

A Failure of Sleep-Dependent Procedural Learning in Chronic, Medicated Schizophrenia

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Background: Schizophrenia patients have difficulty mastering even rote procedural tasks in rehabilitation settings. Although most studies demonstrate intact procedural learning in schizophrenia, recent findings demonstrate that a critical component of procedural learning is dependent on sleep. This study tested the hypothesis that patients with schizophrenia have a deficit in sleep-dependent procedural learning.

Methods: Using a simple, well-characterized test of motor skill learning, the finger tapping motor sequence task (MST), 26 patients with chronic, medicated schizophrenia and 14 demographically matched healthy control subjects were tested on two occasions, 24 hours apart. The main outcome measures were learning of the MST on day 1 (practice-dependent learning) and overnight, sleep-dependent improvement in performance.

Results: Although schizophrenia patients and control subjects did not differ in practice-dependent learning, patients failed to show overnight improvement (4% deterioration) and differed significantly from control subjects who showed a significant 11% improvement.

Conclusions: We present here the first demonstration of a failure of sleep-dependent consolidation of procedural learning in chronic, medicated schizophrenia. This deficit occurred in the context of normal practice-dependent learning within a training session. This behavioral dissociation is consistent with evidence that practice- and sleep-dependent motor learning reflect independent processes and suggests that they are differentially affected in schizophrenia.

Key Words: Cognition, motor skill, procedural learning, schizophrenia, sleep

In contrast to the well-documented deficits in declarative and working memory in schizophrenia (e.g., Aleman et al 1999; Manoach 2003), most studies have demonstrated intact procedural learning (Clare et al 1993; Goldberg et al 1993; Granholm et al 1993; Kern et al 1997; Weickert et al 2002). There is mounting evidence, however, that sleep plays a critical role in learning and memory consolidation, particularly for the procedural learning of perceptual (Gais et al 2000; Karni et al 1994; Stickgold et al 2000a, 2000b) and motor skills (Fischer et al 2002; Walker et al 2002), and the sleep-dependent components of procedural learning have not been investigated in schizophrenia. In this study, we investigated sleep-dependent consolidation of motor skill learning in schizophrenia.

We employed a simple, well-characterized test of motor skill learning, the finger tapping motor sequence test (MST; Karni et al 1998), which has been demonstrated to show sleep-dependent improvement (Walker et al 2002). When young healthy subjects were trained on this task, they showed a 10%–20% improvement in speed after a night of sleep, but not after an equivalent period of daytime wake. Additional nights of sleep led to more improvement, with no additional exposure to the task after the initial training (Walker et al 2003), but sleep deprivation the first night after training blocked all subsequent practice-independent im-

provement (Fischer et al 2002; Walker et al 2002). These findings demonstrate that overnight improvement on this task depends on sleep rather than the mere passage of time. Some studies have reported that overnight improvement on this and other simple motor skill tasks specifically correlates with the amount of stage 2 non-REM sleep in the latter quartile of the night (Smith and MacNeill 1994; Walker et al 2002), although one study found the improvement to be associated with REM sleep (Fischer et al 2002).

Schizophrenia patients often have difficulty mastering even rote tasks in rehabilitation and employment settings (Green 1996). Because their practice-dependent procedural learning appears to be intact (Clare et al 1993; Goldberg et al 1993; Granholm et al 1993; Kern et al 1997; Weickert et al 2002), we reasoned that their failure to master these tasks might reflect a deficit in the sleep-dependent component of procedural learning. We therefore tested the hypothesis that schizophrenia patients would show normal MST learning within a training session, but, unlike healthy subjects, they would fail to show overnight improvement.

