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Spared and impaired sleep-dependent memory consolidation in schizophrenia

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Abstract

Objective: Cognitive deficits in schizophrenia are the strongest predictor of disability and effective treatment is lacking. This reflects our limited mechanistic understanding and consequent lack of treatment targets. In schizophrenia, impaired sleep-dependent memory consolidation correlates with reduced sleep spindle activity, suggesting sleep spindles as a potentially treatable mechanism. In the present study we investigated whether sleep-dependent memory consolidation deficits in schizophrenia are selective.

Methods: Schizophrenia patients and healthy individuals performed three tasks that have been shown to undergo sleep-dependent consolidation: the Word Pair Task (verbal declarative memory), the Visual Discrimination Task (visuoperceptual procedural memory), and the Tone Task (statistical learning). Memory consolidation was tested 24h later, after a night of sleep.

Results: Compared with controls, schizophrenia patients showed reduced overnight consolidation of word pair learning. In contrast, both groups showed similar significant overnight consolidation of visuoperceptual procedural memory. Neither group showed overnight consolidation of statistical learning.

Conclusion: The present findings extend the known deficits in sleep-dependent memory consolidation in schizophrenia to verbal declarative memory, a core, disabling cognitive deficit. In contrast, visuoperceptual procedural memory was spared. These findings support the hypothesis that sleep-dependent memory consolidation deficits in schizophrenia are selective, possibly limited to tasks that rely on spindles. These findings reinforce the importance of deficient sleep-dependent memory consolidation among the cognitive deficits of schizophrenia and suggest sleep physiology as a potentially treatable mechanism.

Keywords: schizophrenia; sleep, memory consolidation; declarative memory; procedural memory; statistical learning

Text

1. Introduction

It is now well-established that sleep plays a critical role in memory consolidation – processes that stabilize and enhance recently encoded memories, integrate them into existing associative networks and extract generalities from their content (Stickgold, 2005; Walker and Stickgold, 2010). Recent work in both humans and animal models has demonstrated the importance of specific brain oscillations, including sleep spindles, in the consolidation of different memory types during sleep (Dudai et al., 2015; Rasch and Born, 2013; Stickgold and Walker, 2013). Schizophrenia (SZ) patients show a specific reduction in sleep spindles (for review see Manoach et al., 2016), a thalamocortical oscillation characterizing non-rapid eye movement (NREM) Stage 2 sleep (N2). Sleep spindles correlate with IQ and are thought to both promote long-term potentiation and enhance memory consolidation (Fogel and Smith, 2011). Chronic medicated SZ patients also have reduced sleep-dependent consolidation of motor procedural memory (Genzel et al., 2015, 2011, Manoach et al., 2010, 2004; Wamsley et al., 2012) and declarative memory for pictures (Göder et al., 2015), deficits that correlate with reduced spindle activity (Göder et al., 2015; Wamsley et al., 2013, 2012). Reduced spindle activity that correlates with cognitive function is also seen in non-psychotic first-degree relatives of SZ patients and early-course antipsychotic drug-naïve SZ patients (Manoach et al., 2014; Schilling et al., 2017) suggesting that the spindle deficit is an endophenotype of SZ (Manoach et al., 2016). The goal of the present study was to better define the scope of the sleep-dependent memory deficit in SZ. Findings of dissociations (*e.g.*, reduced sleep-dependent consolidation of motor procedural memory in the context of intact consolidation of memory for a complex figure; Seeck-Hirschner et al., 2010), suggest that only certain memory types are affected. In the present study we tested the hypothesis that deficits in sleep-dependent memory consolidation of memory are selective and present on tasks that have previously been associated with spindles.

A challenge to studying sleep-dependent memory consolidation in SZ is identifying tasks that allow patients to achieve a comparable level of baseline (pre-sleep) performance to controls. This makes it less likely that any observed group differences in sleep-dependent consolidation reflect encoding differences at baseline. The three tasks utilized meet this criterion and have shown sleep-dependent consolidation in healthy adults (*i.e.*, better performance after sleep than after an equivalent interval of daytime wake). We probed declarative

memory with a Word Pair Task (WPT) that requires learning of semantically unrelated word pairs. Previous work shows that sleep "protects" newly learned word pairs (*i.e.*, results in reduced forgetting and less susceptibility to interference (Ellenbogen et al., 2006; Payne et al., 2012; Wilson et al., 2012). Sleep-dependent protection of WPT performance correlates with the percentage of NREM Stage 3 sleep (N3) during a daytime nap (Baran et al., 2016), percentage of NREM (N2 plus N3) during nocturnal sleep (Mantua et al., 2015) and with sleep spindles (Gais et al., 2002; Lustenberger et al., 2015; Schabus et al., 2008, 2004; Schmidt et al., 2006; Studte et al., 2017). Transcranial direct current stimulation that increases time spent in N3, slow oscillations and the number of slow spindles (8-12Hz) enhances WPT recall (Marshall et al., 2006, 2004) while transcranial alternate current stimulation disrupting slow wave activity impairs it (Garside et al., 2015).

