Delta power in sleep is of increasing interest because of its association with waking performance in neuropsychological tests. In schizophrenia, this link might be impaired because of a decrease in delta power in sleep and pronounced cognitive deficits. The authors analyzed delta power in sleep and neuropsychological performance in 16 patients with schizophrenia on stable medication with amisulpride and 17 healthy subjects. In healthy subjects, the authors found significant positive correlations between morning performance in declarative memory, procedural learning, and attention and delta power, especially in frontal channels. The authors interpret these results in terms of dysfunctions of thalamocortical and prefrontal networks in schizophrenia.

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Delta Power in Sleep in Relation to Neuropsychological Performance in Healthy Subjects and Schizophrenia Patients

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A n extensive body of research provides converging evidence for an important role of sleep in learning, brain plasticity, and cognitive functions.^{1–3} However, crucial questions still remain open—whether memory consolidation is linked to particular sleep stages and whether this interrelationship is altered in pathological mental conditions like schizophrenia.

In addition to its relationship to sleep homeostasis, delta wave activity is considered an important aspect of sleep in the link to cognitive performance. Bodizs et al.⁴ found an association between temporo-lateral low delta (<1.25 Hz) activity during sleep and visual memory performance in epileptic patients. Anderson and Horne⁵ described correlations between frontal low delta (<1 Hz) sleep EEG and neuropsychological tests specific to the prefrontal cortex. Further, a local increase in delta activity (1 to 4 Hz) during sleep after learning correlated with improved performance in an implicit learning paradigm the next morning.⁶

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Schizophrenia is characterized by psychotic and deficit symptoms, such as cognitive impairments. We recently described a correlation of visuospatial memory impairments and a decrease in the amount of slow wave sleep (SWS) in schizophrenia.⁷ Furthermore, in addition to disturbances, especially of non-REM (rapid eye movement) sleep,⁸ a decrease in delta (0.5–4 Hz) activity during sleep has been reported.9 Therefore, we performed delta power analyses in sleep in relation to neuropsychological tasks in healthy subjects and schizophrenia patients. We hypothesized that delta activity is associated with neuropsychological performance in healthy subjects and that this link might be impaired in schizophrenia. Because cognitive symptoms play a major role in quality of life and predict functional outcome in schizophrenia,¹⁰ research in this field is essential and important.

METHOD

Subjects

The original sample comprised 17 schizophrenia inpatients (seven women) diagnosed according to the International Classification of Diseases (subtypes: paranoid [N=15], hebephrenic [N=1], undifferentiated [N=1]) and 17 healthy subjects matched for age, sex and years of education according to the German school system. In one patient only two EEG channels were admitted, so he had to be excluded from spectral analysis. All patients were on a stable regimen of the antipsychotic amisulpride (median dose=600mg, range=100 to 800mg). Three patients received a concomitant sedative medication with zolpidem (10mg/day; two patients) or diazepam (7.5mg/day; one patient). Any participant with a relevant additional medical condition was excluded by medical history, physical examination, and routine laboratory investigation, including urinary drug screening. All participants gave their informed written consent. The study was approved by the local ethics committee and conforms to the Declaration of Helsinki, Finland.

Procedure

Each subject spent two nights in our sleep laboratory. The first night was used for adaptation to the conditions in the sleep laboratory. Sleep was recorded between lights off (regulated by the subjects themselves between 10 p.m. and 12 p.m.) and lights on (at 6:45 a.m.). Prior to polysomnography of the second night and the next morning at 7:30 a.m., we performed neuropsychological tasks. Sleep was recorded employing standard procedures, and the following parameters were measured: Electroencephalographic activity (EEG: Fz, F3, F4, F7, F8, C3, C4, T3, T4, T5, T6, Pz, P3, P4, O1, O2 according to the 10–20 system), electrooculographic activity (EOG) and submental electromyographic activity (EMG). Recordings were visually scored according to standard criteria¹¹ by a trained rater under blind conditions. These results are described elsewhere.⁷

For spectral analysis all EEG electrodes mentioned above were referenced against Fpz. The fast Fourier transform (FFT) algorithm was used, and the truncating error was reduced by applying a Hanning window. The EEG signals were A/D converted at 100 samples per second with a 12 bit resolution. Only artifact-free epochs of 30-second duration were analyzed. The log-transformed absolute power values of the delta range (0.5–4 Hz) of each sleep stage and of all channels were used for further analysis.

