

Delta Sleep Deficits in Schizophrenia

Evidence From Automated Analyses of Sleep Data

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Background: Several, though not all, polysomnographic studies that use conventional visual scoring techniques show delta sleep deficits in schizophrenia. Delta sleep (in particular, ≥ 1 - to 2-Hz frequency range), mediated by thalamocortical circuits, is postulated to be abnormal in schizophrenia. We investigated whether deficits in delta sleep occur in schizophrenia and whether these are primarily related to the illness or are epiphenomena of previous medication use or illness chronicity.

Methods: We compared 30 unmedicated schizophrenic patients and 30 age- and sex-matched controls for sleep data evaluated by visual scoring as well as automated period amplitude analyses and power spectral analyses.

Results: Schizophrenic patients had reduced visually scored delta sleep. Period amplitude analyses showed sig-

nificant reductions in delta wave counts but not rapid eye movement counts; power spectral analyses showed reductions in delta as well as theta power. Delta spectral power was also reduced in the subset of 19 neuroleptic-naive, first-episode schizophrenic patients compared with matched controls. Delta deficits were more pronounced in the greater than 1- to 2-Hz frequency range.

Conclusions: Delta sleep deficits that occur in schizophrenia may be related to the primary pathophysiological characteristics of the illness and may not be secondary to previous neuroleptic use. Automated sleep quantification by means of period amplitude and power spectral analyses can complement the use of conventional visual scoring for understanding electrophysiological abnormalities in psychiatric disorders.

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THE LONG-HELD belief that troubled sleep reflects a troubled mind, as well as the similarity between psychotic phenomena and dreams, has stimulated interest in sleep electroencephalographic (EEG) studies of schizophrenia. Reported sleep abnormalities include reductions in total sleep, sleep continuity, rapid eye movement (REM) latency, and the amounts of stages 3 and 4, or delta sleep (DS).¹⁻⁴ Amounts of REM sleep have been reduced in acute schizophrenia in some studies^{5,6} but increased in others.^{7,8} These discrepancies may reflect differences in clinical state, phase of illness, previous drug use, or variable definitions of REM measures. Rapid eye movement sleep is categorized into phasic (including short-lived events, such as REMs) and tonic (without REMs but with a mixed-frequency background) components.⁹ It remains unclear whether differences in schizophrenia are confined to either component of REM sleep.

Studies of DS abnormalities have also been inconsistent. Deficits in DS have been seen in patients with acute,^{8,10} chronic, and remitted schizophrenia,⁵ as well as in never-medicated,^{7,11} neuroleptic-treated,¹² and unmedicated^{5,8,10,13-15} schizophrenic patients. Nevertheless, some studies of previously medicated^{16,17} and neuroleptic-naive^{4,18} patients do not show such deficits, raising the question of whether DS deficits in schizophrenia are secondary to previous neuroleptic treatment. Studies that failed to find DS differences^{4,16-18} used only conventional visual scoring for evaluation of EEG sleep data; indeed, Ganguli et al¹¹ observed a reduction in automated but not visually scored DS in schizophrenia. Similar findings were recently reported by Kajimura et al.¹⁹ Visual scoring of DS may suffer from subjectivity in ratings; automated approaches may therefore better quantify DS deficiency in schizophrenia.

Recent ground-breaking single-cell studies have shown that mammalian sleep is characterized by 3 synchronous EEG

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SUBJECTS AND METHODS

SUBJECTS

Thirty schizophrenic patients (17 men and 13 women; mean \pm SD age, 30.9 ± 8.5 years) were recruited at the Western Psychiatric Institute and Clinic, Pittsburgh, Pa. The illness duration was 7.8 ± 10.0 years (median, 3.3 years; range, 40.6 years). The Brief Psychiatric Rating Scale scores were 52.1 ± 10.0 (total), 13.3 ± 4.4 (positive symptom subscale), and 7.2 ± 3.8 (negative symptom subscale). Eight patients had suicidal ideations; none had made any recent attempt. Global Assessment Scale score was 30.4 ± 10.8 . The Hamilton Depression Rating Scale (17-item) score was 16.6 ± 7.0 ($n=29$). The age at onset was 23.2 ± 8.3 years. Nineteen patients had received no neuroleptic medications previously; the remaining 11 patients had a mean medication-free period, immediately before the sleep study, of 97.5 ± 98.6 weeks (median, 40 weeks; range, 258 weeks). The patients fulfilled the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* criteria for schizophrenia (19 patients), schizoaffective disorder (8 patients), or schizophreniform disorder (3 patients).²⁴ These patients had been admitted for an acute exacerbation or a new onset of their illness. All patients were interviewed by trained clinicians, blind to sleep data, by means of the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*.²⁵ All clinical data were reviewed in a consensus conference to derive the "best-estimate" diagnoses. Follow-up confirmed a diagnosis of schizophrenia in the patients initially diagnosed as having schizophreniform disorder. Thirty age- and sex-matched healthy subjects (17 men and 13 women aged 30.9 ± 8.2 years) with no personal or first-degree family psychiatric history (based on interviews of each available family member) served as a control group. None of the patients or controls had any recent substance abuse or dependence, significant neurological or medical illness, mental retardation, primary sleep disorder, shift work, or severe obesity; none