The visual discrimination task (VDT) measures visuoperceptual procedural memory, requiring participants to determine the arrangement of a target embedded in a background of distractors (Karni et al., 1994). The target screen is presented briefly and is followed, after a variable interstimulus interval (ISI), by a mask screen, allowing determination of a threshold ISI – the minimum ISI required for 80% accuracy. After sleep, the threshold ISI is reduced (Karni et al., 1994; Stickgold et al., 2000a) and this improvement in performance correlates with percent of time in N3 in the first quarter of the night and rapid eye movement (REM) sleep in the last quarter of the night, but is best predicted by the product of these two sleep parameters, suggesting a two-step consolidation process (Stickgold et al., 2000b).

Finally, we investigated sleep-dependent consolidation of statistical learning using the Tone Task (Durrant et al., 2011). Participants hear a probabilistically determined sequence of notes. They are then asked to identify which of two brief sequences sounds similar. Sleep improves the recognition of novel sequences with the same structure presumably by facilitating the abstraction of statistical rules embedded in the sequences. Post-sleep improvement correlates with time in N3 (Durrant et al., 2013, 2011).

2. Materials and Methods

2.1. Participants

Schizophrenia outpatients (n=28), diagnosed with a Structured Clinical Interview for DSM-IV (SCID; First et al., 1997) and characterized with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987)) were recruited from an urban mental health center. Two patients were unmedicated, and the rest were maintained on stable doses of antipsychotic medications and adjunctive agents (including antidepressants, benzodiazepines and mood stabilizers; Supplemental Table 1) for at least six weeks.

Healthy controls (n=32), screened to exclude personal histories of mental illness with a SCID-Non-Patient Edition; First et al., 2002) or family histories of SZ spectrum disorders or psychosis, were recruited from the community through advertisements.

Potential participants with current diagnoses of sleep disorders, treatment with sleep medications, a history of significant head injury or neurological illness or substance abuse or dependence within the past six months were excluded.

Controls and patients did not differ in age or parental education but there were more males in the schizophrenia group (trend-level difference: p=0.06; Table 1).

The study was approved by the Partners Human Research Committee and participants gave written informed consent. In addition to a base rate of pay, participants received a bonus of $0.05 for each correct response on the memory tasks as an incentive to enhance attention and motivation.

2.2. General Procedure

Training and Test sessions were separated by 24h to avoid circadian effects. Tasks were presented in a fixed order (Figure 1A) and each session lasted approximately 2h. At the beginning of each session, participants filled out the Stanford Sleepiness Scale (SSS; Hoddes et al., 1973)) to measures alertness. At the end of the Test session, participants completed a questionnaire about sleep duration and quality for the previous night, daytime caffeine use and how well-rested they felt.

2.3. Word-Pair Task (WPT)

Stimuli were 24 semantically unrelated word pairs (Payne et al., 2012). The task consisted of four phases: Initial Exposure, Feedback Training, Pre-Sleep Test and Post-Sleep Test (Figure 1B). Participants

were presented with 24 word pairs and instructed to “remember which words go together.” During Initial Exposure, participants studied cue-target word pairs. During Feedback Training, participants were presented with the cue and asked to recall the target; feedback was provided. Pre- and Post-Sleep recall were tested with no feedback.

2.4. Visual Discrimination Task (VDT)

The VDT (Stickgold et al., 2000a) was adapted for a population with SZ by adding a task demonstration, having subjects report the peripheral target orientation *before* rather than after the letter, and monitoring fixation. Participants were tested in a dark room while resting their head on a chin rest 35-40cm from the computer screen. Participants completed the task demonstration to preview the trial structure and practice response key mapping. To initiate each trial, participants fixated a white cross in the center of a black screen and after a jittered interval the target screen would appear (Figure 1C). Fixation was monitored with an eye tracker (EyeLink II, SR Research, Ontario, CA). Target screens contained a rotated “T” or “L” at the center and a horizontal or vertical array of three diagonal bars in the lower-left quadrant. Following the target screen, a blank screen appeared for an ISI of 20-400ms and then a mask. After the mask, participants indicated whether the three diagonal bars were arranged horizontally or vertically and whether the central letter was a T or an L. Each block consisted of 50 trials with a constant ISI. Both Pre and Post-Sleep tests consisted of one block each at ISIs of 400, 300, 200 and 160ms, followed by three blocks each at ISIs of 120 down to 20ms, in decrements of 20ms. The task was discontinued when a participant failed to correctly identify the arrangement of the diagonal lines on at least 66% of the trials for two consecutive blocks. The outcome measure was the detection threshold defined as the interpolated ISI at which the participant’s accuracy for reporting the arrangement of the diagonal lines dropped to 80%.

