ARTICLE

The effects of eszopiclone on sleep spindles and memory consolidation in schizophrenia: a randomized clinical trial

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Sleep spindles, defining oscillations of stage 2 non-rapid eye movement sleep (N2), mediate memory consolidation. Schizophrenia is characterized by reduced spindle activity that correlates with impaired sleep-dependent memory consolidation. In a small, randomized, placebo-controlled pilot study of schizophrenia, eszopiclone (Lunesta®), a nonbenzodiazepine sedative hypnotic, increased N2 spindle density (number/minute) but did not significantly improve memory. This larger double-blind crossover study that included healthy controls investigated whether eszopiclone could both increase N2 spindle density and improve memory. Twenty-six medicated schizophrenia outpatients and 29 healthy controls were randomly assigned to have a placebo or eszopiclone (3 mg) sleep visit first. Each visit involved two consecutive nights of high density polysomnography with training on the Motor Sequence Task (MST) on the second night and testing the following morning. Patients showed a widespread reduction of spindle density and, in both groups, eszopiclone increased spindle density but failed to enhance sleep-dependent procedural memory consolidation. Follow-up analyses revealed that eszopiclone also affected cortical slow oscillations: it decreased their amplitude, increased their duration, and rendered their phase locking with spindles more variable. Regardless of group or visit, the density of coupled spindle-slow oscillation events predicted memory consolidation significantly better than spindle density alone, suggesting that they are a better biomarker of memory consolidation. In conclusion, sleep oscillations are promising targets for improving memory consolidation in schizophrenia, but enhancing spindles is not enough. Effective therapies also need to preserve or enhance cortical slow oscillations and their coordination with thalamic spindles, an interregional dialog that is necessary for sleep-dependent memory consolidation.

INTRODUCTION

Cognitive deficits are a core feature of schizophrenia that often predate its onset and persist throughout its course, even after psychotic symptoms have been effectively treated. Consequently, cognitive deficits contribute to the chronic disability that renders the vast majority of individuals with schizophrenia unable to work [1]. Although ameliorating cognitive deficits is a priority of the schizophrenia research community, effective treatments are lacking [2]. This reflects a lack of mechanistic understanding. Clearly, new approaches are needed to illuminate the pathophysiology of cognitive deficits and identify therapeutic targets.

It is now well established that sleep plays a critical role in memory, contributing to its stabilization, enhancement, and integration into cortical networks [3]. In schizophrenia, a growing literature suggests that abnormal sleep impairs memory consolidation and cognition more generally. Specifically, schizophrenia is characterized by a deficit in sleep spindles [4], a defining electroencephalography (EEG) oscillation of non-rapid eye movement (NREM) stage 2 sleep (N2). Sleep spindles are brief (~1 s), powerful bursts of 12–15 Hz activity organized in a waxing/waning envelope. Spindles correlate with sleep-dependent memory consolidation, learning efficiency, and IQ [5]. Recent work supports a causal role for spindles in memory consolidation: optogenetic studies of rodents [6], and pharmacological [7–9] and neuro-stimulation [10, 11] studies of humans show that increasing spindle activity improves memory, while decreasing it impairs memory [12]. These findings provide an impetus to target spindles to ameliorate cognitive deficits in schizophrenia [13]. The goal of this clinical trial was to determine whether enhancement of spindles using eszopiclone, (Lunesta®), a nonbenzodiazepine sedative hypnotic, improves sleep-dependent memory consolidation in schizophrenia.

In schizophrenia, reduced spindle activity [14–16] is associated with impaired sleep-dependent consolidation of both procedural and declarative memory, and predicts lower IQ and worse executive function [17–19]. Except for increased latency to sleep onset [14, 15], in chronic medicated patients, spindle deficits occur in the context of normal sleep quality and architecture, demonstrating that they are not secondary to sleep disruption [14–16]. Spindle deficits are also seen in adolescents with early-

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Table 1. Participant characteristics.

	Control (n = 29) M ± SD	Schizophrenia (n = 26) M ± SD	t	p
Age (years)	30 ± 6	32 ± 8	1.16	0.25
Sex	8F/21M	5F/21M	χ^2 = 0.47	0.54
Mean parental education (years)	15 ± 3	14 ± 3	−1.13	0.27
Handedness[a]	66 ± 53	81 ± 23	1.25	0.22
Total sleep time (min)[b]	533 ± 111	553 ± 76	0.70	0.49
Sleep efficiency (%)[b]	81 ± 8	83 ± 6	0.67	0.51
WASO (min)[b]	57 ± 26	56 ± 26	0.18	0.86
Rating scale scores/level of severity				
PANSS total		69 ± 14	Mild	
PANSS positive		16 ± 5	Mild	
PANSS negative		20 ± 5	Mild	
PANSS general		34 ± 7	Mild	
SANS		37 ± 12	Minimal	

PANSS Positive and Negative Syndrome Scale, *SANS* Scale for the Assessment of Negative Symptoms, *WASO* wake time after sleep onset. Means, SDs, and group comparisons of demographic data and home-based actigraphy measures of sleep quality in the weeks prior to and between experimental visits. Symptom rating scale scores for patients.
[a]Based on the modified Edinburgh Handedness Inventory [82]. Laterality scores of −100 and +100 denote exclusive use of the left or right hand, respectively.
[b]Based on averaged actigraphy data in the week prior to and between experimental visits.

onset schizophrenia spectrum disorder [20], early course antipsychotic-naive schizophrenia patients, and young nonpsychotic first-degree relatives of schizophrenia patients [19, 21]. These findings, along with the high heritability of spindles [22–24] and their association with schizophrenia risk genes [25], suggest that the spindle deficit in schizophrenia is not due to antipsychotic drugs, psychosis, or chronicity and instead is an endophenotype that contributes to cognitive dysfunction [26].