were taking any regular doses of drugs with known central nervous system effects. All patients and controls signed an informed consent after a full explanation of the study.

SLEEP STUDIES

Polysomnographic recordings (2 or 3 nights) were conducted during the first week of hospitalization, before institution of treatment. Psychotropic medications were avoided during this brief period, with the help of the structured milieu and trained staff on the unit. Neuroleptics were started within 1 week of admission. No as-needed medications were used during the study other than acetaminophen. The controls were studied in the Western Psychiatric Institute and Clinic Sleep Laboratory; patients were studied in their own rooms, connected by cables with the EEG equipment in the same sleep laboratory. Research in our group has indicated that the variability in sleep signals induced by the use of multiple bedrooms is negligible.²⁶ Subjects retired to bed at their habitual "good night time," and were awakened at their habitual waking time (as determined by the subjects, and/or nurse's report of the previous week's sleep schedule). Daytime naps were not permitted. This was monitored for the patients by the hospital staff, and in the healthy controls by direct interviews before sleep studies.

Sleep was recorded on a 24-channel polygraph (78B Grass Instruments, Quincy, Mass) that consisted of an EEG, an electro-oculogram, and a submental chin electromyogram. The EEG consisted of a C4 scalp placement referenced to linked mastoids. All electrode impedances were determined to be less than 5000 Ω . Filter settings for the EEG were 0.3 to 100 Hz. The electromyogram was bipolar, with a filter setting of 10 to 90 Hz. The paper speed was 10 mm/s, and a 50- μ V signal was calibrated to produce a 10-mm deflection at a sensitivity setting of 5.

VISUAL SCORING

All sleep was scored in 60-second epochs by raters blind to clinical data who used standard criteria.²⁷ Unpublished

rhythms: slow oscillations (<1 Hz) generated within the neocortex, as evidenced by their persistence after thalamectomy; delta oscillations (1-2 Hz) generated by thalamocortical neurons; and sleep spindles (7-14 Hz) generated by the reticular thalamic nuclei.²⁰ Thalamocortical dysfunction has indeed been postulated in schizophrenia on the basis of in vivo neuroanatomical²¹ and physiological²² neuroimaging studies. If this is true, more prominent abnormalities in the 1- to 2-Hz component of DS in schizophrenia may be predicted. This hypothesis can be tested by objective quantification of sleep EEG.

Two approaches are used for automated sleep quantification. Power spectral analysis (PSA), using fast Fourier transform, analyzes the frequency domain and quantifies power in all frequencies of a signal.²³ Period amplitude analysis (PAA) analyzes the signal within selected frequency bands (eg, delta, beta, sigma); it seeks to identify discrete transient phenomena, such as delta waves and phasic REM activity, in a series of data by detecting polarity shifts, ie, crossing of EEG voltage from

negative to positive (zero cross). Whereas PSA cannot distinguish between wave amplitude and incidence, PAA can.²³ However, PAA may miss frequency components of the EEG that fail to produce zero crossings because of their subthreshold amplitude. Thus, PAA and PSA may provide valuable additional information missed by conventional sleep stage scoring.

In this study, we tested our hypotheses that (1) schizophrenic patients have reduced DS as determined by visually scored and automated analyses of sleep, (2) such alterations are primary to the illness and are not epiphenomena of illness chronicity or medications, and (3) the reductions are more prominent in the greater than 1- to 2-Hz component of DS.