2.5. Tone Task

The task was adapted from Durrant et al (2011). Stimuli consisted of sequences of pure tones taken from the Bohlen-Pierce scale (frequencies 262Hz, 301Hz, 345Hz, 397Hz and 456Hz). During Exposure, participants listened to a single, structured, continuous tone stream (Figure 1D). Pre- and Post-Sleep tests took place immediately and 24h after Exposure, respectively. During each test trial, participants were presented with a structured and an unstructured 18-tone sequence and asked which sounded “more familiar.” One

sequence was randomly generated and the other was a structured sequence that adhered to the statistical pattern of the exposure stream. The sequence structure is based on a probabilistic transition matrix similar to Durrant et al. (2011) except using first-order rather than second-order transitions. Difficulty was manipulated by varying the number of "likely" transitions in the structured test sequences, with harder sequences having fewer. Equal numbers of easy, medium and hard sequences were pseudorandomly presented during the test. While Durrant et al (2011) set the number of likely transitions in each 18-tone sequence to 14, 11 and 8 for easy, medium and hard sequences, respectively, we used 16, 15 and 14 likely transitions to make the task easier for older controls and patients with SZ.

2.6. Data Analysis

We investigated overnight performance changes using repeated measures ANOVA with the within-subjects factor Session (Pre-Sleep vs. Post-Sleep) and the between-subjects factor Group (patients vs. controls). For the Tone Task we added a within-subjects factor of Difficulty (Easy, Medium or Hard). We used post-hoc t-tests to compare groups on overnight change in performance calculated as the percent change in performance from the Pre- to Post-Sleep test.

3. Results

3.1. Self-report of sleep quality and alertness

Patients reported greater total sleep time, longer latency to initiate sleep, deeper sleep and better sleep quality than controls (Table 2). The groups did not differ significantly in alertness upon awakening, alertness during the day, caffeine consumption or number of arousals during sleep. They did not differ in SSS ratings of alertness at either session (Training − controls: 2.0±1.0[SD], patients: 1.6±0.7, t(58)=1.5, p=0.13; Test − controls: 2.5±1.3, patients: 2.2±1.4, t(58)=.93, p=0.36).

3.2. Word Pair Task.

SZ patients required more Feedback Training to reach criterion (5.4±2.9 vs. 3.1±2.1 trials, t(56)=3.47, p=0.001), but did not differ from controls on the Pre-Sleep Test (controls: 68±11%, patients: 62±14%; t(56)=1.6, p=0.12). Patients, but not controls, showed a significant decline in performance (i.e. forgetting) at the Post-Sleep Test (Figure 2A; Group by Session interaction: F(1,56)=5.0, p=0.03; controls: -3.1±13.5%,

t(30)=1.3, *p*=0.19; patients: -11.5±15.8%, t(26)=3.8, *p*<.001), and significantly greater forgetting than controls (t(56)=2.2, *p*=0.03). Thus, despite similar Pre-Sleep Test performance, patients averaged more than three times the forgetting seen in controls (11.5% *vs*. 3.1%). Similar results were obtained when absolute, rather than relative, forgetting was measured (word pairs forgotten: 0.47 controls *vs*.1.56 patients; t(56)=2.2, p=0.03). Consolidation of the WPT was not correlated with either the number of Feedback Training trials (r=.16, *p*=0.42) or Pre-Sleep Test performance (r=-.27, *p*=0.16) in SZ. In summary, despite comparable pre-sleep recall, unlike controls, patients failed to show evidence of overnight consolidation of word pair learning.

3.3. Visual Discrimination Task

Both groups showed significant overnight improvement (Session main effect: F(1,44)=11.7, *p*=0.001), and performed comparably on all measures of learning and overnight improvement (all *p*'s >0.4). At training, patients displayed an average detection threshold of 133ms, compared to 134ms for controls (t(44)=0.10, *p*=0.93), while the next day thresholds were 110ms and 120ms, respectively (t(44)=0.93, *p*=0.36). Overnight, patients improved by 12±25% (Figure 2B; t(19)=2.1, *p*=0.049; absolute improvement: 23±49ms; t(19)=2.1, *p*=0.047), while controls improved by 8±13% (t(25)=3.1, *p*=0.004; absolute improvement: 14±23ms; t(25)=3.1, *p*=0.004). Improvement in the two groups did not differ significantly (t=0.63, *p*=0.50; absolute improvement: t(44)=.75, *p*=0.42). Overall, no group differences were found in either VDT learning or overnight consolidation.

