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Impairment of visuospatial memory is associated with decreased slow wave sleep in schizophrenia

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Abstract

Cognitive impairments such as memory deficits and sleep disturbances are common clinical features of schizophrenia. Since sleep plays an important role in consolidation of memory, we hypothesize, that there is an interrelationship between distinct alterations in sleep and memory performance in schizophrenia. We studied 17 patients with schizophrenia on stable antipsychotic medication with amisulpride (age range 22–44 years; 7 women) and 17 healthy controls (matched for age, gender and educational level). Sleep was recorded and scored according to the standard criteria by Rechtschaffen and Kales. Immediately before polysomnography and the morning after we performed neuropsychological tasks including Rey–Osterrieth Complex Figure Test and a test for recall of spatial location for testing aspects of declarative memory and a mirror tracing skill for procedural memory. In comparison to healthy controls, the patients showed a significant increase in sleep onset latency and a significant decrease in sleep efficiency and amount of slow wave sleep (SWS). Furthermore, the patients' performance in recall of the Rey-figure and of spatial location the next morning was significantly impaired. These impairments in the tests for visuospatial memory were positively correlated with reduction in the amount of SWS and in sleep efficiency. These results point to a functional interrelationship between regulation of SWS and performance in visuospatial memory in schizophrenia. If these results of our pilot study hold true, they will allow the development of innovative treatment strategies for neuropsychological deficits in patients with schizophrenia.

Keywords: Schizophrenia; Neuropsychology; Memory; Polysomnography; Slow wave sleep

1. Introduction

Schizophrenia is a severely debilitating disorder. Whereas management of the positive symptoms has efficiently been established, treatment of cognitive impairment and neuropsychological deficits still is a challenge in the field. Moreover, it is the latter symptoms that play the major part in quality of life and psychological well-being (Green et al., 2000). Overcoming these debilitating neuropsychological handicaps would considerably improve well-being and psychosocial as well as occupational outcome in these patients. Our approach in this respect is to investigate a putative interrelationship between these neuropsychological deficiencies and variables of polysomnographic night sleep. We hypothesize that memory deficits are associated with impairment in particular variables of night sleep.

On the one hand, there are numerous studies on impairment in learning and memory in individuals with schizophrenia (e.g. Paulsen et al., 1995; Aleman et al., 1999; Mohamed et al., 1999). On the other hand, there is a body of literature on sleep disturbances, such as increased sleep onset latency and sleep fragmentation in patients with schizophrenia compared to healthy controls (e.g. Lauer et al., 1997; for review: Benca et al., 1992;

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Benson and Zarcone, 2000). In addition, several studies found a reduction in SWS or stage 4 sleep in schizophrenia (Hiatt et al., 1985; Keshevan et al., 1998; Poulin et al., 2003). In humans as well as in animals it has been shown that sleep plays a pivotal role in memory consolidation (for review: Peigneux et al., 2001; Stickgold et al., 2001). Consolidation of procedural memory, i.e. the "knowing how", is associated with REM sleep (for review: Smith, 2001). Consolidation of declarative memory i.e. the "knowing that", was shown to be associated with SWS (Plihal and Born, 1997, 1999). With respect to spatial memory, which, if explicit, is a subcategory of declarative memory, animal studies demonstrated that specific hippocampal cells activated during a spatial memory task are reactivated during subsequent sleep (Wilson and McNaughton, 1994). Staba and colleagues (2002) demonstrated in humans, that during SWS hippocampal neurons fired significantly more intensively than during REM sleep. The importance of the hippocampus for declarative or spatial memory is well established (e.g. Teng et al., 2000; for review see: Squire and Zola-Morgan, 1991; Burgess et al., 2002; Shu et al., 2003), and the thalamus plays a critical role for declarative or spatial memory as well (e.g. Zola-Morgan and Squire, 1985; Exner et al., 2001, Van Groen et al., 2002; Van der Werf et al., 2003; for review see: Shu et al., 2003). In schizophrenia, structural and functional abnormalities of the hippocampus have been unanimously demonstrated by a great number of various studies (e.g. Hulshoff Pol et al., 2001; Falkai et al., 2002; Ende et al., 2003; Ehrenreich et al., 2004; for review see Falkai et al., 2001). Abnormalities in the thalamus have also been shown (e.g. Ende et al., 2003; Danos et al., 2003). Moreover, recent studies reported on correlations between abnormalities in the above mentioned brain regions and neuropsychological test performance in individuals with schizophrenia (e.g. Weiss et al., 2003; Salgado-Pineda et al., 2003; for review see: Weiss and Heckers, 2001). Furthermore, the thalamus is known as a key pace maker in the regulation of SWS (Steriade et al., 1993).