RESULTS

VISUALLY SCORED SLEEP

We found significant differences (analysis of variance) between schizophrenic patients and controls in all 3 sleep

data from our laboratory (available on request) indicate comparability between the use of 60-second and the more common 30-second epoch ratings on most sleep parameters. Periodic checks of scoring reliability maintained inter-rater agreement ($\kappa=0.76-0.85$) for major sleep variables. **Table 1** lists sleep variables that were examined. These variables have been defined elsewhere.¹¹

PERIOD AMPLITUDE ANALYSES

The number of delta "counts" (the number of half-waves above and below the baseline at 0.5-2 Hz, 75-200- μ V activity) and number of REMs per minute (REM counts) were measured with a zero-crossing half-wave detector.²⁸ The choice of the amplitude criterion greater than 75- μ V was based on widely used criteria for delta waves in visual scoring.²⁷ This approach generates total as well as average delta counts per minute, thus controlling for differences in non-REM period length.²⁹ An REM count was identified when there were simultaneous (within 115 milliseconds) threshold crossings of opposite polarity by the two electro-oculogram potentials.³⁰ The following variables were examined: total and average delta counts for the whole night and for the first non-REM period, delta ratio (delta counts per minute in non-REM period 1 divided by delta counts per minute in non-REM period 2), and total and average (per minute) REM counts for the whole night.

POWER SPECTRAL ANALYSIS

For each EEG channel, the high-pass filter on the polysomnograph amplifier was set to 0.3 Hz and the low-pass filter to 100 Hz. Electroencephalogram signals were first low-pass filtered by an antialiasing filter (70 Hz; 24 dB/octave). Amplified EEG signals were then analog-to-digital converted (sampling rate, 256 Hz). The digital EEG signals were band-limited to 50 Hz by a digital finite impulse response filter before being decimated from 256 Hz to 128 Hz. Electroencephalogram power

spectra were calculated on the 128-Hz signals for consecutive 4-second epochs and 0.25-Hz frequency bandwidths by a fast Fourier transform routine. Artifact-laden 4-second epochs were identified by an automated procedure.³¹ To obtain matched pairs of power spectra and sleep stage scores, synchronized in time with each other, 60-second spectra were computed as follows: each 60-second spectrum was the average of 4-second spectra for that minute that were not artifact laden. The 60-second spectra were then averaged during non-REM (first 120 minutes) and REM sleep (first 40 minutes) time intervals. These periods were chosen because they represented the maximum durations of sleep data that were available for data analyses in all the subjects. For comparison of power spectra, the 0.25-Hz bins were collapsed into the following frequency ranges: delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), sigma (>12-16 Hz), and beta (>16-32 Hz). Our PSA methods are discussed in detail elsewhere.²⁶

DATA ANALYSES

Data from night 2 were analyzed in all the subjects except for 4 patients who took naps before night 2. For these patients, night 3 data were used. Visually scored and PAA variables were compared between the patients with schizophrenia and the controls by means of analyses of variance. A square-root or logarithmic transformation was used for variables that violated the analysis of variance assumptions of normality or homogeneity of variance. The PSA data were compared by means of repeated-measure multivariate analyses of variance, between diagnostic groups across the frequency bands. Pearson correlations were conducted to examine the relationship between clinical and demographic variables and significant sleep indexes. Random regression analysis (using a special covariance matrix to account for correlated observations and increasing variance) was used to test for significant differences in the slopes of cumulative delta and REM counts across time (**Figure 1**). The level of significance was set at .05 (2 tailed).

domains (ie, DS, REM sleep, and sleep continuity). Schizophrenic patients had reductions in sleep maintenance and DS (in minutes); a trend was seen for reduced DS percentage. Significant reductions in REM time occurred in the first REM period (Table 1).

PERIOD AMPLITUDE ANALYSES

A significant reduction was seen in total delta wave counts. The average delta wave count per minute was significantly reduced in the first non-REM period (**Table 2**). A valuable approach to examine non-REM sleep independent of REM sleep is to estimate delta wave activity during a constant amount of non-REM sleep starting at sleep onset.³² Accumulation of delta counts was significantly reduced during non-REM sleep in schizophrenic patients (Figure 1, left). The REM counts did not differ during REM sleep (Figure 1, right).

We compared the distribution of total delta counts (75-200 μ V) between the 0.5- to 1-Hz and greater than 1- to 2-Hz delta ranges across the 2 groups. Patients had

a greater reduction in the greater than 1- to 2-Hz range than in the slower range, as compared with controls (**Figure 2**).

