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Sleep oscillations and their relations with sleep-dependent memory consolidation in early course psychosis and first-degree relatives

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ABSTRACT

Sleep spindles mediate sleep-dependent memory consolidation, particularly when coupled to neocortical slow oscillations (SOs). Schizophrenia is characterized by a deficit in sleep spindles that correlates with reduced overnight memory consolidation. Here, we examined sleep spindle activity, SO-spindle coupling, and both motor procedural and verbal declarative memory consolidation in early course, minimally medicated psychosis patients and non-psychotic first-degree relatives. Using a four-night experimental procedure, we observed significant deficits in spindle density and amplitude in patients relative to controls that were driven by individuals with schizophrenia. Schizophrenia patients also showed reduced sleep-dependent consolidation of motor procedural memory, which correlated with lower spindle density. Contrary to expectations, there were no group differences in the consolidation of declarative memory on a word pairs task. Nor did the relatives of patients differ in spindle activity or memory consolidation compared with controls, however increased consistency in the timing of SO-spindle coupling were seen in both patients and relatives. Our results extend prior work by demonstrating correlated deficits in sleep spindles and sleep-dependent motor procedural memory consolidation in early course, minimally medicated patients with schizophrenia, but not in first-degree relatives. This is consistent with other work in suggesting that impaired sleep-dependent memory consolidation has some specificity for schizophrenia and is a core feature rather than reflecting the effects of medication or chronicity.

1. Introduction

Schizophrenia is characterized by a deficit in sleep spindles that, in chronic patients, generally presents in the context of unaltered sleep quality and architecture (Ferrarelli et al., 2007; Kozhemiako et al., 2022; Lai et al., 2021; Wamsley et al., 2012). Sleep spindles, a defining feature of stage 2 non-rapid eye movement sleep (N2), are brief (~ 1 s) bursts of ~12–15 Hz synchronous activity initiated by thalamic reticular nucleus (Fernandez and Luthi, 2020). Sleep spindles are propagated to cortex, where they induce long-term potentiation and synaptic plasticity, facilitating overnight memory consolidation (Peyrache and Seibt, 2020; Seibt et al., 2017; Steriade and Timofeev, 2003; Werk et al., 2005). Chronic patients with schizophrenia have reduced sleep-dependent procedural and declarative memory consolidation (Baran et al., 2018; Demirlek and Bora, 2023; Göder et al., 2015; Manoach et al., 2004) that correlates with spindle deficits (Göder et al., 2015; Manoach et al., 2010; Wamsley et al., 2012), pointing to sleep spindles as a potential treatment target for cognitive deficits in schizophrenia. Spindle deficits have also

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been observed in young, early course antipsychotic-naïve schizophrenia patients and non-psychotic first-degree relatives but their specific functional implications for sleep-dependent aspects of cognition is not known (Manoach et al., 2014; Schilling et al., 2017). The goals of the present study were to characterize sleep spindles and their temporal coordination with slow oscillations in early course, minimally medicated psychosis patients and non-psychotic first-degree relatives and to examine their role in the sleep-dependent consolidation of both motor procedural and verbal declarative memory, as well as clinical symptoms. This is important to investigate, to establish whether deficits in spindle-mediated memory consolidation are a core feature of schizophrenia that is present early in its course.

Sleep-dependent memory consolidation relies on the temporal coordination of sleep spindles with neocortical slow oscillations (SOs; ~0.5–1.25 Hz) (Klinzing et al., 2019). In healthy participants, SO-coupled spindles are the best predictor of consolidation, independent of uncoupled spindles (Denis et al., 2021; Solano et al., 2022). In chronic, medicated schizophrenia patients initial findings reveal that SO-spindle timing is largely spared (Demanuele et al., 2016; Mayeli et al., 2022), though an *increased* consistency in the phase of the SO in which spindles occur has been observed (Mylonas et al., 2020). SO-spindle coupling is also associated with memory consolidation in patients (Demanuele et al., 2016; Mylonas et al., 2020). To our knowledge, there are no previous studies that examined SO-spindle coupling or its relations with memory consolidation in early course psychosis patients and first-degree relatives.