3.4. Tone Task

Both groups learned to discriminate between structured and unstructured sequences; Pre-Sleep Test performance was above chance for both groups at all difficulty levels (all *p*'s<0.001). Across difficulty levels, performance ranged from 67% to 81% correct for controls and from 63% to 79% for patients, with higher accuracy on easier trials (main effect of difficulty: F(2,51)=78.2, *p*<.001). However, contrary to expectation, there was no significant overnight improvement in either group and no group differences at any difficulty level (Session main effect: F(1,52)=.03, p=0.87; Group main effect: F(1,52)=.76, *p*=0.39; all interactions: *p*>0.14).

3.5. Correlation of sleep-dependent changes in performance across tasks

In general, overnight changes on one task did not predict changes on other tasks in the same individual (pairwise regression models; all task effects *p*>0.21, all group by task interactions, *p*>0.17).

3.6. Control analyses

Because there were more males in the schizophrenia group, we repeated our main analyses in males only. Restricting the sample to males did not substantially change our findings (Supplement). Neither antipsychotic dosage, measured as chlorpromazine equivalents (Woods, 2003) (all *p*'s≥.48) nor age correlated with overnight improvement on any task. For age these relations did not differ by group (regression of age, group and age by group interaction, all *p*'s≥.12).

4. Discussion

On three tasks of sleep-dependent memory consolidation, SZ patients reached similar performance levels as healthy controls after training, but showed a selective deficit in the sleep-dependent consolidation of word pair learning (WPT). This deficit in sleep-dependent verbal declarative memory consolidation occurred in the context of intact consolidation of visuoperceptual procedural memory (VDT). Previous studies of SZ have shown deficits in sleep-dependent memory consolidation of motor procedural memory on the finger tapping motor sequence task (Genzel et al., 2015, 2011, Manoach et al., 2010, 2004; Wamsley et al., 2012) and visual declarative memory for a picture recognition task (Göder et al., 2015). Sleep-dependent consolidation of both these tasks correlates with sleep spindle density in SZ patients and healthy individuals (Albouy et al., 2013; Barakat et al., 2011; Göder et al., 2015; Nishida and Walker, 2007; Wamsley et al., 2012) and, for the motor sequence task, with the temporal coordination of spindles with cortical slow waves in SZ (Demanuele et al., 2017). Since overnight consolidation of the WPT, but not the VDT, has been shown to correlate with sleep spindles (Gais et al., 2002; Lustenberger et al., 2015; Schabus et al., 2008, 2004; Schmidt et al., 2006; Studte et al., 2017) the present findings are consistent with the hypothesis that deficits in sleep-dependent memory consolidation in SZ are mediated by sleep spindle deficits (for review see Manoach et al., 2016)).

Verbal declarative memory, along with attention and executive function, are the most impaired neurocognitive domains in SZ. Deficits in verbal declarative memory are present in individuals at high-risk for SZ, including non-psychotic relatives (Whyte et al., 2005), and in antipsychotic-naïve first episode patients and chronic patients (Saykin et al., 1994) and remain fairly stable over time, suggesting that they are a trait reflecting genetic risk for SZ (for review see Cirillo and Seidman, 2003). Previous studies have been restricted to studying verbal declarative memory deficits within a single session, typically with delays of approximately 30

min (e.g., Saykin et al., 1994) similar to the delay in the WPT Pre-sleep Test. The present study demonstrates for the first time a seemingly independent deficit in the sleep-dependent consolidation of verbal declarative memory in SZ. Although patients needed more exposure to the word pairs to reach criterion, they showed a comparable level of recall 30 minutes after the end of training and their encoding deficit did not correlate with their overnight deficit. It is possible that sleep-dependent deficits in verbal memory exacerbate the effects of verbal encoding deficits to worsen functional disability.

Despite the impairment of sleep-dependent verbal declarative memory consolidation in the present study and of motor procedural memory in prior work, SZ patients showed intact sleep-dependent consolidation of visuoperceptual procedural memory. Examination of performance indicates that the absence of a group difference is unlikely to reflect ceiling or floor effects or reduced sensitivity of this task compared with the WPT. Rather than correlating with sleep spindles, this type of memory has mostly been shown to correlate with N3 early in the night and rapid eye movement (REM) sleep late in the night (Aeschbach et al., 2008; Karni et al., 1994; Stickgold et al., 2000b).