The considerable cross-species knowledge of sleep spindle physiology guided our selection of eszopiclone. Spindles are generated in the thalamic reticular nucleus (TRN) [27], a thin net-like structure comprising entirely γ-aminobutyric acid (GABA)-ergic neurons, which is the major inhibitory nucleus of the thalamus [28]. Spindle initiation by the TRN depends on powerful and prolonged inhibition of thalamocortical neurons [29] followed by rebound spike bursts that entrain cortical neurons to oscillate at spindle frequency [30]. In schizophrenia, postmortem studies reveal TRN abnormalities that may disrupt spindle generation [31–33]. Eszopiclone prolongs inhibitory postsynaptic currents in $GABA_A$ receptors of TRN neurons, which increases the burst firing that generates spindles [34]. In our previous randomized, placebo-controlled, double-blind pilot study, eszopiclone increased spindles in schizophrenia but did not significantly improve memory, perhaps reflecting the small sample, between-subjects design, and that memory is a less direct assay of drug effects than spindles [35]. The present, larger, double-blind crossover study, which included healthy controls, investigated whether eszopiclone could both increase spindles and improve memory. Despite increasing spindles, eszopiclone again failed to improve memory. To understand this failure, we investigated whether eszopiclone disrupted cortical slow oscillations (SOs) and their coordination with spindles. SOs are large amplitude ~1 Hz oscillations that reflect the rhythmic depolarization (upstates) and hyperpolarization

(downstates) of large populations of cortical pyramidal neurons [36]. SOs group spindles in their excitable upstates [37, 38] and compelling recent evidence indicates that memory consolidation relies on this phase locking [6], including in schizophrenia [38].

METHODS

Participants
Thirty-nine outpatients with schizophrenia and 48 healthy individuals enrolled, and 26 patients and 29 controls completed the study (Supplementary Fig. S1). Patients were recruited from an urban mental health center. Diagnoses were confirmed with the Structured Clinical Interview for DSM-IV [39]. Symptom severity was rated with the Positive and Negative Syndrome Scale [40] and the Scale for the Assessment of Negative Symptoms [41]. Two patients were unmedicated and the rest were maintained on stable doses of antipsychotic and adjunctive medications for at least 6 weeks prior to enrolling and throughout the study (Table S1).

Healthy controls, screened to exclude a personal history of mental illness [42] and a family history of schizophrenia spectrum disorder or psychosis, were recruited from the community through advertisements. Potential participants were screened to exclude pregnant and breastfeeding women, and individuals with diagnosed sleep disorders, intellectual disability, hepatic impairment, or a history of significant head injury, neurological disorder, or recent substance abuse (within 6 months). Patient and control groups did not differ significantly in age, sex, handedness, mean parental education, or home-based actigraphy measures of sleep quality (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 $0.05 for each correctly typed sequence on the memory task.

Procedures
Overview. This was a double-blind, placebo-controlled, crossover study (Fig. 1a). One week prior to their first sleep visit, participants had an introductory/screening visit for informed consent, clinical assessments, liver function tests, urine toxicology, and pregnancy screening. They toured the Clinical Research Center and were given sleep diaries to indicate bedtimes and wake-up times, and an actigraphy wrist band to wear until study completion (Supplementary Methods). The MGH Clinical Trials Pharmacy randomly assigned included participants in each group to have an eszopiclone (3 mg) or placebo visit first using www.randomization.com (block size: 4).

Sleep visits (eszopiclone, placebo) were separated by 1 week and each involved two consecutive nights of polysomnography (PSG). Eszopiclone or placebo administration was at 10:00 p.m., 30 m before bedtime. Participants were allowed to sleep up to 10 h. They engaged in their usual daytime activities, but were asked not to nap, as confirmed by actigraphy. On the second night of each visit, participants trained on the Motor Sequence Task (MST), a procedural memory test, at 8:30 p.m. Testing occurred at 9:30 a.m., followed by a control sequence 10 m later. The primary outcome measure was N2 spindle density (number/minute) and the secondary measure was overnight MST improvement.