Methods and Materials

Subjects

Outpatients with schizophrenia ($n = 26$) were recruited from an urban mental health center (Table 1). All had been maintained on a stable dose of antipsychotic medications for at least 6 weeks. Twenty-two took atypical agents (resperidone, clozapine, aripiprazole, or olanzapine), three took typical agents (fluphenazine or perphenazine), and one took both types of medication (aripiprazole and fluphenazine). Four patients were taking anticholinergic medications, and thirteen were taking diverse adjunctive medications for anxiety, agitation, concurrent mood disturbance, or a combination of these. Diagnoses were confirmed with Structured Clinical Interviews for DSM-IV (First et al 1997). Clinical status was characterized with the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962), the Positive and Negative Syndrome Scale (PANSS; Kay et al

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Table 1. Means, Standard Deviations, and Group Comparisons of Demographic Data and Rating Scale Scores

Subject Characteristics	Healthy Subjects (n = 14)	Schizophrenia Subjects (n = 26)	t	p
Age	44 ± 6	45 ± 9	.27	.79
Sex	9M / 5F	18M / 8F	Phi = .05	.99
Laterality Score (Handedness)	88 ± 19	67 ± 55	1.38	.18
Parental Education (years) ^a	13 ± 2	13 ± 2	.12	.91
Age of Onset		26 ± 9		
Length of Illness (years)		19 ± 10		
			Average Level of Severity	
BPRS		19 ± 10	Mild	
PANSS Positive		15 ± 5	Mild	
PANSS Negative		17 ± 7	Mild	
SANS		34 ± 15	Questionable	
AIMS		3 ± 2	None to minimal	
Simpson-Angus		3 ± 4	None to minimal	

The Phi value is the result of a Fisher's Exact Test.

AIMS, Abnormal Involuntary Movement Scale; BPRS, Brief Psychiatric Rating Scale; F = female; M = male; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms.

^aOne healthy and three schizophrenia subjects were unable to provide this information.

1987), and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1983). Movement abnormalities were characterized with the Abnormal Involuntary Movement Scale (AIMS, National Institute of Mental Health 1974) and the Simpson-Angus Rating Scale (Simpson and Angus 1970).

Healthy control subjects (n = 14) without a history of psychiatric illness were recruited from the community by newspaper advertisements. Both healthy and schizophrenia subjects were screened to exclude substance abuse or dependence within the past 6 months, sleep disorders, as well as any independent conditions that might affect brain function. The 26 schizophrenia patients and 14 control subjects did not differ in age, gender, laterality score on a handedness questionnaire (modified Edinburgh Handedness Inventory; White and Ashton 1976), or parental education. All subjects gave written informed consent, and the study was approved by the Institutional Review Board of the Massachusetts Department of Mental Health.

Procedures

Finger Tapping Motor Sequence Task (MST). The MST requires subjects to press four numerically labeled keys on a standard computer keyboard with the fingers of their left hand, repeating a five-element tapping sequence (e.g., 4-1-3-2-4) "as quickly and as accurately as possible" for a period of 30 sec. The keys V, B, N, and M were used, relabeled as 1, 2, 3, and 4. During finger-tapping trials, the numeric sequence was displayed in white against a green background at the top of the screen to minimize any working memory requirement. Each key press produced a white dot, forming a row from left to right. Once the row reached the edge of the screen, each subsequent key press removed a dot, right to left. When the dots had all been removed, further key presses added them again. The time and value of

each key press was recorded, and each 30-sec trial was automatically scored for the number of correct sequences and the number of errors. Each trial was followed by a 30-sec rest period, during which the screen was red and the number of seconds remaining before the start of the next trial was displayed as words, not numerals. After the countdown reached five, the words were replaced with tones, one per second, leading to the start of the next trial. Each session consisted of 12 trials.

Sternberg Item Recognition Paradigm (SIRP). A subset of the subjects performed a 30-min working memory task, the SIRP, shortly before or after the MST. The use of this task was discontinued due to concerns about possible interference with learning of the MST and because a sample of healthy young subjects failed to show any overnight improvement on the SIRP (Mason, unpublished data).

Experimental Design

Subjects were tested on 2 consecutive days between 9 AM and 6 PM, but always at the same time on both days. The two sessions, separated by 24 hours, constituted a single test of overnight improvement. All subjects were remunerated for participating in the study. In addition to a base payment for each session, they earned a bonus of two cents for each correctly typed sequence.

Protocol 1: MST and SIRP. We first studied 10 schizophrenia patients and 12 control subjects with both the SIRP and the MST. Half of each group performed the SIRP first and half performed the MST first during each session.

Protocol 2: MST Only. Performing the SIRP in the same session as the MST could conceivably lead to either fatigue or interference effects that might affect motor learning. To establish that the failure of overnight improvement in the schizophrenia group of Protocol 1 was not due to performing a second task (the SIRP) in the same session, we tested an additional 10 schizophrenia subjects and 2 control subjects on the MST alone.