Neuropsychological Tasks

We used Trail Making Tests A and B for testing attention, cognitive flexibility and psychomotor speed in the evening and in the morning.¹² Declarative memory was assessed by the nonverbal Rey-Osterrieth Complex Figure Test (copy in the evening and announced recall in the morning).¹³ For testing procedural learning we used a mirror-tracing skill. Subjects were to trace carefully inside the doubled lines of a triangle (for warming up, data not evaluated) and a star in the evening and in the morning. Direct visual access to the platform with the figures was prevented by a 30- by 22-cm board. The figures could only be seen via a 26- by 18-cm mirror. We assessed the overnight improvement (ratio of drawing time in the morning to drawing time in the evening). Aspects of spatial memory were measured by a test established by Smith and Milner.¹⁴ Eleven toys are placed on a board. In the evening the only task is to guess on the retail price of each item. In the morning the task is to correctly replace all 11 items on the empty board. The distance between the assigned and original position of the objects is measured, and all numbers are added up. For measurement of executive function we performed the Tower of Hanoi (four disk version). To assess verbal intelligence, we used the Mehrfach-Wortschatz-Intelligenz-Test (Multiple Choice Word Fluency Test; MWT-B).¹⁵

Statistics

As the data do not constantly meet criteria for normal distribution, we used nonparametric statistics and provide median and range as descriptives. A Mann-Whitney test (two-tailed) was used to compare healthy subjects and patients. The relationship between sleep and neuropsychological parameters was examined by nonparametric correlations (Spearman-Rho, two-tailed). The level of significance was set at 5%. No adjustment of the error probabilities for multiple testing was performed because of the explorative nature of the study. Therefore, all results have been treated with particular caution and have been considered for their consistency with other results.

RESULTS

Delta Power in Healthy Subjects Versus Schizophrenia Patients

There were no significant differences between healthy subjects and schizophrenia patients regarding age (31 years [24 to 43 years] versus 31 years [22 to 44 years], respectively), premorbid verbal intelligence (107% [92% to 136%] versus 112% [97% to 143%], respectively) and education (13 years [9 to 13 years] versus 12 years [9 to 13 years], respectively; always median and range). The median of the Positive and Negative Syndrome Scale (PANSS) total score¹⁶ was 77 (range = 52 to 112). In almost all neuropsychological tasks patients performed significantly worse in the morning and in the evening; only mirror tracing revealed no significant differences between patients and comparison subjects.⁷ Delta power in SWS was significantly reduced in schizophrenia patients in comparison to matched healthy subjects in temporal and occipital channels (Table 1). There were no significant differences of delta power in Stage 2 sleep and REM sleep in patients versus comparison subjects.

Interrelationship Between Delta Power and

Neuropsychological Performance in Healthy Subjects There were no significant correlations between performance of any neuropsychological task and age, verbal intelligence, or education level. As shown in Table 2, all significant correlations in healthy subjects were seen in this way: the higher the delta power in sleep, the better the waking performance or overnight improvement in different neuropsychological tasks. A highly significant correlation was seen between recall of the Rey figure and delta power in SWS in a left frontal channel. A high number of significant correlations was found between neuropsychological tasks and delta power in SWS. There was a lower number regarding Stage 2 sleep and only few concerning REM sleep. Delta power in SWS or Stage 2 sleep was mainly significantly correlated with performance in tests carried out in the morning. Most of the significant correlations were found in frontal channels.

Interrelationship Between Delta Power and Neuropsychological Performance in Schizophrenia Patients and Healthy Comparison Subjects There were no significant correlations between age, total PANSS score or dosage of amisulpride and performance in any neuropsychological task in schizophrenia patients. Similar to the results of healthy subjects, patients with schizophrenia showed the highest number of significant correlations in neuropsychological performance with delta power in SWS. There were only few significant correlations of neuropsychological performance and delta power in Stage 2 sleep and REM sleep (Table 3).

Because five of 16 patients with schizophrenia showed a duration of SWS of less than 4 minutes, only 11 patients (all with duration of SWS of longer than 18 minutes) were included in the correlation analyses of delta power in SWS compared with 11 healthy subjects matched for age, sex, and education level (Table 4). For SWS in both groups significant positive correlations were found with TMT-A, in comparison subjects mainly with morning execution and in schizophrenia patients mainly with performance in the evening. Whereas a predominance of significant positive correlations between neuropsychological performance and delta power in frontal channels was seen in healthy subjects, this was not so in schizophrenia patients. In contrast to healthy subjects, schizophrenia patients' better performance on the Tower of Hanoi puzzle correlated with a lower delta power in different sleep stages.