Motor Sequence Task. The MST is the most extensively validated probe of sleep-dependent memory consolidation. We have reported on its sleep dependence in health [43] and on the failure of sleep-dependent improvement in schizophrenia, despite normal learning during training [16, 18, 44]. Performance is measured as the number of correctly typed sequences per trial (Fig. 1b). Learning during training is calculated as the percent change in correct sequences from the first trial to the average of the last three training trials. The main outcome measure, overnight improvement, is the percent increase in correctly typed
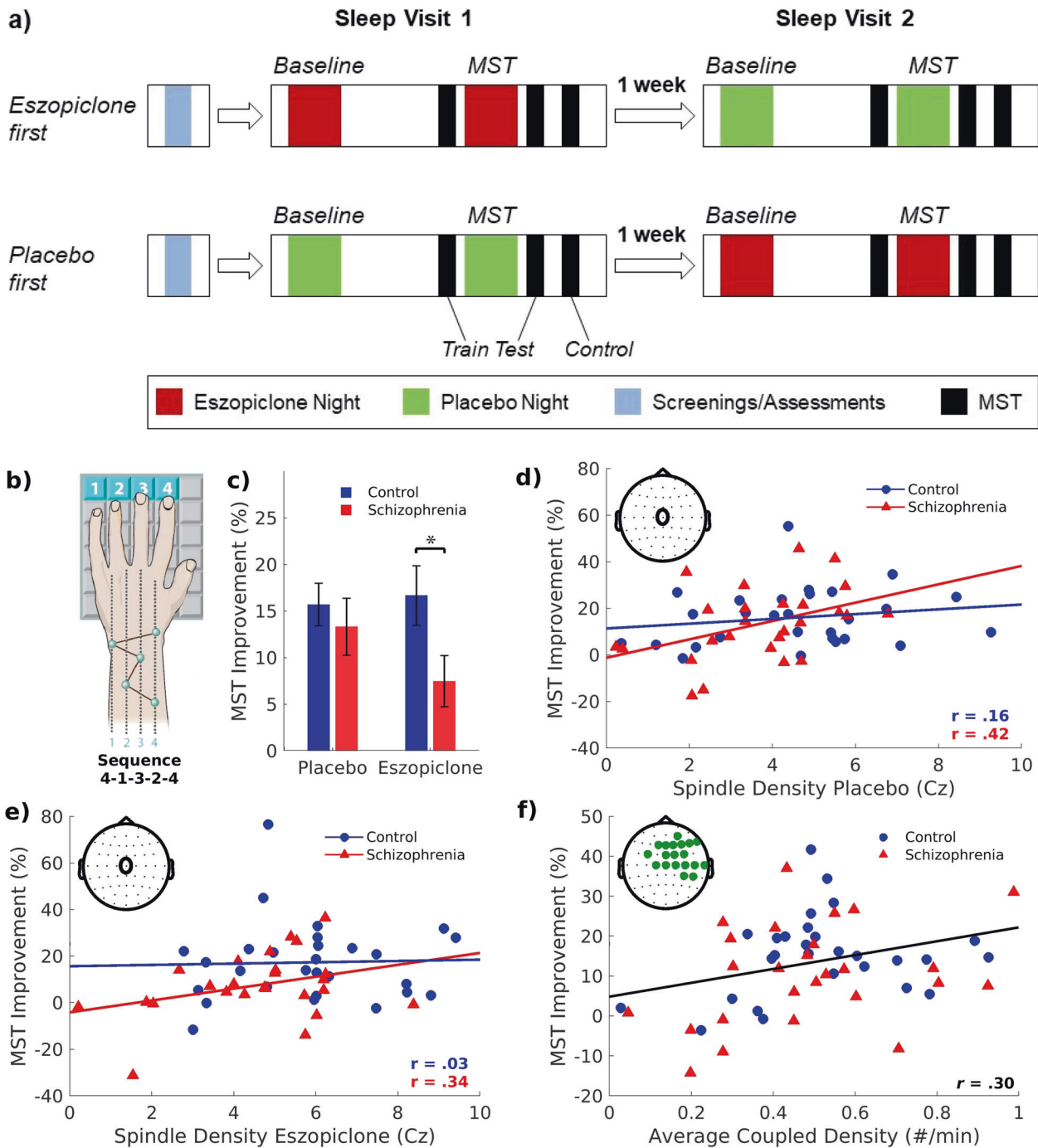
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Fig. 1 Finger tapping Motor Sequence Task (MST) administration and results. a Participants, randomized to the placebo or eszopiclone visit first, had an introductory/screening visit and two sleep visits, a week apart. Sleep visits involved polysomnography on two consecutive nights (Baseline, MST). Different MST sequences were employed for the two sleep visits and their order was counterbalanced within groups. There is no transfer of learning between MST sequences [83]. Participants trained on the MST before bedtime of the second night and were tested in the morning. Ten minutes after testing, participants trained on a new "control" sequence to evaluate the possibility of eszopiclone "hangover" effects on MST performance. Prior to each MST administration, participants completed the Stanford Sleepiness Scale (SSS) to measure subjective alertness [84]. **b** The MST requires participants to repeatedly type a five-digit sequence (e.g., 4–1–3–2–4) on a numerically labeled keyboard with the left hand, "as quickly and accurately as possible" for twelve 30 s trials separated by 30 s rest periods. The sequence is displayed at the top of the screen and dots appear beneath it with each keystroke. Participants train before sleep and test on an additional 12 trials after sleep. **c** Bar graphs of group differences in overnight MST improvement on placebo and eszopiclone with SE bars. Asterisk denotes $p < 0.05$. **d** Spindle density at electrode location Cz (inset) on the MST night plotted against overnight MST improvement by group for the placebo and **e** eszopiclone visits. **f** Density of spindle–SO events on the MST nights plotted against overnight MST improvement, averaged over the placebo and eszopiclone visits, in the cluster showing a significant correlation (inset). The regression line for the combined groups and visits is shown.

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sequences from the average of the last three training trials at night to the first three test trials the following morning [43].

Actigraphy. Standard scoring algorithms quantified time in bed (TIB), total sleep time (TST), sleep efficiency (TST/TIB) and wake time after sleep onset (WASO).

Polysomnography. Data were acquired at 400 Hz with an Aura LTM64 system (Grass Technologies, Astro-Med, Inc., RI) and EEG caps (Easycap GmbH, Herrsching, Germany) with 58 EEG, 2 submental electromyography, and 2 electrooculography electrodes. Each 30 s epoch was visually scored according to standard criteria [36] as WAKE, REM, N1, N2, or N3 by raters blind to visit, group, and night. EEG data were pre-processed and analyzed using BrainVision Analyzer 2.0 (BrainProducts, Germany) and Matlab (MathWorks, Natick MA). Data were band-pass filtered at 0.3–35 Hz and notch filtered at 60 Hz. Independent Component Analysis removed cardiac artifacts and remaining artifacts were visually identified and removed. Electrodes displaying significant artifacts for more than 30 m were spatially interpolated.