POWER SPECTRAL ANALYSES

The EEG spectral power was significantly reduced in the non-REM sleep of schizophrenic subjects (**Figure 3**). Reductions were seen only in the delta and the theta ranges. Power reductions were more prominent in the greater than 1- to 2-Hz delta range as compared with the 0.5- to 1-Hz range (group \times frequency range interaction, $F_{1,58}=5.56$; $P=.02$).

CLINICAL CORRELATIONS

None of the sleep variables were correlated with illness duration (partialing out the effect of age, known to correlate inversely with DS³³). Medication-naive schizophrenic patients ($n=19$; 13 men and 6 women; age, 27.9 ± 7.1 years), as compared with age- and sex-matched

controls (n=19; 13 men and 6 women; age, 28.0 ± 6.9 years), had significantly reduced delta spectral power in non-REM sleep ($F_{1,36}=5.05$; $P=.03$). Among previously treated patients (n=11), medication-free duration was unrelated to any of the sleep parameters except for REM density ($r=-0.61$; $P=.05$). There were no significant correlations between Brief Psychiatric Rating Scale scores and DS variables.

COMMENT

The primary finding of this study was that DS reductions were evident by visual scoring, PAA, and PSA in schizophrenia. Schizophrenic patients also showed reduced sleep time and sleep continuity. However, obser-

vations of reduced average delta counts in the first non-REM period, reduced delta wave accumulation in continuous non-REM minutes, and reduced delta power in PSA suggest that sleep discontinuity is unlikely to explain the observed DS deficits. Reductions in delta power in the neuroleptic-naive, first-episode schizophrenic patients, as well as the lack of a relationship between DS and illness duration or medication-free duration, suggest that these findings are primary to schizophrenia and not simply epiphenomena of medication or illness chronicity. Because of the small sample of previously neuroleptic-treated patients (n=11), however, one cannot rule out subtle correlations between DS and medication-free duration. Follow-up sleep studies of a subset of these patients have shown that DS deficits, unlike REM sleep changes, are persistent, suggesting that the former may be trait related.³⁴ Deficits in DS have been found to be associated with enduring traits of schizophrenia, such as negative symptoms,^{11,19,35} ventriculomegaly,^{2,36} attentional impairment,³⁷ poor outcome,³⁸ and impaired frontal lobe metabolism.³⁹ We have argued that these observations and the presence of DS deficits in the first-episode, treatment-naive patients are consistent with the neurodevelopmental model of the schizophrenic illness.⁴⁰

Reduced DS is also seen in depression, suggesting that this finding may be diagnostically nonspecific.^{1,41} However, controlled studies show that REM amounts, especially in the first REM period, are increased and delta ratios are decreased in depression.¹ In our study, total REM sleep amounts and delta ratios were not altered in schizophrenia. The duration of the first REM period was shorter, but PAA disclosed no difference in REM counts, suggesting a deficit in tonic but not phasic REM activity. Earlier reports of increases in REM sleep in previously treated schizophrenic patients^{7,10,42} may be related to neuroleptic effects; acute withdrawal of neuroleptics increases REM time.^{4,43} This possibility is consistent with our observation of a negative correlation between REM density and medication-free duration. Thus, schizophrenia may be associated with DS deficits and reductions, not increases, in the duration of the first REM period; this pattern of findings might distinguish schizophrenia from depressive disorders.

Table 1. Polysomnographic Variables in Schizophrenic and Healthy Subjects

Parameter	Mean ± SD		F	P
	Schizophrenia (n=30)	Controls (n=30)		
Total recording period, min	448.6 ± 53.4	455.0 ± 45.8	0.25	.62
Total sleep time, min	347.6 ± 69.8	429.4 ± 44.0	29.5	<.001
Sleep maintenance,* %	87.5 ± 10.8	96.6 ± 3.1	30.3	<.001
Sleep efficiency,* %	77.9 ± 13.9	94.4 ± 3.3	68.0	<.001
Sleep latency,* min	51.8 ± 52.1	10.6 ± 7.1	27.6	<.001
Awake time after sleep onset, min†	49.3 ± 43.2	15.0 ± 13.6	22.6	<.001
Delta sleep, min†	35.0 ± 30.1	53.1 ± 27.4	6.8	.01
% Delta sleep†	9.9 ± 8.3	12.2 ± 5.9	3.1	.09
Rapid eye movement (REM) latency, min†	60.9 ± 27.0	69.1 ± 30.3	1.01	.32
REM latency—awake, min†	57.8 ± 24.6	68.4 ± 29.8	1.7	.20
REM density	1.5 ± 0.6	1.4 ± 0.5	0.2	.68
REM density, 1st REM	1.21 ± 0.79	1.02 ± 0.47	1.32	.26
REM min, total	78.6 ± 27.4	107.6 ± 25.7	2.53	.12
REM duration, 1st REM, min	13.6 ± 9.6	20.9 ± 8.0	10.23	.002
REM %	22.6 ± 6.3	24.9 ± 5.1	2.53	.12