Among psychotic disorders, spindle deficits may be specific to schizophrenia and do not appear to be fully accounted for by medication side effects or disease chronicity (Ferrarelli et al., 2010; Manoach et al., 2014). Emerging research has documented spindle deficits in early course, antipsychotic naive patients, as well as first-degree relatives of patients (D'Agostino et al., 2018; Kaskie et al., 2019; Schilling et al., 2017), but not in individuals with other psychotic disorders in either early course (Manoach et al., 2014) or chronic (Ferrarelli and Tononi, 2017) samples. These findings suggest that the sleep spindle deficit in schizophrenia is an endophenotype reflecting genetic risk for schizophrenia (Ferrarelli, 2021; Manoach et al., 2016; Schilling et al., 2022).

In the present study, we utilised a four night experimental protocol and high-density electroencephalography (EEG) to investigate these gaps in the literature. Specifically, we hypothesised that 1) Early course patients and relatives would show a deficit in sleep spindle density compared to healthy controls. 2) Patients and relatives would also show reduced overnight procedural and declarative memory consolidation. 3) Sleep spindles, particularly those coupled to slow oscillations, would correlate with overnight memory consolidation. We also hypothesised that any deficits in early course patients would be driven by schizophrenia patients compared to individuals with non-schizophrenia psychoses.

2. Methods

2.1. Participants

Forty-two early-course, minimally medicated patients with a psychotic disorder (EC; 18-35 yrs), 42 familial high risk first-degree relatives of psychosis patients (FHR; 12-25 yrs), and 57 healthy controls (HC, 12–35 yrs) enrolled. Of those, 17 EC, 23 FHR and 27 HC participants met inclusion criteria and completed the study (Fig. S1), with majority of dropouts being due to the Covid 19 pandemic. Patients were recruited from Harvard affiliated hospital outpatient programs in Boston, MA. Early course was defined as <5 yrs. from psychosis onset and < 1 year of lifetime exposure to antipsychotic drugs (APD). Patients were required to be unmedicated or on stable doses of antipsychotic and adjunctive medications for at least 6 weeks prior to study enrolment. Based on the Structured Clinical Interview for DSM-IV TR (SCID; (First et al., 2015) or the Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL; (Kaufman et al., 1997) and review of medical records, EC participants were characterized into schizophrenia (ECsz; $n = 7$) or other psychotic disorders (ECnsz; $n = 10$) groups (Table S1). Diagnoses were determined by diagnostic consensus meetings. The familial high risk (FHR) group consisted of individuals with no personal history of psychosis (confirmed with SCID or K-SADS-PL) but a first-degree relative with a diagnosis of schizophrenia ($n = 20$) or schizoaffective disorder ($n = 3$) based on interview of either the affected relative or a reliable informant other than the index subject by an experienced psychiatrist and supplemented by medical records, when available. FHR participants were confirmed to not be taking any antipsychotic medications. Healthy controls (HC) were recruited from the community by advertisements and were excluded for a personal history of mental illness confirmed by the SCID-Non-Patient Edition, a family history of psychotic disorders, and current treatment with any medication known to affect sleep or cognition.

General exclusion criteria included substance abuse or dependence within the past 6 months; unstable medical conditions that may affect sleep (e.g., diabetes, thyroid disease); pregnancy/breast feeding; a history of head injury resulting in prolonged loss of consciousness (>one day) or neurological sequelae; intellectual disability; a diagnosed sleep disorder other than insomnia; neurological disorders such as epilepsy. All participants also completed a screening test for the finger tapping motor sequence task (MST). This screening test required participants to type at least 24 correct sequences of "1–2–3-4" during two 30 s trials with the left hand to be eligible for the main study. Healthy controls were demographically matched to the EC and FHR groups on age ($F(2,64) = 1.63$, $p = .20$) and sex ($\chi^2(2) = 3.56$, $p = .17$). ECsz and ECnsz were matched in terms of age ($t(17) = 1.47$, $p = .16$) but not mean parental education ($t(17) = 3.48$, $p = .004$; lower in ECsz) or the severity of positive or negative symptoms (all $ps < 0.007$; more severe symptoms in ECsz). Demographics and clinical characteristics are shown in Table 1 (See Table S2 for demographics and clinical characteristics of participants who withdrew). All participants gave written informed consent and study procedures were approved by Beth Israel Deaconess Medical Center and Massachusetts General Hospital IRBs.