Protocol 3: Extra Practice. Schizophrenia patients typed fewer sequences on day 1 than control subjects. To be certain that the failure of overnight improvement in schizophrenia was not an artifact of reduced practice, six additional patients performed two, rather than one, sessions of the MST on day 1, separated by a 10-min break.

Test-Retest Reliability. The variability in overnight improvement seen in schizophrenia patients was greater than that seen in normal subjects and might have reflected either individual differences or within subject variability. Establishing test-retest reliability would suggest that the degree of overnight improvement is a stable feature of patients with schizophrenia. To test reliability, 10 patients repeated the 2-day MST protocol using an alternate sequence (2-3-1-4-2). The time between the two experiments ranged from 21 to 338 days (mean 162 ± 105 days). We computed the intraclass correlation coefficient (ICC) to quantify the reliability of overnight improvement. The ICC represents the proportion of total variance accounted for by the variability between rather than within subjects.

Data Analysis

The main outcome measures were practice-dependent learning on day 1 and overnight improvement, from day 1 to day 2. These measures were based on the number of correct sequences completed per 30-sec trial, and reflect both the speed and accuracy of performance. We compared schizophrenia and control groups on the outcome measures using both simple *t* tests and an exponential model of asymptotic learning.

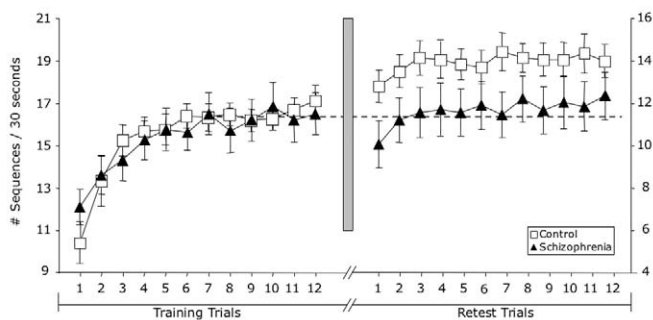


Figure 1. Motor skill learning across training and retest trials for healthy control subjects ($n = 14$, open squares) and schizophrenia patients ($n = 20$, closed triangles). The data point for each trial represents the group average \pm SE. The y axes represent the number of correct sequences typed in each 30-sec trial. Note that the y axes are scaled separately for control subjects (left) and patients (right) to better illustrate the qualitative similarity of learning curves on day 1 and the failure of overnight improvement in the schizophrenia group only. The dashed line is positioned at the mean value of the last three training trials for both the control and patient groups. The shaded bar represents the passage of 24 hours, including a night of sleep. Patients and control subjects did not differ in the amount of learning during training, but only control subjects showed significant overnight improvement.

Simple Comparisons. Performance at the end of the session on day 1 was compared with performance at the beginning of that session (practice-dependent “day 1” learning) and with performance at the beginning of the next session, on day 2 (overnight improvement). Practice-dependent learning was calculated as the percent increase in correct sequences typed from the first trial to the average of the last three trials on day 1 (one control, who typed the wrong sequence during the first trial of day 1, was excluded from this analysis). Overnight improvement was calculated as the percent increase from the average of the last three trials of day 1 to the average of the first three trials of day 2. Pearson Product–Moment correlation coefficients were used to describe the relationships between motor learning and clinical rating scale scores.

Exponential Model. In addition to comparing performance from the beginning and end of each session, we used modeling techniques to fit the learning curves across the two sessions for the control and schizophrenia groups, thereby making use of all of the trials. Exponential models capture monotonic increases in performance from trial to trial and are appropriate in situations when the improvement between successive trials steadily decreases and performance asymptotes. Specifically, the averaged data for each group was fit to the equation, $Y = I + C(1 - R^{t-1}) + Dd + e$, where Y = correct sequences typed on trial t ; I = initial performance (average score on trial 1); C = change in performance from trial 1 to the asymptote (amount learned); $1 - R$ = the learning rate; t = trial number; D = overnight improvement; $d = 0$ (for day 1) or $d = 1$ (for day 2); and e is a stochastic error term. The best fit values for the coefficients of the models, R , I , C , and D were calculated for the two groups and were compared using z tests.