*Log linear transformation used for analysis.

†Square root transformation used for analysis.

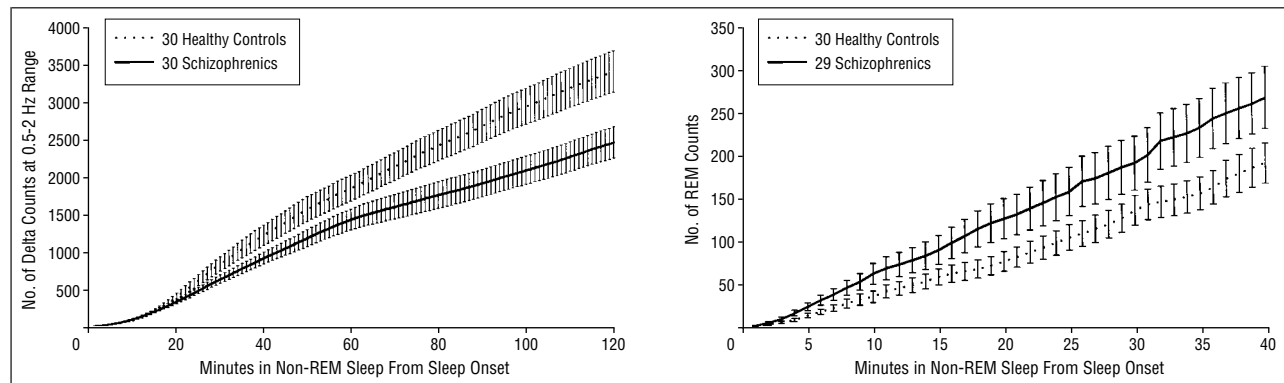


Figure 1. Accumulation of delta wave counts (mean ± SE) of non-rapid eye movement (REM) sleep (left) and REM activity counts (right) in schizophrenic and healthy control subjects. With random regression analyses, the difference in rate of accumulation of delta waves in non-REM sleep between the 2 groups was significant across 120 minutes ($F_{1,58}=7.44$; $P=.008$). The REM activity counts during the first 40 minutes of REM sleep did not differ significantly ($F_{1,57}=1.94$; $P=.17$).

Table 2. Period Amplitude Analyses in Schizophrenic and Control Subjects

Parameter	Mean ± SD		F	P
	Schizophrenia (n=30)	Controls (n=30)		
Total delta counts (whole night)*	3986 ± 1810	5620 ± 2431	8.4	.005
Average delta counts/min (whole night)	14.6 ± 5.9	17.3 ± 7.0	2.6	.11
Delta counts in non-rapid eye movement (REM) period 1*	1576 ± 1166	2257 ± 1387	3.68	.06
Average delta counts/min in non-REM period 1	24.1 ± 12.7	31.9 ± 17.1	4.03	.05
Delta ratio†	1.6 ± 1.1	1.6 ± 0.8	0.2	.64
Total REM counts*	526.2 ± 424.1	702.9 ± 504.8	2.26	.14
Average REM counts	6.34 ± 4.4	6.3 ± 4.3	0.1	.72

*Square root transformation used for analysis.

†Log linear transformation used for analysis.