Therefore, we hypothesize that impaired visuospatial, so to speak hippocampus-related, memory is associated with reduced amounts of SWS in individuals with schizophrenia. We investigated memory performance overnight in the morning after polysomnography in patients with schizophrenia and in healthy matched controls. We tested for procedural and visuospatial memory. To the best of our knowledge, except for a paper looking only for REM sleep parameters (Taylor et al., 1992), this is the first study applying polysomnography and memory testing in parallel and trying to link these parameters in patients with schizophrenia. So, this pilot study is meant to stimulate further research in this area and to maybe enable innovative treatment strategies for cognitive impairment in individuals with schizophrenia.

2. Methods

2.1. Subjects

The sample consisted of 17 inpatients with schizophrenia, diagnosed according to ICD 10 (sub-types: paranoid ($n = 15$), hebephrenic (1), undifferentiated (1) schizophrenia). The age ranged from 22 to 44 years (median 31 years), with 7 female and 10 male patients. All patients were on stable medication with the antipsychotic amisulpride (median dose 600 mg, range between 100 and 800 mg). Four patients received a concomitant sedative medication with zolpidem (10 mg/day; two patients), diazepam (7.5 mg/day) or promethazine (50 mg/day). Any relevant additional medical condition was excluded by medical history, physical examination and routine laboratory investigation including urinary drug screening. Seventeen healthy subjects matched for age, sex and educational level were introduced as controls (median age 31 years; 10 males and 7 females). Educational levels of patients and controls were assessed by years of education according to the German school system. All patients and probands gave their informed written consent. The study was approved by the local ethics committee and conforms to the Declaration of Helsinki.

2.2. Procedure

Each patient and control 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 patients and probands themselves between 10 pm and 12 pm) and lights on (at 6:45 am). We used this individualized lights off procedure in order to avoid lying in bed in the dark room without being tired enough to sleep particularly for the psychotic patients. We aimed at conditions for falling asleep as comfortable as possible under the experimental condition. Prior to polysomnography of the second night and the next morning at 7:30 am after a light breakfast without caffeine we performed neuropsychological tasks. Sleep was recorded employing standard procedures and the following parameters were measured: Electroencephalographic activity (EEG; C3-A2 and C4-A1), electrooculographic activity (EOG) and submental electromyographic activity (EMG). Recordings were visually scored according to standard criteria (Rechtschaffen and Kales, 1968) by a trained rater under blind condition. The following parameters were computed: Time in bed (time from lights off to lights on in minutes), sleep onset latency (time from lights off to the first epoch of stage 2 sleep in minutes), total sleep time (in minutes), slow wave sleep (SWS, in minutes) and rapid eye movement (REM) sleep (in minutes), sleep efficiency (ratio of total sleep time to

time in bed in percent), number of awakenings, SWS latency (time from sleep onset to the first epoch of stage SWS in minutes), REM latency (time from sleep onset to the first epoch of stage REM sleep in minutes) and total REM density (ratio of 3-s mini epochs including rapid eye movements to the total number of 3-s mini epochs of REM sleep).