Unexpectedly, neither group showed significant consolidation of statistical learning on the Tone Task. Previous reports in healthy young adults reported significant sleep-dependent enhancement with both overnight sleep and daytime naps, which was associated with N3 (Durrant et al., 2013, 2011). Although the participants in the present study were older (31±7 vs. 22±6 yrs), age explained less than 1% of total variance. Another possible source of the failure of overnight improvement is that modifications made the task too easy. Several studies have found sleep-dependent improvement on memory tasks to depend on task difficulty or the success of individual subjects in learning it (Peters et al., 2007; Tucker and Fishbein, 2008). Indeed, Durrant et al. (2011) only observed sleep-dependent improvement when baseline performance was 60% or lower and not when 70% or higher. In the current study, both groups showed baseline performances greater than 60% at all difficulty levels, and above 70% for medium and easy levels.

The present findings of impaired overnight preservation of word pair associate learning in the context of intact visuoperceptual learning add to the previous literature showing deficient sleep-dependent consolidation of motor procedural learning and declarative memory for pictures. Although we did not have a wake control condition in the present study, we attribute the preserved post-sleep word pair performance in controls to

sleep-dependent consolidation of the memory that protects it from wake-related deterioration and hypothesize that this was absent in patients. This is based on the finding that patients did not show greater forgetting of word pairs after a 30m interval of wake than controls, and on previous studies showing greater forgetting of word pairs after 12 hours of wake versus sleep in healthy individuals (Wilson et al., 2012). Our finding of reduced sleep-dependent consolidation of verbal declarative memory in SZ complements a previous report that only controls, not SZ patients, showed better declarative memory for pictures after 12 hours of sleep versus wake (Göder et al., 2015).

Importantly, sleep-dependent memory deficits in SZ may be treatable. Sleep-dependent memory consolidation is thought to rely on the precise temporal coordination of three cardinal oscillations of NREM sleep: spindles, hippocampal sharp wave ripples and cortical slow waves (Mölle et al., 2011; Siapas and Wilson, 1998). In healthy individuals zolpidem enhances sleep-dependent protection of WPT encoding while increasing spindle density and spindle-cortical slow wave coupling (Mednick et al., 2013; Niknazar et al., 2015). In SZ, both spindle density and the temporal coordination of spindles with cortical slow waves correlate with better sleep-dependent consolidation of motor procedural memory (Demanuele et al., 2017). This raises the possibility that increasing spindles and their coordination with other NREM oscillations may improve sleep-dependent memory deficits.

Several study limitations warrant consideration. First, because we did not record sleep on the night between the training and test sessions, we could not investigate the relations of sleep with overnight memory consolidation. We therefore base our hypothesis that reduced overnight consolidation on the WPT in SZ reflects abnormal sleep on the literature showing spindle deficits in SZ (reviewed in Manoach et al., 2016) and that overnight WPT consolidation correlates with spindles (Gais et al., 2002; Lustenberger et al., 2015; Schabus et al., 2008, 2004; Schmidt et al., 2006; Studte et al., 2017). While we did not include a wake control condition to demonstrate that overnight changes in task performance were sleep-dependent, this has been demonstrated in previous studies of healthy individuals for the tasks that we employed. Studies now in progress are assessing the relation of sleep parameters to WPT consolidation in both SZ and health. Another limitation is that patients were treated with a variety of antipsychotic drugs (APDs) and adjunctive agents that may have affected sleep and sleep-dependent memory consolidation. APDs are sedating and may also have

contributed to the longer sleep times reported by SZ patients. Chronic use of APDs tends to normalize sleep architecture (Hinze-Selch et al., 1997; Krystal et al., 2008; Maixner et al., 1998; Taylor et al., 1991), and withdrawal is associated with a progressive deterioration of sleep quality (Nofzinger et al., 1993), but their effects on the spectral content of sleep, including spindles, is largely unexplored. Previous findings that early course antipsychotic-naïve patients with SZ and non-psychotic first-degree relatives of SZ patients have spindle deficits that correlate with cognitive performance make it unlikely that the spindle deficits and consequent memory consolidation deficits are due to chronicity or treatment with APDs (Manoach et al., 2014; Schilling et al., 2017).

In summary, the present findings extend the known deficits in sleep-dependent memory consolidation in SZ to verbal declarative memory, a core, disabling cognitive deficit, and demonstrate that sleep-dependent consolidation of a visuoperceptual procedural memory task is unaffected. They support the hypothesis that sleep-dependent memory consolidation deficits in SZ are selective and limited to those tasks for which consolidation depends on spindles. Our findings reinforce the importance of deficient sleep-dependent memory consolidation among the cognitive deficits of SZ and suggest abnormal sleep as a potentially treatable mechanism.