Results

Protocol 1: MST and SIRP

Schizophrenia patients ($n = 10$) did not show any overnight improvement ($t(9) = .94$, $p = .37$). On average, their performance fell by $6 \pm 6\%$ (mean \pm SE) for the first three trials of day 2. Control subjects ($n = 12$), in contrast, showed a $12 \pm 3\%$ improvement

overnight ($t(11) = 4.16$, $p = .002$) and significantly more improvement than the schizophrenia patients ($t(20) = 2.72$, $p = .01$). At the same time, the two groups did not differ significantly in practice-dependent learning on day 1 ($t(19) = .48$, $p = .64$).

Protocol 2: MST Only

Schizophrenia patients who performed only the MST ($n = 10$), did not differ in practice-dependent learning from the patients in Protocol 1 ($t(18) = 1.09$, $p = .29$) and, like the patients in Protocol 1, failed to show any overnight improvement ($-.8 \pm 3.3\%$; $t(9) = .40$, $p = .77$). Two control subjects also participated in Protocol 2.

Protocols 1 and 2 Combined

Because the schizophrenia patients in the two protocols did not differ, the data from Protocols 1 and 2 were combined and are depicted in Figure 1 ($n = 20$ patients; $n = 14$ control subjects). For the combined groups, patients again showed no overnight improvement ($3 \pm 4\%$ deterioration), and significantly less than control subjects ($t(32) = 3.00$, $p = .005$) who showed a significant $11 \pm 3\%$ improvement ($t(13) = 4.66$, $p = .0004$). Despite the lack of overnight improvement, patients did not differ from control subjects in practice-dependent learning on day 1 (patients: $134 \pm 279\%$; control subjects: $88 \pm 93\%$; $t(31) = .57$, $p = .57$). Excluding a patient who was an outlier due to having typed only one correct sequence during the first trial (1267% improvement, 4.06 SD above the group mean), rendered the groups even more similar in practice-dependent learning (patients: $74 \pm 83\%$; control subjects: $88 \pm 93\%$; $t(30) = .43$, $p = .67$). This patient was excluded from all subsequent analyses of practice-dependent learning.

Protocol 3: Extra Practice on Day 1

Although control subjects (Protocols 1 and 2 combined) typed an average of 186 ± 23 sequences correctly in the 12 trials on day 1, schizophrenia patients typed significantly fewer, only 123 ± 46 ($t(33) = 4.55$, $p < .0001$). Thus, the failure of overnight improvement in the schizophrenia group could have, in theory, resulted from a failure to reach a threshold level of practice needed to trigger sleep-dependent processes. To test this possibility, an additional group of six patients performed the MST twice on day 1, averaging 314 ± 95 correct sequences across the 24 trials, almost 70% more than the control subjects, who only performed

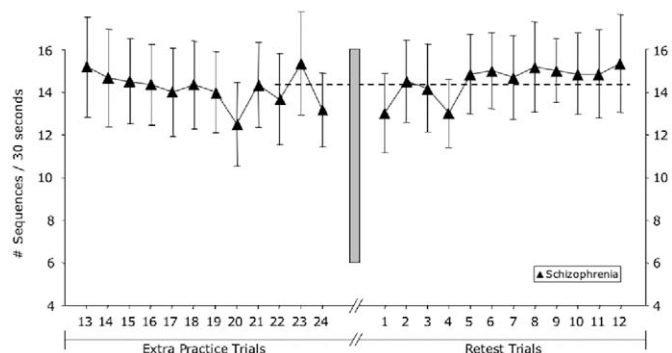


Figure 2. Motor skill learning for schizophrenia patients ($n = 6$) during extra practice and retest trials. The data points for each trial represent the group average \pm SE bars. Although these patients performed almost 70% more trials than control subjects on day 1, they still failed to show significant overnight improvement. The dashed line is positioned at the mean value of the last three extra practice trials. The shaded bar represents the passage of 24 hours including a night of sleep.

the MST once. Despite the additional training, these patients still showed no overnight improvement (Figure 2, $.7 \pm 6\%$ deterioration; $t(5) = .57, p = .60$).