2.3. Questionnaires and cognitive testing

Patients and control subjects completed the following sleep questionnaires: (1) the Pittsburgh sleep quality questionnaire (Buysse et al., 1989) as a measure for subjective sleep quality during the last two weeks and (2) the evening and morning sleep questionnaires of the German Sleep Society with questions concerning the current physical and psychological condition and the sleep quality of the preceding night (Hoffmann et al., 1997).To assess verbal intelligence the "Mehrfach-Wortschatz-Intelligenz-Test" (Multiple Choice Word Fluency Test; MWT-B, Lehrl, 1977) was used in the morning after polysomnography. The results were converted to the Wechsler Adult Intelligence Scale-Revised intelligence quotient (WAIS-R IQ) using standard tables. For measurement of executive function we performed the Tower of Hanoi (four disc version). Trail Making Test parts A and B was used as a control for attention, mental flexibility and psychomotor speed in the evening and in the morning (Reitan, 1958).

Aspects of declarative memory were assessed by the non-verbal Rey–Osterrieth Complex Figure Test (copy in the evening and announced recall in the morning; Osterrieth, 1944). For testing of spatial memory we performed a test established by Smith and Milner (1981 and 1989). Eleven toys are placed on a board measuring 60 by 60 cm and presented to patients and controls. In the evening the only task is to name the toys and 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. For assessment of performance in the recall of spatial location the distance between the assigned and original position of the objects was measured and all numbers were added up. For testing procedural learning we used a mirror-tracing skill. Patients and controls 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. The figures had an overall width of 20 cm and the distance between the doubled lines were 1 cm. 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 drawing time and the number of errors (crossing any line with the stylus).

2.4. Statistics

As the data do not meet criteria for normal distribution, we used non-parametric statistics and provide median and range as descriptives. A Mann–Whitney test (two-tailed) was used to compare patients and controls and median-split was used to compare subgroups of patients regarding sleep efficiency and SWS. The

Table 1
General parameters and neuropsychological tests (median and range) in schizophrenic patients and normal controls

	Schizophrenic patients ($n = 17$)		Normal controls ($n = 17$)		P-value (Mann–Whitney)
Age (years)	31	(22–44)	31	(22–43)	0.86
Education (years at school)	12	(9–13)	13	(9–13)	0.59
MWT-B (premorbid intelligence)	112	(97–143)	107	(92–136)	0.99
Visuospatial (declarative) memory					
Rey copy evening (points)	36	(21–36)	36	(34–36)	0.38
Rey recall morning (points)	16	(6–29)	24	(13–34)	0.01
Spatial recall (cm)	70	(39–333)	49	(30–125)	0.04
Procedural memory					
Mirror tracing evening (s)	151	(62–307)	117	(68–240)	0.47
Mirror tracing evening (number of errors)	9	(1–152)	5	(0–33)	0.38
Mirror tracing morning (s)	70	(51–187)	65	(30–195)	0.31
Mirror tracing morning (number of errors)	7	(0–154)	2	(0–16)	0.02
Other functions					
TMT A evening (s)	34	(25–56)	27	(18–47)	<0.01
TMT A morning (s)	32	(21–283)	22	(16–79)	0.07
TMT B evening (s)	73	(34–153)	54	(20–72)	<0.01
TMT B morning (s)	62	(35–194)	50	(28–70)	0.01
Tower of Hanoi (pulls)	23	(15–35)	16	(15–35)	<0.01

MWT-B = Multiple Choice Word Fluency Test; Rey = Rey–Osterrieth Complex Figure Test; Spatial recall = Sum of deviation of 11 toys located by subjects in the morning after presentation the evening before; TMT-A = Trail Making Test part A, TMT-B = Trail Making Test part B.

relationship between sleep and memory parameters was examined by non-parametric correlations (Spearman-Rho). Fisher's exact test was applied to test the equality of proportions. The level of significance was set at 5%.