2.2. Procedures

All participants completed an initial screening visit to provide informed consent, undergo diagnostic interviewing and clinical characterization, complete self-report measures, and perform the MST screening test. If they met criteria for inclusion, they returned for cognitive assessments (including the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein and Green, 2006). After completing all screening and baseline assessments, participants were given a tour of the Clinical Research Center (CRC) sleep monitoring rooms to familiarize them with the overnight stay portion of the study.

Approximately 1 week after the initial visit, participants completed two experimental visits, separated approximately by 1 week (Fig. 1). For each visit, participants spent two consecutive nights at the CRC for polysomnography (PSG) monitoring of sleep. Prior to the visit, participants were instructed to: 1) keep their typical daily schedules in the week preceding the study visits and not to nap during study days (confirmed with wrist actigraphy); 2) avoid alcohol and recreational drugs 24 h prior to visits and; 3) avoid caffeine intake on the day of the visits. The first night of each visit served as a baseline and the second as an experimental night during which participants trained on the procedural (MST) or declarative (Word Pairs Test) memory tasks prior to bed and were tested after awakening the following morning. See Fig. 1 and the Supplement for details of the memory tasks. The MST visit always occurred first. We prioritized collection of MST data since it is the most extensively validated measure of sleep-dependent memory consolidation and chronic schizophrenia patients show deficits (Manoach et al., 2010, 2004; Wamsley et al., 2012). Participants engaged in their usual activities during the day.

Table 1
Sample demographics and clinical characterization.

	HC N = 27	FHR N = 23	EC N = 17	stat	p
Age (yrs)	24 ± 4	23 ± 6	21 ± 4	1.63	0.20
Sex (%)				3.56	0.16
Female	47.1	69.6	44.4		
Male	52.9	30.4	55.6		
Ethnicity (%)				5.30	0.07
Hispanic or Latino	18.5	4.3	0		
Not Hispanic or Latino	81.5	95.7	100		
Race (%)				11.77	0.07
Asian	18.5	17.4	5.9		
Black or African American○	7.4	13.0	41.2		
White	63.0	69.6	47.1		
Other, not specified	11.1	0	5.8		
Marital status (%)				0.75	0.69
Married or sustained relationship	7.4	13.0	5.9		
Never married	92.6	87.0	94.1		
Mean parental education (yrs)	16.0 ± 2.75	15.9 ± 3.44	14.8 ± 3.3	0.79	0.46
Handedness [a]	60.6 ± 50.2	49.5 ± 62.7	55 ± 54.4	0.23	0.80
Subjective sleep quality (PSQI [b])	2.63 ± 1.98	5.64 ± 4.23	7.12 ± 4.4	9.34	<0.001
Diurnal preference (MEQ [c])	51.1 ± 11.4	47.9 ± 10.2	48 ± 10.7	0.67	0.52
MCCB overall composite score[d]	48.3 ± 9.8	48.4 ± 12.8	40.4 ± 16.8	2.10	0.13
Symptom Severity (PANSS [e])					
PANSS total	–	36.0 ± 6.14	53.1 ± 15.4	22.84	<0.001
PANSS positive	–	7.27 ± 0.63	11.6 ± 4.91	17.22	<0.001
PANSS negative	–	8.77 ± 2.39	14.7 ± 6.01	17.91	<0.001
PANSS general	–	19.9 ± 4.45	26.8 ± 6.76	14.54	<0.001
Psychosis proneness (Chapman)[f]					
Total	10.2 ± 9.7	12.9 ± 8.22	34 ± 21.4	18.57	<0.001
Perceptual aberration	1.22 ± 2.7	2.74 ± 4.42	8.82 ± 9.05	10.47	<0.001
Magical ideation	2.19 ± 3.5	3.09 ± 1.88	11.5 ± 7.22	26.40	<0.001
Social anhedonia	6.78 ± 5.6	7.09 ± 5.28	13.7 ± 9.16	6.59	0.003
Estimated IQ					
WASI-II[g]	106 ± 13.1	112 ± 15.02	101 ± 13.3	2.54	0.09
AMMONS[h]	100 ± 11.2	106 ± 15.1	97.2 ± 12.6	2.16	0.12