Spindle measures. After referencing to the common average [45], spindles were automatically detected in the 12–15 Hz band-pass-filtered data at each electrode using a wavelet-based algorithm [18, 46]. The threshold for spindle detection, nine times the median signal amplitude of artifact-free epochs, maximized between class ("spindle" vs. "non-spindle") variance [47] in schizophrenia and control samples from a previous study [18].

In addition to N2 spindle density, we measured the amplitude, duration, frequency, and sigma power (12–15 Hz) of individual spindles based on 4 s epochs centered on the point of spindle detection. Amplitude was the maximal voltage; frequency was the spectral peak following fast Fourier transform (FFT) decomposition, sigma power was the mean FFT-derived power spectral density, and duration was the half-height width of the wavelet energy. N2 sigma power was calculated as power spectral density ($\mu V^2/Hz$) by FFT using 8 s Hanning windows with 50% overlap.

SOs and their coordination with spindles. After referencing to the linked mastoids (6/220 records were excluded due to noise in the mastoids and/or sweat artifacts), SOs were automatically detected using a published method [38, 48] and spindles were detected using the algorithm described above. To identify SOs, the raw EEG at each electrode was filtered at 0.5–4 Hz using a two-way least-squares finite impulse response filter [49]. Consecutive positive-to-negative zero crossings within 0.8–2 s (corresponding to 0.5–1.25 Hz) were marked as candidate SOs (Fig. S2a). After excluding waveforms with peak-to-peak amplitudes >300 µV as artifacts, waveforms with amplitudes in the upper 25% were defined as SOs (Supplementary Fig. S2b) [50, 51]. We measured SO amplitude, duration, and density.

We identified spindle–SO events when a spindle peaked during the SO and measured their density, the SO phase at spindle peak, and the consistency of this phase locking (Supplementary Fig. S2c). We derived the SO phase from the Hilbert transform of the filtered data. The mean SO phase was calculated using circular statistics [52]. The length of the mean SO phase vector indexes the consistency of the spindle–SO phase locking. To ensure reliable measures, SO phase and phase-locking consistency were only calculated at electrodes with ≥20 coupled events.

Statistical analyses
Eszopiclone effects. Linear mixed-effects models investigated eszopiclone effects on sleep parameters with Group, Drug (Placebo, Eszopiclone), and Night (Baseline, MST), and their interactions as

fixed effects and Subject as a random effect. As there were no significant effects or interactions with Night and omitting Night from the models did not substantially change the results, analyses are based on the averaged two nights of each sleep visit. Paired and two-sample circular tests (Watson–William F-test) evaluated the effects of Group, Drug, and their interaction on SO phase [52, 53]. Eszopiclone effects on overnight MST improvement were tested with a linear mixed-effects model that included Group, Drug, and their interaction as fixed effects and Subject as a random effect. One patient's MST data from the eszopiclone visit was excluded from analyses as a statistical outlier (>3 SD).

Relations of sleep parameters with memory consolidation. We used data from the MST nights in Pearson's correlations of overnight MST improvement with spindle density at electrode Cz, to compare with previous studies [18, 35, 38]. We then regressed overnight MST improvement against spindle density and spindle–SO parameters at each electrode using Group, Drug, and their interactions as fixed effects and Subject as a random effect. To examine MST relations with SO phase, we performed circular-linear correlations for each group and visit.

Multiple comparisons correction. We corrected for multiple comparisons across electrodes using a nonparametric cluster-based method [54] implemented in MATLAB. For each term in the model, clusters were formed from adjacent electrodes that met an uncorrected threshold of $p < 0.05$. The cluster statistic (t_{sum}) was the sum of the test statistics of the electrodes within the cluster. Permutation distributions were created by randomly shuffling the labels (Group, Drug) 10,000 times at each electrode and retaining the cluster with the maximum statistic for each permutation. The cluster-level corrected p-value is the probability that the observed cluster would be found by chance under the permutation distribution.

RESULTS
As N2 spindle activity differentiates schizophrenia patients from controls and correlates with sleep-dependent MST improvement [18, 38], and spindle and SO parameters differ in N2 and N3 (Stage 3 NREM sleep) [37, 38], we focus on N2. N3 findings are in Supplementary Results and Supplementary Figs. S4–7.

Measurement reliability
As in prior work [37], spindle, SO, and spindle–SO coordination parameters were highly reliable across nights for both groups at both visits (Supplementary Methods and Supplementary Fig. S3).

Eszopiclone effects
Sleep quality and architecture. PSG measures of sleep quality and architecture did not differ by Group (Supplementary Table S2). For both groups, eszopiclone improved sleep quality, increasing TST ($p = 0.002$) and sleep efficiency ($p = 0.003$), and decreasing WASO ($p = 0.04$). Eszopiclone also affected sleep architecture, increasing N2 (percent: $p < 0.001$; duration: $p < 0.001$) and decreasing REM (percent: $p = 0.001$; duration: $p = 0.04$) for both groups. In patients ($t(25) = 2.73$, $p = 0.01$), but not controls ($t(28) = -0.13$, $p = 0.90$), eszopiclone decreased N3% (GroupXDrug: $p = 0.02$). Eszopiclone also decreased N1 duration for controls ($t(28) = 2.25$, $p = 0.03$) but increased it for patients ($t(25) = -2.15$, $p = 0.04$; GroupXDrug: $p = 0.003$).