DISCUSSION

To our knowledge, this is the first report studying the interrelationship of delta power in sleep and neuropsy-

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chological performance in healthy subjects and schizophrenia patients. For healthy subjects, the main findings were significant positive correlations between performance in declarative memory, procedural learning, and attention/cognitive flexibility with delta power, especially in SWS and in frontal channels. In schizophrenia patients, significant positive correlations were only seen between delta power and performance in attention/cognitive flexibility. In addition, significant negative correlations were found to exist between performance in executive functions and delta power in sleep.

The findings of significant correlations between delta power in sleep and performance in neuropsychological tasks in healthy subjects are in line with recent published studies. Power in the delta or low delta range was also associated with performance in recall of the Rey figure in epileptic patients,⁴ with performance in tests specific to the prefrontal cortex in older people⁵ and

EEG channels	Comparison Subjects (N=17) Median	Range	Patients With Schizophrenia (N=16) Median	Range	p value (Mann–Whitney
F7	58.7	56.9-60.3	57.9	55.1-61.1	0.18
F3	57.8	57.8-54.6	58.6	54.7-60.3	0.74
Fz	59.6	57.1-61.6	59.0	57.2-61.6	0.79
F4	58.3	55.6-61.3	58.7	55.7-60.3	0.85
F8	58.8	56.5-59.9	57.9	54.0-62.5	0.31
T3	61.8	60.3-63.7	60.7	58.0-64.1	0.09
C3	62.2	60.1-63.6	61.1	56.6-63.8	0.19
C4	62.0	59.9-63.6	61.7	58.7-63.9	0.36
T4	58.0	54.9-63.2	59.9	56.0-62.6	0.71
T5	64.3	62.3-66.1	63.6	61.6-65.6	0.049*
P3	64.0	62.0-65.7	63.2	60.6-65.8	0.17
Pz	64.2	63.0-66.4	63.6	61.7-66.3	0.15
P4	63.8	62.2-65.8	63.2	61.3-65.9	0.29
Т6	64.0	62.2-65.9	63.2	61.3-65.3	0.02*
01	64.6	62.7-66.5	63.3	61.7-66.3	0.04*
O2	64.6	62.7-66.7	63.4	61.5-66.1	0.03*

*p<0.05

 TABLE 2.
 Channels With Significant Correlations (r = in parentheses) Between Delta Power in Different Sleep Stages and Performance in Neuropsychological Tasks in Comparison Subjects

	SWS (N=17)	Stage 2 Sleep (N=17)	REM Sleep (N=17
TMT-A evening	F7 (0.57)* F4 (0.62)**	F4 (0.52)*	F3 (0.54)* F4 (0.69)** C3 (0.54)*
TMT-A morning	F7 (0.49)* F3 (0.59)* Fz (0.52)*	F3 (0.53)*	_
	F4 (0.68)** F8 (0.50)* C3 (0.48)*	F4 (0.54)*	
	T4 (0.61)** T5 (0.49)* Pz (0.51)*	T4 (0.65)**	
TMT-B evening		_	_
TMT-B morning	F7 (0.63)*	T4 (0.49)*	_
Mirror tracing overnight improvement	C3 (0.49)*	T5 (0.49)* T6 (0.53)* O2 (0.50)*	_
Rey figure recall in the morning	F7 (0.78)*** T4 (0.48)*	_	—
Spatial recall in the morning Tower of Hanoi	F7 (0.49)*		F3 (0.49)*
*p<0.05; **p<0.01; ***p<0.001			

TABLE 3.	Channels With Significant Correlations (r = in
	parentheses) Between Delta Power in Different Sleep
	Stages and Performance in Neuropsychological Tasks
	in Patients With Schizophrenia

	Stage 2 Sleep (N=16)	REM Sleep (N=16)
TMT-A evening	F7 (0.68)** C4 (0.60)*	_
TMT-A morning	_	_
TMT-B evening	_	_
TMT-B morning	_	_
Mirror tracing overnight improvement	—	—
Rey figure recall in the morning	T4 (-0.54)*	_
Spatial recall in the morning		_
Tower of Hanoi	T3 (-0.57)*	Pz (-0.59)*
	O1 (-0.57)*	O1 (-0.56)*
	O2 (-0.62)*	O2 (-0.59)*

*p<0.05; **p<0.01

TABLE 4.Channels With Significant Correlations (r = in
parenthesis) Between Delta Power in SWS and
Performance in Neuropsychological Tasks in
Schizophrenia Patients and Matched Comparison
Subjects