3. Results

3.1. Neuropsychological test performance and results on sleep in the patients versus the controls

Patients and controls were well matched for age and years of education; the groups did not differ with respect to premorbid intelligence (see Table 1). Recall of the Rey-figure in the morning and spatial recall were significantly worse in the patients. Whereas mirror tracing in the evening did not reveal any differences between the patients and the controls, in the morning the patients made more errors than the controls at comparable velocity, with regard to procedural memory. Performance in the TMT-A and TMT-B was worse in the patients with significant differences in the evening and in the morning (only TMT-B). As expected, patients consistently demonstrated significantly impaired executive functions as evidenced by the Tower of Hanoi compared to the controls. Patients and controls differed significantly with respect to the self-rated quality of sleep during the preceding 2 weeks (PSQI) with the patients rating for lower sleep quality (Table 2). However, the self-rated quality of the sleep during the experimental night did not differ between patients and controls, nor did the self-rated tiredness in the evening before and the morning after the experimental night. Polysomnographic measurements showed that the amount of SWS was significantly decreased in the patients with significantly increased SWS latency; sleep onset latency was significantly increased as well as time in bed and sleep efficiency was significantly decreased in the patients versus the controls. In a subgroup-analysis of 13 patients without concomitant medication and 13 matched controls the between-group differences basically remained unchanged with regards to the polysomnographic variables (time in bed [$p = 0.002$], sleep onset latency [$p = 0.007$], amount of SWS [$p = 0.06$], SWS latency [$p = 0.03$], sleep efficiency [$p = 0.1$] and with respect to the neuropsychological tasks (performance in spatial recall [$p = 0.02$], in recall of the Rey-figure [$p = 0.1$], in the mirror tracing skill in the morning [$p = 0.07$], and in the other functions – TMT-A/B and Tower of Hanoi).

3.2. Interrelationship between neuropsychological test performance and polysomnographic night sleep

When we did correlational analysis on all neuropsychological and sleep variables we found that the amount of SWS and sleep efficiency were significantly positively correlated with the recall of the Rey-figure in the morning and remarkedly negatively correlated with spatial recall in the patients only, as can be seen in Table 3. This means that the higher the amount of SWS and sleep efficiency the better are the test results on visuospatial memory. High performance in spatial recall in the patients also correlated significantly with short

Table 2
Questionnaires and EEG sleep measurements (median and range) in schizophrenic patients and normal controls

	Schizophrenic patients ($n = 17$)		Normal controls ($n = 17$)		P-value (Mann–Whitney)
Questionnaires					
PSQI	9	(2–15)	4	(1–5)	<0.01
Quality of sleep	3	(2–4)	4	(2–5)	0.09
Tiredness (evening)	3	(1–5)	3	(1–6)	0.82
Tiredness (morning)	4	(2–6)	4	(2–5)	0.36
Polysomnography					
Time in bed (min)	509	(305–555)	435	(385–528)	<0.01
Sleep onset latency (min)	28	(8–128)	11	(3–59)	0.01
Total sleep time (min)	425	(198–509)	377	(310–429)	0.11
Sleep efficiency (%)	83.9	(65–94)	90.0	(72–98)	0.03
Number of awakenings	20	(10–42)	14	(9–28)	0.02
Sleep stage 1 (min)	38	(12–142)	28	(10–56)	0.05
Sleep stage 2 (min)	248	(113–319)	201	(160–242)	0.11
SWS latency (min)	21	(11–119)	13	(8–24)	<0.01
SWS (min)	22.5	(0–83)	55.0	(21–142)	0.02
REM-latency(min)	77	(25–157)	75	(0–151)	0.73
REM sleep (min)	85	(35–140)	87	(46–144)	0.76
REM density (%)	7.9	(3.6–20.7)	5.4	(2.3–15.7)	0.10

PSQI = Pittsburgh sleep quality index of the last two weeks (0 = best sleep quality).
Quality of sleep (1 = very bad to 5 = very good).
Tiredness scale (1 = exhausted to 6 = fresh).