Spindle density. Compared with controls, patients showed widespread reductions in N2 spindle density (Table 2 and Fig. 2). Eszopiclone increased spindle density similarly in both groups at all electrodes (partial-$\eta^2 = 0.30$; 95% confidence interval (95% CI): 0.15, 0.49; controls: partial-$\eta^2 = 0.27$; 95% CI: 0.09, 0.53; schizophrenia: partial-$\eta^2 = 0.34$; 95% CI: 0.15, 0.59).

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Table 2. Group and Drug main effects on spindles, slow oscillations, and their coordination.

	Group main effect			Cluster statistics			Drug main effect			Cluster statistics		
	Control (M±SD)	Schiz. (M±SD)	Control vs. Schiz. (partial-η^2)	No. of electrodes	t_{sum}	p	Placebo (M±SD)	Eszopicl. (M±SD)	Eszopicl. vs. Placebo (partial-η^2)	No. of electrodes	t_{sum}	p
Spindles												
Density (#/min)	2.6±1.3	1.9±1.0	0.10	32	76	0.03*	2.2±1.3	2.6±1.3	0.30	58	277	<0.001*
Amplitude (μV)	12.4±2.8	11.8±3.5	0.01	-	-	-	12.0±3.2	12.3±3.1	0.04	-	-	-
Frequency (Hz)	13.07±0.33	13.02±0.38	0.01	-	-	-	13.14±0.37	13.07±0.36	0.17	33	−106	<0.001*
Duration (s)	0.84±0.07	0.83±0.09	0.01	-	-	-	0.83±0.08	0.85±0.08	0.30	49	197	<0.001*
Spindle sigma (μV²/Hz)	8.7±4.2	8.0±4.7	0.01	-	-	-	8.8±4.6	9.8±5.3	0.13	27	76	0.006*
N2 sigma (μV²/Hz)	0.63±0.34	0.54±0.32	0.02	-	-	-	0.61±0.35	0.70±0.40	0.16	33	106	0.002*
Slow oscillations (SO)												
Density (#/min)	4.5±0.6	4.9±1.0	0.06	-	-	-	4.7±0.8	4.8±0.8	0.04	-	-	-
Amplitude (μV)	66±15	65±17	0.002	-	-	-	69±16	62±15	0.37	58	−329	<0.001*
Duration (s)	1.06±0.04	1.06±0.05	0.02	-	-	-	1.05±0.04	1.07±0.04	0.22	37	144	0.002*
Spindle–SO coordination												
Coupled density (#/min)	0.48±0.21	0.47±0.23	0.01	-	-	-	0.44±0.21	0.51±0.22	0.26	55	238	<0.001*
Consistency	0.41±0.13	0.53±0.15	0.18	37	−123	0.01*	0.49±0.15	0.44±0.15	0.20	54	−190	<0.001*
Phase (°)	8±25°	2±22°	0.02	-	-	-	6±24°	4±24°	0.04	-	-	-

Means, SDs, and effect sizes are based on data averaged across nights. Descriptive statistics are averaged across electrodes within significant clusters (otherwise across all electrodes). * denotes that the cluster meets a corrected threshold of p < .05.

Spindle characteristics and N2 sigma power. The groups did not differ in individual spindle characteristics or N2 sigma power (Table 2 and Supplementary Fig. S4). Eszopiclone increased the sigma power and duration of individual spindles, decreased their frequency, but did not change their amplitude. N2 sigma power increased on eszopiclone. Eszopiclone effects did not differ by Group.

SOs and their coordination with spindles. Patients did not differ from controls in SO parameters (density, amplitude, duration), the density of spindle–SO events, or SO phase, but showed increased phase consistency (Table 2 and Supplementary Fig. S4). Spindles preferentially peaked during SO upstates at all electrodes regardless of group or visit (Fig. 3a).

Eszopiclone did not affect SO density but reduced SO amplitude and increased SO duration (Fig. 3b). Eszopiclone increased the density of spindle–SO events. Although eszopiclone did not change the mean SO phase, the timing of this coupling became less consistent—spindles peaked at more variable phases of the SO. As SOs group spindles in their upstates, weaker (i.e., lower amplitude) SOs might have contributed to less consistent phase locking. Supporting this hypothesis, lower SO amplitude predicted less consistent phase locking (Fig. 3c and t_{sum}(41 electrodes) = 113, $p = 0.002$), an effect that did not differ by Group or Drug.

Overnight MST improvement. Although they did not differ in learning during training ($F(1,50) = 1.37, p = 0.25$), patients showed a trend to less overnight improvement than controls (Fig. 1c; $F(1,52) = 3.17, p = 0.08$; partial-$\eta^2 = 0.06$; 95% CI: 0, 0.23). Eszopiclone did not significantly affect overnight improvement ($F(1,52) = 1.00, p = 0.32$; partial-$\eta^2 = 0.02$; 95% CI: 0, 0.18) and there was no Group by Drug interaction ($F(1,52) = 1.97, p = 0.17$, partial-$\eta^2 = 0.04$; 95% CI: 0, 0.17).