As in previous studies (Walker et al 2003) we also calculated the error rate as the number of errors divided by the number of correct sequences typed. This measure is subject to large fluctuations due to the restricted range of errors and is therefore less sensitive than our primary outcome measure of number of correct sequences completed per trial. Control subjects showed a mean decrease in error rate overnight ($-6.3\% \pm 43\%$) and patients an overall increase in error rate ($11.5\% \pm 55\%$), but the groups did not differ significantly from each other [$t(37) = 1.05, p = .30$]. One patient was omitted from these analyses due to an error rate of zero during the last three trials of Day 1. Both groups showed less improvement in error rate than the 35% overnight improvement previously reported for young healthy subjects (Walker et al 2003).

Relations of Motor Learning and Rating Scale Scores

Practice-dependent learning on day 1 was not significantly correlated with scores on the AIMS ($r = -.03, p = .89$), Simpson-Angus ($r = .07, p = .75$), the positive and negative symptom subscales of the PANSS ($r = -.14, p = .52$ and $r = .04, p = .86$, respectively), the BPRS ($r = -.29, p = .18$), or SANS ($r = .29, p = .17$). Nor was overnight improvement significantly correlated with scores on any of the movement disorder or clinical rating scales (AIMS, $r = .16, p = .49$; Simpson-Angus, $r = -.13, p = .58$; PANSS positive, $r = .10, p = .63$; PANSS negative, $r = .20, p = .34$; BPRS, $r = .00, p = .99$; SANS, $r = .03, p = .90$). Practice-dependent learning and overnight improvement were not significantly correlated in either group (healthy, $r = -.04, p = .90$; schizophrenia, $r = -.13, p = .53$).

Test-Retest Reliability

Ten schizophrenic patients from Protocols 1 and 2 returned 21-338 days later to be trained and tested on a second motor sequence. Individual patients showed a similar amount of overnight change on the two occasions as indicated by an ICC of .66. Stability of performance was not significantly related to the number of days that elapsed between test and retest ($r = .20, p = .59$).

Exponential Model

The exponential model provided a good fit to the data for both the schizophrenia and control groups (Protocol 1 and 2 combined; Figure 3). Table 2 presents the coefficient estimates for each of the terms in the model for each group. These analyses confirm that although patients typed fewer correct sequences on the initial trial (I), they did not differ from the control subjects with regard to the amount learned (C), or the learning rate ($1-R$). The only significant difference between the two groups in learning was in the amount of overnight improvement (D). Only the control group showed significant overnight improvement (control subjects, $p < .0001$; patients, $p = .998$). This analysis confirms our hypothesis that schizophrenia patients are specifically deficient in sleep-dependent learning and not in either the rate or amount of practice-dependent learning seen during a 12-trial training session.

Discussion

Unlike healthy control subjects, three consecutive samples of schizophrenia patients (Protocols 1-3) failed to show any overnight improvement on a task of motor skill learning, and this

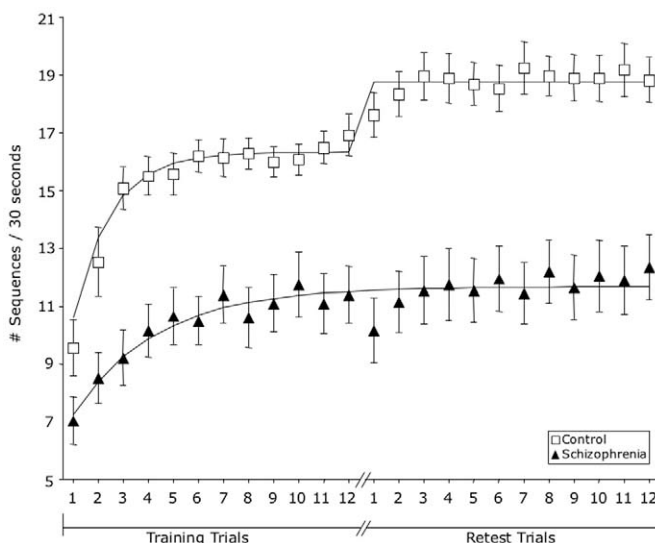


Figure 3. Exponential model of motor learning for control subjects ($n = 14$, open squares) and schizophrenia patients ($n = 20$, closed triangles) across training and retest trials. The models provide a good fit for the group-averaged data (\pm SE). The diagonal lines on the x-axis represent the passage of 24 hours including a night of sleep. Although patients typed fewer correct sequences on the initial trial, they did not differ from control subjects with regard to the amount or rate of learning. The groups differed significantly in the amount of overnight improvement. The null hypothesis of no overnight improvement was rejected for control group ($p < .0001$), but not for the patient group ($p = .998$). See Table 2 for the model coefficient estimates.