Table 3
Correlations ($p < 0.1$) of memory and sleep parameters

	Schizophrenic patients		Normal controls	
Memory-test parameter	Sleep parameter	r	Sleep parameter	r
Rey recall morning (points)	Sleep efficiency	0.49*	–	
	Slow wave sleep	0.51*		
Spatial recall (cm)	Sleep onset latency	0.60*	–	
	Total sleep time	−0.53*		
	Sleep efficiency	−0.46(*)		
	Slow wave sleep	−0.43(*)		
Mirror tracing morning (s)	–		Sleep onset latency	0.48(*)
			Sleep efficiency	−0.48*

Spearman Rho $^{*}p < 0.05$; $(^{*})p < 0.1$.
Rey = Rey–Osterrieth Complex Figure Test; Spatial recall = Sum of deviation of 11 toys located by subjects in the morning after presentation the evening before.

sleep onset latency and long total sleep time. In the controls, there were no significant correlations between sleep parameters and visuospatial memory. Only within the group of patients there was a significant negative correlation between age and amount of SWS and REM sleep, but not with any memory test parameter.

In Table 4 we performed a median-split in the group of patients by the amount of SWS (22.5 min) and analysed the neuropsychological scores in both subgroups. Those patients with high amounts of SWS demonstrated significantly better performance in spatial recall. There were no significant differences in premorbid intelligence, in PANNS-scores, in quality of sleep or tiredness, in time in bed, in performance of TMT-A or TMT-B, in daily dosages of amisulpride or the presence or absence of concomitant medication. As expected, the patients with more SWS were younger than those with less than 22.5 min of SWS. When we performed a median-split in the group of patients by sleep efficiency (83.9%), as shown in Table 5, the patients with better sleep efficiency again performed better in spatial recall ($p < 0.1$). None of the other tests and variables demonstrated significant differences between these groups. When the group of controls was split by identical

Table 4
Slow wave sleep (Cut off: 22.5 min (= median))

	Patients with 22.5 min or more of SWS	Patients with less than 22.5 min of SWS	*P*-value
Number	9	8	
Age (years)	24	34	0.01
MWT-B (premorbid intelligence)	107	118	0.47
PANNS	70	80	0.24
Dosage amisulpride (mg)	600	700	0.17
Number of patients with concomitant medication	1	3	0.29*
Quality of sleep	3	3	0.89
Tiredness (evening)	3	4	0.68
Tiredness (morning)	3	4	0.14
Time in bed (min)	524	476	0.32
Other functions			
Tower of Hanoi (pulls)	21	23	0.82
TMT-A evening (s)	38	32	0.61
TMT-A morning (s)	28	34	0.67
TMT-B evening (s)	81	68	0.67
TMT-B morning (s)	72	55	0.28
Visuospatial (declarative) memory			
Rey copy evening (points)	36	36	0.89
Rey recall morning (points)	22	10	0.20
Spatial recall (cm)	46	93	0.03
Procedural memory			
Mirror tracing morning (s)	70	65	0.57

Two tailed Mann–Whitney test, * = Fisher's exact test.
PANNS = The positive and negative syndrome scale (Kay et al., 1989).
Quality of sleep (1 = very bad to 5 = very good), Tiredness scale (1 = exhausted to 6 = fresh).

Table 5
Sleep efficiency (Cut off: 83.9% (= median))

	Patients with a sleep efficiency of 83.9% or more	Patients with a sleep efficiency of less than 83.9%	*P*-value
Number	9	8	
Age (years)	24	33	0.17
MWT-B (premorbid intelligence)	107	118	0.41
PANNS	70	70	0.48
Dosage amisulpride (mg)	600	700	0.17
Number of patients with concomitant medication	2	2	>0.99*
Quality of sleep	3	3	0.61
Tiredness (evening)	3	3	0.76
Tiredness (morning)	3	4	0.42
Time in bed (min)	524	497	0.54
Other functions			
Tower of Hanoi (pulls)	21	19	0.42
TMT-A evening (s)	38	37	0.89
TMT-A morning (s)	28	33	0.74
TMT-B evening (s)	81	65	0.24
TMT-B morning (s)	72	63	0.96
Visuospatial (declarative) memory			
Rey copy evening (points)	36	36	0.67
Rey recall morning (points)	22	13	0.2
Spatial recall (cm)	46	93	0.07
Procedural memory			
Mirror tracing morning (s)	70	93	0.84