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Tables

Table 1. Participant Characteristics. Means ± standard deviations and group comparisons of demographic data.

	Schizophrenia (n=28)	**Healthy Controls (n=32)**	**t**	***p***
Age (yrs)	31.6 ± 7.2	31.9 ± 6.3	.19	.84
Parental Education (yrs)	14.4 ± 3.2	14.7 ± 3.3	.42	.68
Sex	6F / 22M	15F / 17M	X^2=4.41	.06
			Average Level of Severity	
PANSS Total	71 ± 13		*mild*	
PANSS Positive	17 ± 5		*mild*	
PANSS Negative	19 ± 5		*mild*	
PANSS General	35 ± 6		*mild*	

PANNS, Positive and Negative Syndrome Scale (Kay et al., 1987)

Table 2. Means ± standard deviations and group comparisons of subjective ratings of sleep and daytime alertness for the interval between Training and Testing sessions

	Schizophrenia	**Healthy Controls**	**t**	***p***
Sleep latency (min)**	21 ± 14	12 ± 10	2.9	0.006
Arousals (number)	0.5 ± 0.8	0.9 ± 1.1	1.4	0.15
Sleep depth (1-5)*	1.6 ± 0.8	2.2 ± 1.1	2.1	0.04
Sleep quality (1-5)*	2.5 ± .85	3 ± .89	2.0	0.05
Total sleep time (hr)**	8.4 ± 1.8	7.1 ± 1.2	3.1	0.003
Well-rested (1-5)*	3.5 ± 0.8	3.0 ± 0.9	2.0	0.05
Alertness upon awakening (1-5)	2.2 ± 1.1	2.4 ± 1.2	0.7	0.48
Alertness during the day (1-5)	2.2 ± 1.0	2.5 ± 0.9	1.0	0.32
Caffeinated beverages (cups)	0.9 ± 0.9	1.2 ± 1.6	0.8	0.45

1-5 scales: 1 = very high (good), 5 = very low (poor). ** $p \leq .01$, * $p \leq .05$.

Figure Captions

Figure 1. **Study Procedures. (A) Design.** Participants were trained on three tasks in a fixed order during Training and were Tested 24h later. **(B) Word Pair Task**. During Initial Exposure, each word pair was displayed for 5s, with an interstimulus interval (ISI) of 100ms, and participants were instructed to "remember which words go together." During subsequent phases, the middle 20 pairs were presented in a random order to avoid primacy and recency effects. During Feedback Training, participants were shown the first word of each pair (cue) and asked to verbally report its associate (target). The experimenter typed their response and it was displayed on the screen below the cue for 2s. If the response was incorrect, the correct target word was displayed in red above the incorrect response for 2s. This procedure was repeated until at least 12 of the targets (60%) were recalled correctly or until the list had been repeated 10 times. The Pre-Sleep Test started approximately 30m later, after training on the Tone Task. **(C) Visual Discrimination Task**. After a jittered interval (200-280ms), a target screen (Panels 1, 2) that contained a rotated "T" or "L" at the center and a horizontal or vertical array of three diagonal bars in the lower-left quadrant was presented for 16ms (fixation points and target arrays are displayed in bold for illustration purposes only). The array of diagonal bars was ~2.5° in length and was located ~5° from the center. The target screen was followed by a blank screen for an ISI of 20-400ms and then a mask for 16ms (Panel 3). Upon termination of the mask screen, the screen went black and participants indicated with button presses whether the diagonal lines were arranged horizontally (H) or vertically (V), and whether there was a T or an L at fixation. This was followed by the return of the fixation screen. **(D) Tone Task**. The task consisted of three phases: Exposure, Pre-Sleep Test and Post-Sleep Test. Exposure involved listening to a single structured stream of 1818 tones lasting 400s. Each tone lasted 200ms, with a 20ms gap between tones. Pre and Post-Sleep tests took place immediately and 24h after Exposure, respectively, and consisted of a forced-choice recognition test. Bottom: In each of 84 trials participants were presented with two 18-tone sequences (4s each) and asked to indicate which sequence sounded more familiar.

Figure 2. Overnight change in performance. Y axes show percent change in performance from the Pre- to Post-Sleep test in healthy controls (gray bars) and SZ patients (black bars) for **(A) Word Pair Task, (B) Visual**

Discrimination Task and **(C) Tone Task**. Error bars are standard errors of the mean. *p<.05, **p<.01, ***p<.001, n.s.: not significant.