Note. Sex, ethnicity, race, and marital status are shown as a percentage of the sample. All other data are displayed as mean ± standard deviation.

[a] Handedness calculated with the Edinburgh handedness inventory (Oldfield, 1971), where a higher number indicates stronger right-hand preference (theoretical range -100-100).

[b] Total score on the Pittsburgh sleep quality index (PSQI, Buysse et al., 1989). Higher score indicates worse subjective sleep (theoretical range 0–21).

[c] Morningness-Eveningness Questionnaire (MEQ, Horne and Ostberg, 1976). Higher score indicates stronger morning preference (theoretical range 16–86).

[d] MATRICS Consensus Cognitive Battery (MCCB; MCCB; Nuechterlein and Green, 2006) an index of general cognitive functioning derived by equal weighting of all MCCB cognitive domain scores. Scores reflect age and sex corrected t-scores.

[e] Positive and Negative Syndrome Scale (PANSS, Higher score indicates more severe symptoms (total scale theoretical range 30–210).

[f] Chapman scales. Higher score indicates higher endorsement of psychotic-like experiences (total scale theoretical range 0–104).

[g] WASI-II = Wechsler Abbreviated Scale of Intelligence-Revised.

[h] AMMONS = Ammons quick test. Group differences assessed via ANOVA or chi-square test as appropriate. Patients showed significantly higher symptomatology on total PANSS and all subscales than relatives. On all Chapman scales, the main effect of group was driven by higher symptomatology in patients compared to both relatives and controls (*ps* < 0.004), with no significant difference between relatives and controls (*ps* > 0.33).

2.3. Polysomnography

Data were acquired at 400 Hz with either an Aura LTM64 (Grass Technologies, Astro-Med, Inc., RI) or a Natus Embla RDx (Natus Medical Inc., CA) system and EEG caps (Easycap GmbH, Herrsching, Germany) with 58 EEG electrodes positioned in accordance with the 10–20 system along with 2 mastoids, 2 EOG and 2 submental EMG sensors. Sleep scoring was performed to standard criteria by scorers blind to group, visit, and condition (Iber et al., 2007). Artifacts were identified and removed automatically using Luna (https://zzz.bwh.harvard.edu/luna/). EEG data were preprocessed using custom MATLAB scripts and EEGLAB routines. Data were re-referenced to the average of the two mastoids, bandpass filtered between 0.3 and 35 Hz, and notch filtered at 60 Hz.

2.4. Power spectral density

Estimates of power spectral density (PSD) were obtained for stage 2 NREM (N2) sleep at all electrodes. PSD was estimated using Welch's method with 5 s Hamming windows and 50 % overlap utilizing the derivative of the EEG time series to minimize $1/f$ scaling (Cox et al., 2017).