Post hoc analyses revealed that patients, but not controls, showed a trend to worse overnight improvement on eszopiclone compared with placebo (44% reduction; $t(24) = 1.89, p = 0.07$). This is unlikely to reflect an eszopiclone "hangover" effect in the morning, as learning of the control sequences did not differ by drug ($F(1,47) = 1.30, p = 0.26$; Group × Drug: $F(1,47) = 0.14, p = 0.71$), nor did subjective level of alertness (Stanford Sleepiness Scale: $F(1,45) = 0.03, p = 0.86$; Group × Drug: $F(1,47) < 0.001, p = 0.98$).

Relations of overnight MST improvement with spindle density

Replicating prior studies [18, 35, 38], overnight MST improvement correlated with spindle density at Cz in schizophrenia (placebo: $r = 0.42, p = 0.03$; trend-level for eszopiclone: $r = 0.34, p = 0.10$; Fig. 1d, e), but not in controls (placebo: $r = 0.16, p = 0.41$; eszopiclone: $r = 0.03, p = 0.87$). Although there were no clusters in which spindle density predicted overnight MST improvement, the density of spindle–SO events predicted improvement in a cluster overlying the motor cortex contralateral to the hand that performed the task (t_{sum}(19 electrodes) = 43, $p = 0.04$; Fig. 1f). This relationship did not differ by Group or Drug. Moreover, spindle–SO density was a significantly better predictor of memory consolidation than spindle density alone ($t(57) = 112, p < 0.001$) based on comparing the goodness of fit of the two models across all electrodes using the Bayesian Information Criterion [55].

Control and descriptive analyses

In patients, antipsychotic drug dosage (chlorpromazine equivalents) [56] did not correlate with spindle density or overnight MST improvement at either visit, but higher doses predicted a greater increase in spindle density on eszopiclone (t_{sum}(8 electrodes) = 22, $p = 0.03$). Spindle density did not correlate with any measure of symptom severity. Overnight MST improvement did not correlate with other neuropsychological measures, suggesting that sleep-
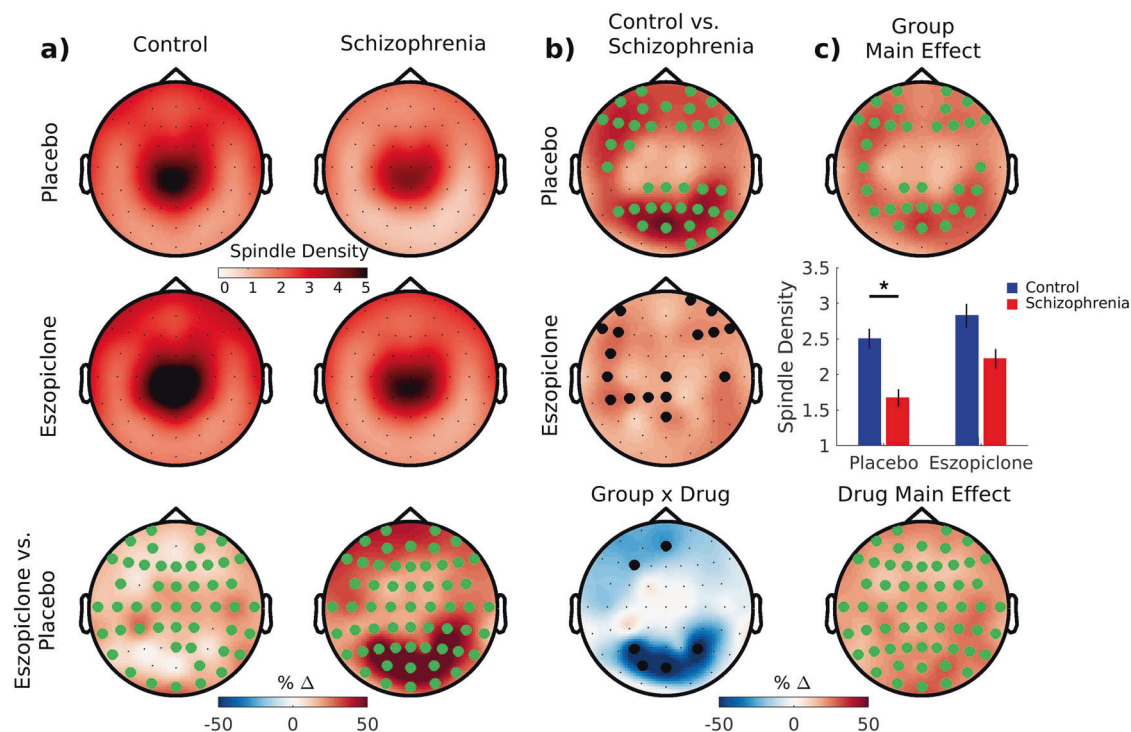
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Fig. 2 Eszopiclone effects on N2 sleep spindle density. a Topographical maps of spindle density averaged across nights of the placebo and eszopiclone visits for each group and the comparison of the two visits. Electrodes with a cluster-corrected $p < 0.05$ are highlighted in green. **b** Group difference maps (top and middle rows) show significantly greater spindle density in controls than patients on placebo (two significant clusters), but not eszopiclone. Electrodes highlighted in black correspond to $p_{uncorrected} < 0.05$. Bottom row: Group by Drug interaction showing electrodes where the eszopiclone effect of increasing spindle density was nonsignificantly greater in patients ($p_{uncorrected} < 0.05$). **c** Top: main effect of Group on spindle density showing a significant cluster. Middle: bar graph of spindle density averaged across the electrodes in the significant cluster with SE bars. Bottom: Drug main effect—eszopiclone increased spindle density at all electrodes.

dependent memory consolidation is a separate domain of cognitive function (Supplementary Results).