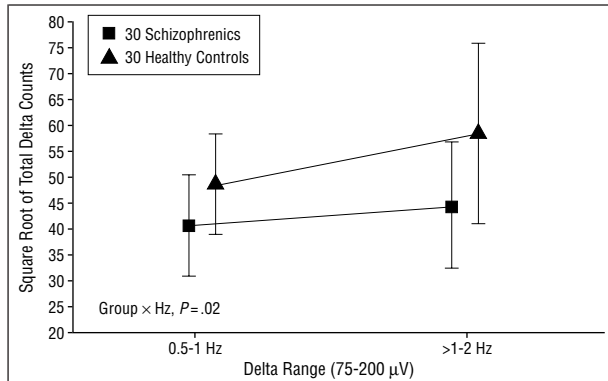


Figure 2. Total delta counts, in the frequency range of 0.5 to 1 Hz vs >1 to 2 Hz, in the schizophrenic and control subjects. Repeated-measures analysis of variance showed significant group × delta range interaction, with the delta counts being more reduced in the 1- to 2-Hz frequency range ($F_{1,58}=4.05$; $P=.05$).

Our observation of a more prominent deficit in the greater than 1- to 2-Hz range of DS may reflect thalamocortical dysfunction in schizophrenia. This view is consistent with observations that the components of DS less than 1-Hz may be generated in the neocortex, while the greater than 1- to 2-Hz components result from thalamocortical oscillations.²⁰ Our observation is also supported by observations of reduced thalamic volume,²¹ synaptic density,⁴⁴ and metabolism²² in schizophrenia. Nevertheless, the following caveats are noteworthy. First, the 0.5- to 1-Hz activity may reflect neocortical delta wave activity only in part, since delta waves less than 0.5 Hz are not detected by our methods. Second, several major feedback loops and multiple neurotransmitter pathways innervate the thalamus, including projections from the cortex, basal forebrain, brainstem, and hypothalamus. Any or all of these may be involved in the generation of DS.^{45,46} Finally, the specificity of a thalamocortical dysfunction for schizophrenia remains unclear; studies of other major psychiatric disorders, such as depression and alcoholism, are needed to address this issue.

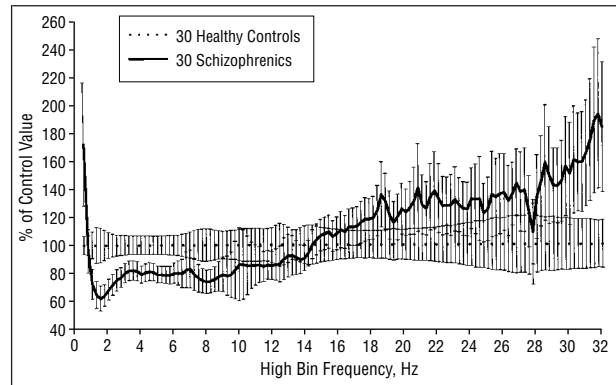


Figure 3. Electroencephalogram spectral power (mean ± SEM) in the first 120 minutes of non-rapid eye movement sleep after sleep onset in schizophrenia expressed as percentage of control values for each 0.25-Hz bin (0.25-32 Hz). The schizophrenic patients had significantly reduced power in delta ($F_{1,58}=7.89$; $P=.007$) and theta ($F_{1,58}=4.58$; $P=.04$) frequency ranges.

Conventional visual sleep scoring represents an arbitrary division of a continuous measure where no sharp demarcations exist, eg, between stages 2 and 3 and between stages 3 and 4. Methodological variables, such as epoch length (eg, 30 seconds vs 60 seconds), may influence scoring,²⁷ although the use of uniform criteria for patient and control groups minimizes the influence of this confound on observed differences. Furthermore, since DS is defined on both frequency and amplitude criteria, alterations in delta waves not reaching formal amplitude criteria (eg, <75 μ V), such as medication or aging effects,⁴⁷ may be disregarded. Automated techniques are free from such limitations and can detect EEG changes missed by visual scoring. In our study, PSA showed delta and theta power reductions. Theta power reductions may explain stage 2 non-REM sleep deficits in some studies¹⁸; stage 2 sleep is associated with mixed theta and alpha frequency activity.⁶ The PAA showed no differences in REM activity counts, suggesting that tonic, and not phasic, REM sleep may be reduced in schizophrenia. The PAA and PSA may thus provide complementary information of value in understanding the pathophysiological characteristics of schizophrenia.

Further studies are needed to investigate the functional neuroanatomy of sleep in schizophrenia by means of state-of-the-art neuroimaging techniques.^{48,49} The possibility that polysomnographic alterations may indicate risk for the illness merits investigation in relatives at risk for schizophrenia. Finally, altered sleep homeostasis needs to be studied by means of naturalistic challenges such as sleep deprivation along with quantified sleep analyses.⁵⁰

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