2.5. Sleep spindles

Sleep spindles were automatically detected using a wavelet-based detector that has been validated for use in both healthy individuals and people with schizophrenia (Wamsley et al., 2012; Warby et al., 2014). The raw EEG signal was subjected to a time-frequency decomposition using complex Morlet wavelets with a peak frequency of 13.5 Hz and a 3 Hz bandwidth centered on the wavelet peak. Spindles were detected on each channel by applying a thresholding algorithm to the extracted wavelet scale (i.e., 9 times the median signal amplitude of all artifact-free data for a minimum of 400 ms). This threshold empirically maximized between-class ("spindle" vs "non-spindle") variance in previous samples of schizophrenia and control patients with 12–15 Hz spindles (Wamsley et al., 2012) As in prior studies, we focused on N2 sleep (Mylonas et al., 2020; Wamsley et al., 2013, 2012). Our primary outcome measure was spindle density, calculated as spindles per minute of artifact free N2 sleep. We also extracted N2 spindle amplitude - the maximal voltage of a 4 s window centered on the peak of the detected spindle, N2 spindle duration – the duration in seconds between the start and the end of the detected spindle, and N2 spindle energy (or Integrated Spindle Activity; ISA; D'Agostino et al., 2018) – calculated as the integral of the spindle envelope over its duration.

2.6. Slow oscillations and their coupling with spindles

Slow oscillations (SOs) were automatically detected at every electrode (Staresina et al., 2015). First, data were bandpass filtered between 0.5 and 4 Hz, and all positive-to-negative zero crossings were identified. Candidate SOs were marked if two such consecutive zero crossings fell 0.8–2 s apart, corresponding to 0.5–1.25 Hz. Peak-to-peak amplitudes for all candidate oscillations were determined, and oscillations in the top quartile (i.e. with the highest amplitudes) at each electrode were retained as SOs. We extracted N2 slow oscillation density (number of SOs per minute of artifact free N2 sleep), as well as slow oscillation peak-to-peak amplitude (μV).

To identify SO-spindle coupling events, EEG data were bandpass filtered separately for Delta (0.5-4 Hz) and Sigma (12-15 Hz). Then, the Hilbert transform was applied to extract the instantaneous phase of the