DISCUSSION
In this placebo-controlled, randomized, double-blind crossover study, eszopiclone robustly increased N2 sleep spindle density but did not enhance sleep-dependent memory consolidation. This study confirms pilot findings in schizophrenia [35], extends them to healthy people, and raises an important question: if spindles are a mechanism of memory consolidation and patients have reduced spindle density that correlates with worse memory, why does increasing spindles not improve memory? Recent complementary rodent and human studies, along with the present findings, converge on an explanation. Sleep-dependent memory consolidation relies not only on spindles, but on their temporal coordination with cortical SOs. Here we report that spindles coupled to SOs predicted memory consolidation significantly better than spindles alone. Eszopiclone altered SO morphology and reduced the consistency of SO phase locking with spindles. This suggests that eszopiclone disrupted the thalamocortical dialog necessary for the consistent, precisely timed spindle–SO coupling that mediates memory. We conclude that interventions to improve sleep-dependent memory consolidation need to not only increase spindles, but also preserve SOs and the fidelity of their coupling with spindles.

During NREM sleep, cortical SOs coordinate both spindle generation in the TRN and the reactivation of memory representations during hippocampal sharp-wave ripples (100–200 Hz) [57, 58]. Ripples nest in the troughs of spindles, which preferentially peak during SO upstates [37, 38, 48, 51, 59–61]. The orchestration of these three cardinal NREM oscillations

mediates the transformation of new memories from temporary indexing in the hippocampus to longer-term representation in the cortex [61, 62]. The importance of this triple phase locking for memory is supported by recent studies. In mice, optogenetic induction of spindles on the rising phase of SOs leads to coupling with ripples and enhanced memory, whereas suppression of spindles at this phase impairs memory [6]. Similarly, ripple-triggered electrical stimulation of the cortex induces triple-coupled spindles and enhances memory [63]. In older people, the degradation of spindle–SO coupling is associated with increased forgetting [50]. In schizophrenia, spindle density, and spindle–SO timing together predict overnight MST improvement significantly better than either alone, suggesting that both are essential [38].

In the present study, spindle density predicted overnight MST improvement at Cz in schizophrenia, replicating previous findings [18, 35, 38], but the density of spindle–SO events correlated with improvement significantly better than spindle density alone in both groups. The correlated cluster overlay motor cortex contralateral to the hand that performed the MST, consistent with studies showing increased spindle activity in brain regions involved in learning that correlates with improved memory consolidation [64–66], including on the MST [67]. Rodent studies provide a higher resolution view of possible mechanisms. Spindle–SO events enhance calcium activity in pyramidal neurons more than isolated spindles and SOs [68] and motor cortex neurons activated during motor learning are reactivated during NREM sleep, promoting dendritic spine formation [69]. Calcium activity and spine formation underlie the synaptic plasticity necessary for memory. Collectively, this work suggests that regionally specific spindle–SO events mediate memory, and that spindle–SO events are a better biomarker of memory than spindles alone.
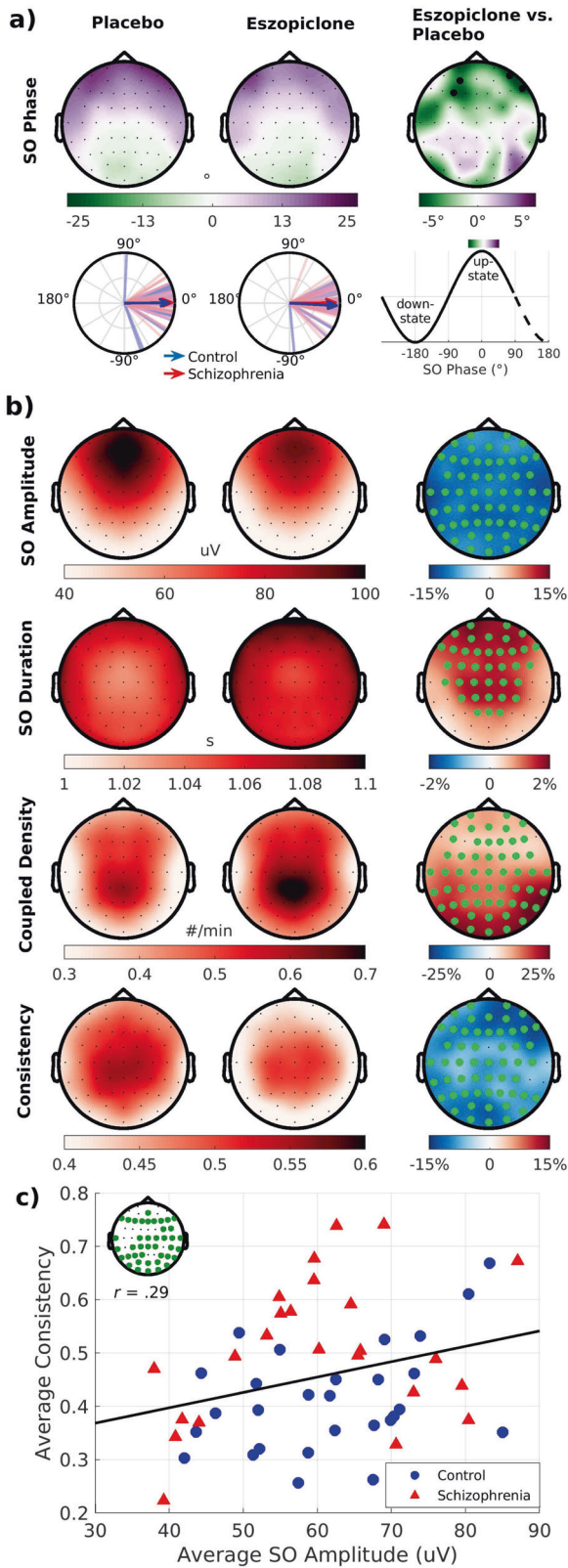
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Fig. 3 Eszopiclone effects on N2 SOs and their coordination with spindles. a Topographical maps of mean SO phase at spindle peak during the placebo and eszopiclone visits (averaged across groups and nights) and a statistical map of their difference. Electrodes highlighted in black meet a threshold of $p_{uncorrected} < 0.05$. Circular plots show SO phase at Cz. Lines represent the mean SO phase for each participant. Arrows represent the group means and their lengths represent the consistency of the spindle-SO phase-locking across participants. Right column: mapping of SO phase to topographical maps and circular plots. **b** Topographical maps of SO and spindle–SO coordination parameters during the placebo and eszopiclone visits and statistical maps of their difference. Electrodes with a cluster-corrected $p < 0.05$ are highlighted in green. **c** Plot of the relation of SO amplitude with spindle–SO phase consistency, averaged over the placebo and eszopiclone visits, in the cluster showing a significant correlation (inset shows significant cluster). Regression line is for the combined groups and drug visits.