	SWS Comparison Subjects (N=11)	SWS Schizophrenia Patients (N=11)
TMT-A evening	F7 (0.68)*	Fz (0.61)* F4 (0.66)* F8 (0.66)* T3 (0.69)* C3 (0.72)* C4 (0.88)** P3 (0.63)* Pz (0.63)* P4 (0.66)* O2 (0.62)*
TMT-A morning	Fz (0.63)* F4 (0.73)* C3 (0.64)* T4 (0.67)*	Fz (0.65)*
TMT-B evening TMT-B morning Mirror tracing overnight improvement Rey figure recall in the morning Spatial recall Tower of Hanoi	F7 (0.77)* F7 (0.62)* —	
*p<0.05; **p<0.01		

with improvement in a procedural learning task in young healthy subjects.⁶ Although Anderson and Horne⁵ reported a strong link between frontal low delta power in non-REM sleep and a Tower test in old healthy subjects, we did not find this in young healthy subjects. This might be due to a different test procedure, because only a three-disk version applied to schizophrenia patients was preferentially sensitive to frontal lobe lesions, while the four-disk version used in our study was sensitive to basal ganglia disease.¹⁷

Because slow wave activity is the basis of non-REM sleep, it is not surprising that an association of performance in neuropsychological tasks was mainly found with delta power in SWS and Stage 2 sleep, but rarely in REM sleep. The highly significant correlation of performance in recall of the Rey figure and delta power in SWS in healthy subjects supports earlier studies that emphasize the importance of SWS versus REM sleep in the consolidation of declarative memory.¹⁸ The association of improvement of performance in a mirror tracing skill with delta power in SWS and Stage 2 sleep confirms the importance of non-REM sleep also in consolidation of procedural memory.³ The predominance of significant results in frontal channels in healthy subjects in our study is in line with other studies emphasizing the importance of frontal regions for performance of the Trail Making Test¹⁹ and for declarative memory processes.^{20,21}

It was demonstrated by intracellular recordings in cats that certain oscillations in SWS enhance the responsiveness of thalamic and cortical neurons and it was therefore assumed that SWS may consolidate memory traces acquired during wakefulness in corticothalamic networks.²² The intense discharge of neocortical neurons during the depolarization phase of the slow oscillations might provide signals that are used in synaptic reorganization, plasticity and the consolidation of information acquired in waking.^{22,23} Therefore, it was assumed that slow oscillations reflect a cortical reorganization of waking circuits⁵ and might help synaptic consolidation.⁶

In this study we analyzed the frequency range of 0.5 to 4 Hz, because in schizophrenia patients a decrease in classical delta activity in SWS was shown,⁹ which was confirmed by our results. Regarding the known origin of delta waves within the thalamus and within the cortex, Keshavan et al.⁹ assumed a thalamocortical dysfunction in schizophrenia. In line with this, a large num-

ber of papers are showing anatomical and functional alterations of the thalamus in schizophrenia.^{21,24,25}

Cognitive deficits, considered to be key features of schizophrenia since the first descriptions of this disorder, are often linked to prefrontal dysfunction, also a consistent finding in schizophrenia research.^{21,26,27} According to our hypothesis, we confirmed the results of a decrease in delta power in SWS. Additionally, the associations between especially frontal delta power and neuropsychological morning performance in healthy subjects were not found in patients with schizophrenia. Because a decrease in delta power in patients was only seen in temporal and occipital, but not frontal channels, it might be speculated that the above-mentioned link between delta activity and synaptic consolidation and plasticity^{22,23} was additionally disturbed in schizophrenia.

Our results concerning the schizophrenia subjects are of course limited by the fact that our patients were not drug-free. Systematic data on the impact of amisulpride on delta power in sleep in schizophrenia have not yet been published. But in our previous paper⁷ we reported typical alterations, especially of non-REM sleep parameters in our patients on stable medication with amisulpride as known from the literature of drug-naïve patients.⁸ Furthermore, we did not find significant

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correlations between the dosage of amisulpride and delta power in any EEG channel. Because our patients, as opposed to comparison subjects, also showed diminished delta power in SWS, as did drug-free patients,⁹ our patients seem to be quite typical in this respect.

In conclusion, we found further indications for the importance of especially frontal delta oscillations for neuropsychological performance in healthy subjects. Correlations cannot delineate causal relationships, but a diminution of this link might indicate disturbances in thalamocortical and prefrontal networks in schizophrenia. Future studies need to confirm and to extend these pilot results in a greater number of subjects. It should be analyzed further if applications of delta activity-enhancing drugs, such as gaboxadol,²⁸ could yield positive correlations between delta power and neuropsychological performance in schizophrenia patients. Finally, we believe that spectral analysis of sleep EEGs might provide new insights into processes of cognitive dysfunctions in a complex disorder like schizophrenia.

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