Figure 1

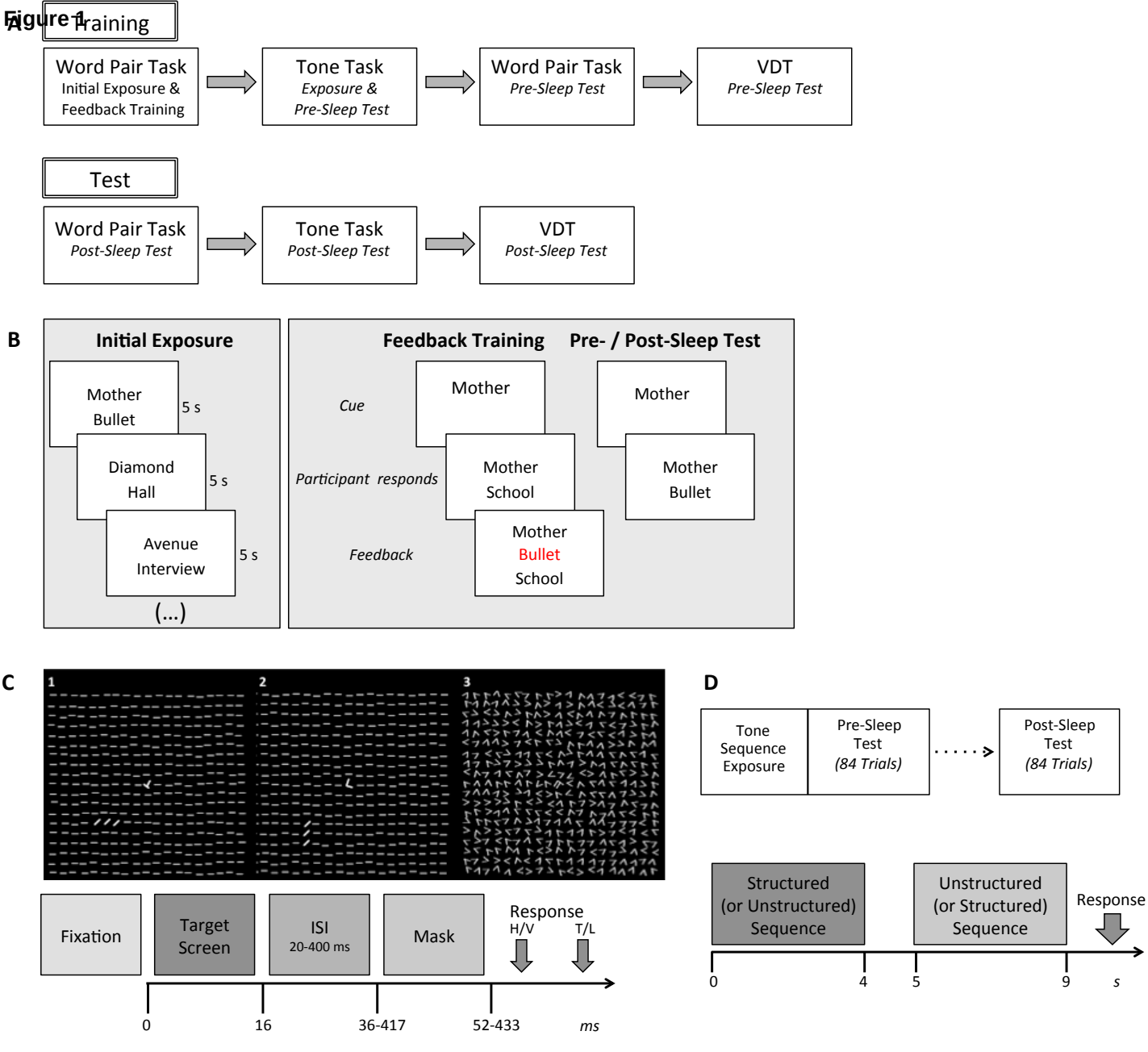
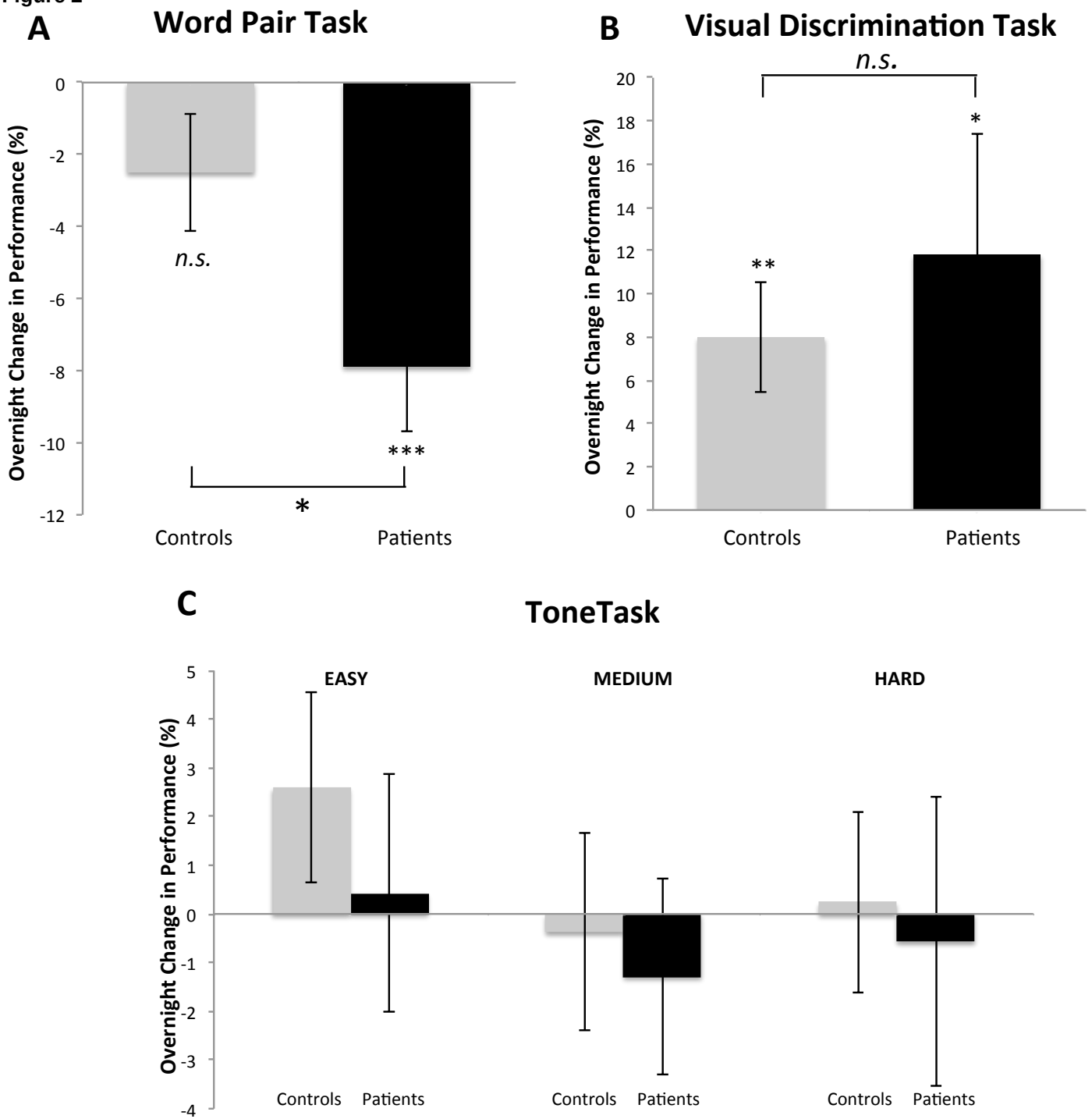