finding showed reasonable stability when individual subjects were retested at a later date. This represents the first demonstration of a failure of sleep-dependent consolidation of procedural learning in chronic, medicated schizophrenia. This failure occurred in the context of normal rates and amounts of practice-based learning within a training session and could not be accounted for by reduced practice during the training session. These findings are consistent with previous demonstrations of intact practice-dependent procedural learning in schizophrenia (Clare et al 1993; Goldberg et al 1993; Granholm et al 1993; Kern et al 1997; Weickert et al 2002). Instead, we have identified a failure specifically of the sleep-dependent component of procedural learning. This behavioral dissociation in schizophrenia complements recent work in healthy subjects that establishes that practice- and sleep-dependent aspects of learning on the MST are uncorrelated and appear to reflect discrete processes of motor learning (Walker et al 2003). Indeed, we found that practice- and sleep-dependent learning were not correlated in either the control or the schizophrenia group.

These findings raise a number of important questions regarding both the locus of the failure and its underlying mechanism. Regarding the locus of the failure, a number of distinct possibilities exist: 1) defective stabilization of the initial learning before sleep may lead to a failure to activate normal sleep-dependent processes, 2) the failure to activate sleep-dependent processes may be secondary to inadequate or poor quality sleep, or 3) the sleep-dependent processes themselves may be deficient in schizophrenia and therefore incapable of producing performance enhancement.

With regard to the first possibility, although improvement within the initial session was intact, encoding may have been incomplete or it may have been subsequently degraded, perhaps because of interference from other sensorimotor activity, and this

Table 2. Coefficient Estimates and Their Standard Errors (in Parentheses) for the Exponential Model of Motor Learning

	<i>I</i>	<i>C</i>	<i>R</i>	<i>D</i>
Healthy (<i>n</i> = 14)	10.685 (.707)	5.797 (.737)	.514 (.098)	2.447 ^a (.368)
Schizophrenia (<i>n</i> = 20)	7.316 (.892)	4.463 (1.018)	.742 (.136)	.001 ^a (.799)
<i>p</i> Value	.003 ^b	.17	.29	.005 ^b

I is the initial performance rate (average score on trial 1); *C* is the change in performance rate from trial 1 to the asymptote (amount learned); *R* represents the learning rate; *D* models overnight improvement. The *p* values are based on two-sided *z* tests comparing the healthy control and schizophrenia groups.

^aThe null hypothesis of no overnight improvement was rejected for control subjects ($p < .0001$), but not for the patient group ($p = .998$).

^bSignificant group difference at $p \leq .05$.

may have led to a failure to trigger sleep-dependent processes. Skilled motor performance is thought to be acquired in several stages including within-session improvement, followed by several hours of stabilization during wakefulness (Karni et al 1998) during which time the initial learning becomes resistant to interference (Walker et al 2003), followed by sleep-dependent consolidation that produces enhanced performance. It remains untested whether normal stabilization of MST learning occurs in schizophrenia.

A second possibility is that a significant sleep disturbance underlies the failure of overnight improvement. Schizophrenia is characterized by moderately disturbed sleep consisting primarily of reduced amounts of slow wave sleep and shortened REM latency (for review, see Keshavan et al 1990). These abnormalities have been documented in some (Keshavan et al 1998; Poulin et al 2003), but not all, studies of first-episode, neuroleptic-naïve patients (Lauer et al 1997); are not specific to schizophrenia (Hoffmann et al 2000); and appear to characterize only a subgroup of patients (Keshavan et al 1990). Other studies have documented reductions in stage 2 sleep (Lauer et al 1997), although, again, this is not consistently observed (e.g., Poulin et al 2003). In our study, because we did not measure sleep, we cannot rule out the possibility that a sleep disturbance is responsible for the failure of overnight improvement in schizophrenia.