Two tailed Mann–Whitney test, * = Fisher's exact test.
PANNS = The positive and negative syndrome scale (Kay et al., 1989).
Quality of sleep (1 = very bad to 5 = very good), Tiredness scale (1 = exhausted to 6 = fresh).

procedures regarding sleep efficiency and SWS there were no significant differences between the sub-groups (data not shown).

4. Discussion

The present study is the first one of its kind to investigate the interrelationship between specific measures of night sleep and performance in different aspects of memory in individuals with schizophrenia and in healthy matched controls. We hypothesized that there is an association between performance in visuospatial, primarily hippocampus-related memory and amount of SWS. Our data support this hypothesis. We found that those patients with high amounts of SWS performed significantly better in the spatial recall task than those patients with low amounts of SWS. Furthermore, we found a significant positive correlation between the amount of SWS and the recall of the Rey-figure in the morning. Therefore, we suggest that there indeed might be an interrelationship between the disturbance of sleep and the impaired memory performance in individuals with schizophrenia. This might inspire new perspectives in treatment.

Our results on cognitive impairment and sleep disturbance in individuals with schizophrenia are in line with reports by other groups. Similarly to the reports by Kolb and colleagues (1983) or Silverstein and colleagues (1998) we found that the schizophrenic patients did not differ significantly on the copy condition of the Rey-figure, whereas they performed poorly on the recall condition in comparison to healthy controls. For assessing recall of spatial location we used a test introduced by Smith and Milner (1981 and 1989). In this particular task implicit learning abilities as well as visuospatial memory are measured. Though it is not a pure declarative test, Smith and Milner demonstrated, that patients with hippocampal lesions had an abnormally rapid forgetting of such information. Our finding of a significantly worse performance by schizophrenic patients in this test is in line with impairment in visuospatial and spatial memory tasks as discussed already as a functional correlate of hippocampal pathology (Friege et al., 2002; Wood et al., 2002). We used a mirror tracing skill to test procedural learning, and as others before us, we too found only a mild non-significant impairment in schizophrenic patients (Scherer et al., 2003). These results are in line with normal REM sleep parameters we and others (e.g. Lauer et al., 1997; Keshevan et al., 1998; Poulin et al., 2003) demonstrated in schizophrenic patients, as it is established that there is an interrelationship between REM sleep and procedural memory (Smith, 2001).

Furthermore our patients like many schizophrenic patients before (e.g. Lauer et al., 1997; for reviews: Benca et al., 1992; Benson and Zarcone, 2000) showed impaired sleep continuity (i.e. prolonged sleep onset latency, reduced sleep efficiency and increased number of awakenings) compared to normal controls. Particularly with respect to sleep efficiency and the number of awakenings concomitant medication might play a role because in the analysis of the patients on amisulpride only compared to matched healthy controls number of awakenings were no longer different significantly nor by trend. Our individualized lights-off procedure led to a significantly longer time in bed by about 1 h in the patients. As sleep efficiency refers to time in bed, this difference between the groups is relevant for this measure. In combination with the significantly prolonged sleep onset latency in the patients the decreased sleep efficiency in the patients might primarily be due to prolonged sleep onset latency. Furthermore, the patients on amisulpride only differ from controls in sleep onset latency and sleep efficiency but not in number of awakenings. Thus, the issue of sleep efficiency might rather be an issue of falling asleep than of keeping sleep. Further studies might more carefully monitor sleep continuity with these respects.