A
Training
Word Pair Task
Initial Exposure &
Feedback Training
Tone Task
Exposure &
Pre-Sleep Test
Word Pair Task
Pre-Sleep Test
VDT
Pre-Sleep Test
Test
Word Pair Task
Post-Sleep Test
Tone Task
Post-Sleep Test
VDT
Post-Sleep Test
B
Initial Exposure
Mother
Bullet
5 s
Diamond
Hall
5 s
Avenue
Interview
5 s
(...)
Feedback Training
Pre- / Post-Sleep Test
Cue
Participant responds
Feedback
Mother
Mother
School
Mother
Bullet
School
Mother
Mother
Bullet
C
1
2
3
Fixation
Target
Screen
ISI
20-400 ms
Mask
Response
H/V
T/L
0
16
36-417
52-433
ms
D
Tone
Sequence
Exposure
Pre-Sleep
Test
(84 Trials)
Post-Sleep
Test
(84 Trials)
Structured
(or Unstructured)
Sequence
Unstructured
(or Structured)
Sequence
Response
0
4
5
9
s

Figure 2


A
Word Pair Task
Overnight Change in Performance (%)
0
-2
-4
-6
-8
-10
-12
n.s.
***
*
Controls
Patients
B
Visual Discrimination Task
n.s.
*
**
Overnight Change in Performance (%)
20
18
16
14
12
10
8
6
4
2
0
Controls
Patients
C
ToneTask
EASY
MEDIUM
HARD
Overnight Change in Performance (%)
5
4
3
2
1
0
-1
-2
-3
-4
Controls
Patients
Controls
Patients
Controls
Patients