The hypothesis that we prefer is that the failure of overnight improvement reflects a deficit in the sleep-dependent processes responsible for the consolidation of new learning and occurs in the context of essentially normal sleep architecture (i.e., in the absence of changes either in total REM sleep or stage 2 non-REM sleep, both of which have been suggested to mediate the overnight consolidation of learning on this task; Fischer et al 2002; Walker et al 2002). This claim is not, as it may appear, contradictory. Sleep-dependent learning is likely to rely not so much on specific, supraordinal brain states such as REM sleep, but on discrete brain processes linked to these states, such as REM-associated pontogeniculooccipital (PGO) waves. For example, in rats, both the amount of REM sleep and the density of P-waves (the rat equivalent of PGO waves) increase dramatically after initial avoidance learning, and correlate strongly with the retention of learning following sleep (Datta 2000); however, experimentally induced P-waves, in the context of REM deprivation, also support postsleep retention and thus replace the normal requirement for REM sleep. This suggests that it is P-waves, rather than REM sleep, that are necessary for this sleep-dependent memory consolidation (Datta et al 2004). Similarly, in schizophrenia, a deficit in sleep spindles in conjunction

with normal amounts of stage 2 sleep could lead to a failure of overnight improvement. This hypothesis is based on the finding that overnight improvement of the MST specifically correlates with the amount of stage 2 non-REM sleep in the latter quartile of the night (Walker et al 2002), when spindle activity is maximal.

While this initial behavioral study identifies a failure of overnight improvement, it cannot distinguish between the possible loci of failure described earlier. It will be necessary to replicate these findings in a group in which sleep is recorded polysomnographically to determine whether these sleep-dependent processes fail as a function of changes in overall sleep quantity and architecture. Our findings also fail to explain the mechanism of this disturbance. Again, a number of possibilities present themselves, including medication effects, chronicity effects, and, perhaps most intriguingly, a core deficit related to the etiology of schizophrenia.

With regard to medication effects, all of the patients in our sample were taking antipsychotic medications, four were taking anticholinergic medications, and half were taking other adjunctive medications. Treatment with antipsychotic medications is well known to affect sleep (for review, see Monti and Monti 2004). Most studies, however, report a normalization of sleep measures for both typical and atypical agents (e.g., Maixner et al 1998; Salin-Pascual et al 1999), making it unlikely that these drugs lead to sleep disturbances that underlie the failure of sleep-dependent consolidation at any of the loci described here. Although the sample is too small for a formal analysis, comparing overnight improvement by medication did not suggest differential effects. A study of unmedicated or, ideally, medication-naïve patients would be required to exclude the possibility that medications contribute to our findings.

Another possible cause of this deficit is the progression of the illness or diverse nonspecific effects of chronic illness. Our sample was limited to chronically ill patients, with an average duration of illness of 19 ± 10 years. Studies to assess medication and chronicity effects are currently underway. If the failure of sleep-dependent consolidation observed here is found to be independent of chronicity and medication, it would suggest that this failure instead reflects brain abnormalities that are associated with the pathophysiology of schizophrenia. For example, this failure may contribute to a more fundamental breakdown in mechanisms of task automation. Although the possibility of defective automation in schizophrenia has been raised previously (Granholm et al 1996; Manoach et al 2000), automation per se has not been a focus of study in schizophrenia. Nonetheless, abundant incidental evidence, including neuroimaging studies of working memory (Jansma et al 2004; Manoach 2003) suggests that such a deficit exists.

Over the last 10 years, our understanding of the role of sleep in learning and memory consolidation has become increasingly refined (Maquet 2001). Regardless of the locus of the failure of overnight improvement and its underlying basis, the finding of a failure in sleep-dependent procedural learning has important implications for understanding and treating cognitive dysfunction in schizophrenia. Aside from its obvious importance for the consolidation of recent procedural learning, the need to allocate increased executive resources to task components that would otherwise be relatively overlearned as a function of sleep would diminish the resources available for other, higher-order, task components. We hypothesize that this failure of sleep-dependent learning represents a breakdown, not in the overall structure of sleep, but rather in specific memory consolidation processes that are normally activated during sleep and that may normally

contribute to the process of task automation. Further study is necessary to determine whether sleep-dependent processes fail as a function of sleep itself and to identify the mechanism of this failure.

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