Our patients had a marked reduction in the absolute duration of SWS in comparison to normal controls. A decrease of SWS has been described in several previous studies (Feinberg et al., 1969; Hiatt et al., 1985). Keshevan and colleagues (1998) demonstrated that also in longterm non-medicated schizophrenic patients delta sleep is significantly decreased compared to healthy controls. Poulin et al. (2003) recently reported a significant decrease in stage 4 sleep in drug-naïve first-episode schizophrenic patients. Thus, even if the majority of the studies showing SWS decreases in schizophrenia are not done in drug-naïve patients and even if the first systematic study in drug-naïve patients by Lauer et al. (1997) did not find a significant effect on SWS in percent of sleep period time the impairment in SWS in schizophrenia might not be solely due to medication effects. Thus, our patients are quite typical individuals with schizophrenia. However, what effect the stable medication with amisulpride has in our patients with this respect cannot be answered by our study. Systematic data on the impact of amisulpride on sleep in schizophrenic patients have not yet been published. In healthy subjects amisulpride was devoid of any relevant effect on EEG or cognitive performance (Patat et al., 1999; Rosenzweig et al., 2002). Furthermore, it is unlikely that the concomitant medication used in four patients in our study is responsible for the differences seen between patients and controls because the most relevant results remained unchanged when we compared the subgroup of patients without concomitant medication and matched healthy controls.

We found that the amount of SWS, sleep efficiency, sleep onset latency and total sleep time were correlated with the performance in the spatial recall paradigm or in recall of the Rey-figure. Whereas sleep efficiency, sleep onset latency and total sleep time are general sleep measures and still might be correlated on the basis of the common sense association ''good and long sleep is good for neuropsychological performance'', the correlation with the amount of SWS is more specific. Furthermore, the correlation in particular with the spatial recall and the Rey paradigm but not with a procedural learning skill shows, that there is not a general effect on any neuropsychological test performance. Moreover, the significant difference between the subgroups split by amount of SWS particularly in the spatial recall paradigm is in line with the hypothesis that there is a functional interrelationship between SWS and spatial or declarative memory. This was already shown by sleep deprivation experiments in young healthy humans (Plihal and Born, 1997, 1999).

SWS and declarative as well as visuospatial memory are regulated particularly in the hippocampus and the thalamus. In both structures a memory task-related hypoactivity in schizophrenic patients was shown by functional neuroimaging (e.g. Heckers et al., 1998; Crespo-Facorro et al., 1999; Hazlett et al., 1999; Weiss et al., 2003). Furthermore, our results support recent models of memory consolidation during sleep. Buzsaki (1998) developed a model of hippocampal–neocortical interactions in which the flow of information entering and leaving the hippocampus is dependent on the brain's state of activity. He suggested, that the transfer of stored representations from the hippocampus to neocortical areas takes place during SWS. So, one might speculate that disturbed SWS impairs significantly neocortical encoding of information acquired during the day. This is congruent with detailed analyses showing that the impairment of memory in schizophrenia is caused by encoding and retrieval deficits (Paulsen et al., 1995; Aleman et al., 1999). It is a clinical correlate that therapies requiring advanced learning and memory functions are almost certain to be ineffective in schizophrenic patients (Aleman et al., 1999; Pilling et al., 2002). Therefore, we suggest that improving SWS might improve declarative memory impairment and functional outcome in schizophrenia. In healthy subjects, however, an increase in SWS might not necessarily further improve these memory functions because we did not find any correlation between SWS and neuropsychological tasks. This might be an indication for the presumption, that a critical basic amount of SWS is needed for consolidation of visuospatial memory.

Our pilot study was not designed to differentially investigate all aspects of the complex functions in memory with respect to sleep. However, these pilot results encourage further research on the putative functional

interrelationship between schizophrenia, different kinds of memory and sleep regulation. Research in this direction might lead to novel and successful strategies for treating neuropsychological deficits in schizophrenia more effectively, which continues to be a challenge in the field as mentioned at the beginning.

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