any associations between SWS parameters and positive symptoms (including conceptual disorganization) and REM latency, respectively (data not presented). Moreover, the results of the multivariate regression analysis left us with about 75% of the variance of REM latency unexplained by positive symptomatology, the only parameter investigated that showed a significant β-coefficient. Therefore, drawing any conclusion from these findings would be far too speculative.

One might argue that the present observations were obtained in a highly selected study sample that is not representative of the general population of schizophrenic patients (e.g., all patients fulfilled the DSM-III-R diagnostic criteria of a schizophrenic disorder, paranoid type, all of them were investigated during the acute state of the illness, and all of them had never been treated with psychotropic medications). However, with our restrictive inclusion criteria, we ensured not only a homogenous study sample that clearly exceeds the homogeneity of patient samples investigated previously, but we also controlled for clinical, pharmacologic, and, in part, familial sources of variance that can affect sleep. A further criticism might be that we did not control for the *Type I* error rate. A respective correction of the α-level, however, would result in fewer observations reaching the level of significance. Therefore, the lack of such a strategy cannot be held responsible for the failure to observe any significant differences between the SWS and REM sleep pattern in schizophrenic patients and normal controls. Although we and others (Ganguli et al. 1987; Tandon et al. 1992) assessed sleep data of only one night and, therefore, statements about the stability of the findings cannot be drawn, we consider the probability as low that the results might essentially change when performing two or more nights of sleep recordings. Finally, the sizes of the present subsamples investigated are relatively small (which may limit the power of our observations). However, they exceed or are equal to sample sizes of drug-naive schizophrenic patients investigated by others and, more importantly, there is little disagreement in the subsample related observations between the present study and others (Ganguli et al. 1987; Tandon et al. 1992).

In conclusion, in the present polysomnographic study performed on 22 drug-naive patients with a schizophrenic disorder, paranoid type, we found a clear disturbance of sleep initiation and maintenance, which is unspecific because it can also be observed in other psychiatric disorders and primary sleep disorders. No evidence emerged, however, that an SWS deficit, a shortened REM latency, and increased REM density indices are characteristic features of sleep in schizophrenia, paranoid type. This conclusion may apparently be extrapolated to schizophrenic disorders per se after consideration of the findings of other studies performed in diagnostically heterogenous samples of drug-naive schizophrenic patients (Jus et al. 1973; Ganguli et al. 1987; Tandon et al. 1992). An unexpected finding of the present study was the relatively high interindividual variability of SWS and REM sleep observed in the patients. However, except for the positive symptomatology, which accounted for only 25% of REM latency variability, none of the evaluated patient characteristics (severity of negative symptomatology, duration of illness, subchronic/chronic course of illness, family history of affective disorders or neuroradiologic alterations) were associated closely enough with any of the SWS or REM sleep measurements to regard them as significant for the interindividual variability. It may well be, therefore, that a *diagnostically homogenous* group of schizophrenic patients does not necessarily cover a *biologically homogenous* one. Nevertheless, our results demonstrate that the commonly claimed sleep pattern in schizophrenia (an SWS deficit, a shortened REM latency, and an increased REM density index) is not present in drug-naive paranoid schizophrenic patients. Moreover, our observations and those given in the literature suggest that previous findings in so-called "drug-free" schizophrenic patients are significantly influenced by long-lasting central effects induced by cessation of prior and (often) chronic neuroleptic treatment. Therefore, we recommend that future investigations of schizophrenia deal carefully with the issue of prior neuroleptic medication. Without the exact knowledge of how long neuroleptic medication interferes with neurobiologic measurements after drug cessation, only studies on drug-naive patients will provide sufficient information about the genuine neurobiologic alterations in schizophrenia.

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