groups spindles in SO upstates [71]. Less synchronized SO expression, reflected in lower amplitude SOs, may lead to more variable coupling with spindles. Supporting this hypothesis, lower SO amplitude predicted less consistent coupling. This suggests that by altering SOs, eszopiclone disrupted the thalamocortical dialog necessary for consistent, precisely timed spindle–SO coupling.

The present study was limited to studying the role of spindle–SO synchrony in memory, as it is difficult to measure hippocampal ripples without invasive recordings. Our recent study of amnestic patients, however, demonstrates that although an intact hippocampus is not necessary to learn the MST, it is necessary for its sleep-dependent consolidation [72]. In schizophrenia, postmortem studies show a selective loss of hippocampal interneurons [73]. These interneurons contribute to ripple generation [74] and ripple-spindle coordination [75] raising the intriguing possibility that their loss may contribute to impaired sleep-dependent memory in schizophrenia [17, 44, 76]. Although it is not possible to test this hypothesis directly, rodent models of schizophrenia show reduced coordination of ripples with spindles and SOs [77], and impairments in ripple-associated memory replay [78]. We recently found that eszopiclone suppresses hippocampal ripples in rats [79]. Zolpidem, in contrast, increases ripples in rats [80], increases spindles and spindle–SO coupling in humans [9], and improves sleep-dependent memory [7–9]. This illustrates that spindle increases alone do not predict memory improvement. Collectively, these findings reinforce the importance of complementary animal and human studies for measuring all three NREM oscillations and their coordination when evaluating promising new pharmacological and noninvasive brain stimulation approaches to enhancing memory [13].

Several limitations of the present study warrant consideration. Almost all patients took antipsychotic and adjunctive medications. Antipsychotic dosage was not related to spindle density at either sleep visit, but correlated with increased spindle density on eszopiclone. As patients were maintained on stable clinically indicated medication regimens during participation, controls were not medicated, and eszopiclone effects did not differ by group, our findings of increased spindle density but no memory improvement on eszopiclone are unlikely to be confounded by pharmacotherapy.

Another concern is that the present schizophrenia sample differed from previous ones [16, 18, 44, 81] by not showing a significant deficit in overnight MST improvement, despite being similar both demographically and in symptom severity. Previous samples have shown a wide range of improvement and the lack of a significant deficit here may reflect that behavioral measures of memory consolidation are more distal and therefore less sensitive, and more variable indices of thalamocortical integrity than

Eszopiclone reduced spindle–SO phase consistency, suggesting that it disrupted thalamocortical communication. Although the thalamus can generate sleep spindles in isolation, their propagation and synchronization across the cortex requires reciprocal interactions [70]. The synchronous spiking of cortical neurons

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spindles, requiring larger sample sizes for reliable estimates. Sample size, however, does not limit the primary conclusion that increasing spindles with eszopiclone does not improve memory, as both groups showed robust eszopiclone effects on spindle density and either no effect (controls, $p = 0.79$) or a nonsignificant worsening (patients, $p = 0.07$) of sleep-dependent memory consolidation. It also replicates our pilot study in which eszopiclone failed to improve memory in a schizophrenia sample that did show a significant memory deficit [35].

In summary, although eszopiclone increased spindles, it disrupted both SO expression and spindle–SO synchrony, and failed to improve memory. We conclude that coordinated NREM sleep oscillations are promising targets for improving cognition in schizophrenia but that enhancing spindles is not enough. Effective therapies will also need to preserve or enhance cortical SOs, hippocampal ripples, and their precise temporal coupling with spindles, an interregional dialog necessary for sleep-dependent memory consolidation.

AUTHOR CONTRIBUTIONS
DSM and RS conceived and designed the trial, and contributed to all aspects of its completion. DM, BB, CD, and RC contributed to conceptualization, methods development, data analysis, and writing. BB, TV, BS, RAF, DC, EP, and CEC contributed to data acquisition, sleep scoring, artifact rejection, and data analysis. AM contributed to task design and programming. DH oversaw all medical aspects of the clinical trial. MV consulted to statistical analysis and study design. All authors reviewed and commented on the finished product.

ADDITIONAL INFORMATION
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