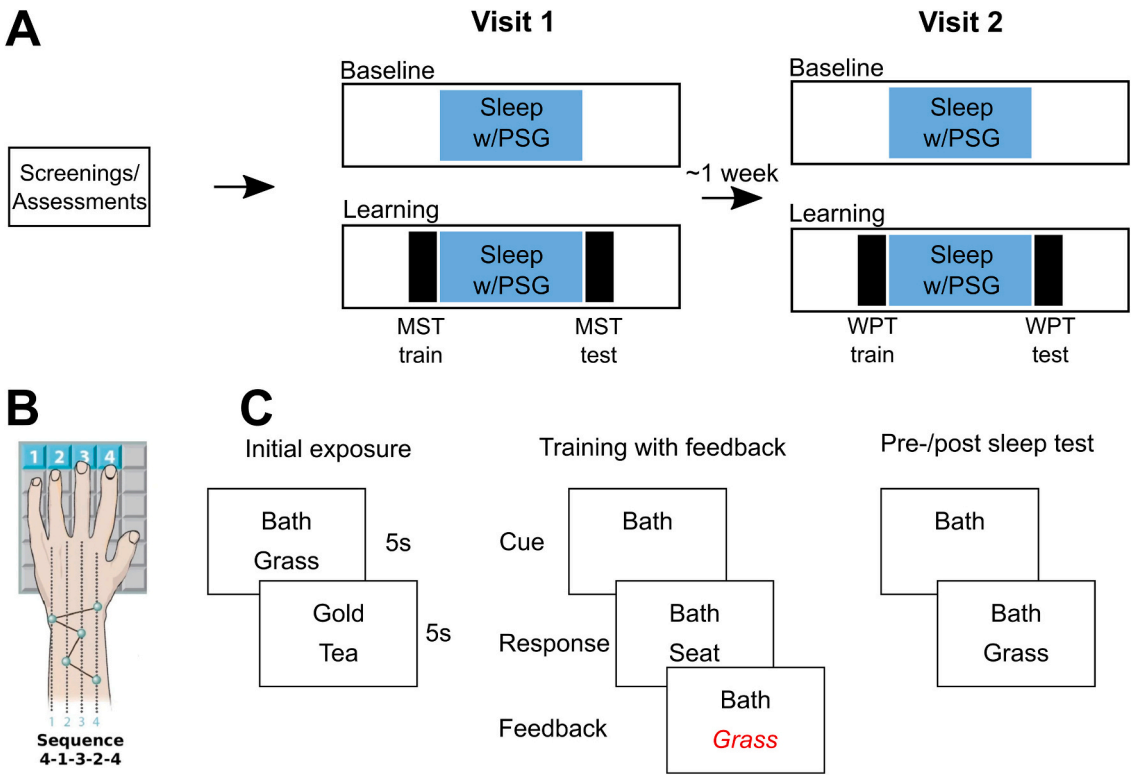

Fig. 1. Study protocol. **A** - Timeline of the study. Following baseline screenings and assessments, which included an introductory visit to the sleep laboratory, participants took part in a four night overnight sleep protocol divided into two separate visits approximately one week apart. Each visit consisted of two consecutive nights, a baseline night and a learning night. On Visit 1, the learning night consisted of training on the motor sequence task (MST) prior to sleep, and being tested the following morning.. During Visit 2, the learning night consisted of training and testing on the word pairs task (WPT) in the evening, and being re-tested the following morning. **B** - Motor sequence task. In the evening participants were trained (12 30s trials with interleaved 30s breaks) to type a five-digit sequence as quickly and accurately as possible. The following morning, participants were tested on an additional 12 trials after sleep. Overnight improvement was calculated as the percent increase in correctly typed sequences from the average of the last three training trials at night to the first three test trials the following morning. **C** - Word pairs task. Participants were exposed to pairs of words. Following initial exposure, participants were shown the top word of each pair and were asked to recall its associate. If they answered incorrectly, participants were shown the correct word. This procedure continued until participants correctly recalled 60 % of the target words. Before and after sleep, participants performed a cued recall test where each cue word was shown once, and participants had to recall the target word. No feedback was given on these tests. Overnight change in word pair memory was calculated as the relative change in recall between post- and pre-sleep tests [(post-sleep recall – pre-sleep recall) / pre-sleep recall)].

Delta signal and the instantaneous amplitude of the Sigma signal. For each detected spindle, the time of peak amplitude was determined. If the spindle peak occurred during a detected SO (i.e., between two positive-to-negative zero crossings), a SO-spindle coupling event was scored, and the phase angle of the slow oscillation at the peak of the spindle was determined. Finally, we extracted the number, density and percentage of coupled spindles, average coupling phase (°) and coupling consistency, measured as the mean length of the vector plotted in polar coordinates (Berens, 2009) during N2 sleep.

2.7. Statistical analysis

2.7.1. Group differences on sleep parameters

Linear mixed-effects models were run to investigate group differences in sleep parameters at each electrode with Group (HC, FHR, EC), Visit (Visit 1, Visit 2), Night (Baseline, Learning), and their interactions entered into the model as fixed effects and participant entered as a random effect. In all models, age was included as a continuous covariate.

To assess differences in coupling phase, circular two-way ANOVA models were used to first assess the effect of Group and Visit (Baseline Visit 1, Baseline Visit 2) and their interaction on coupling phase. To elucidate potential differences in Night, further circular ANOVA models were implemented with Group and Session (Baseline, Learning) and their interaction as factors, performed separately for Visit 1 and Visit 2.

2.7.2. Group differences in sleep-dependent memory consolidation

MST: As an initial pre-processing step, outlier MST trials were removed (Supplement). One-way ANCOVA was used to assess group differences in practice-dependent learning (calculated as the percent increase in correctly typed sequences from the first training trial to the average of the last three included trials of training) and sleep-dependent improvement (calculated as the percent increase in correctly typed sequences from the average of the last three training trials at night to the first three test trials the following morning) with the factor Group (HC, FHR, EC) and age entered as a covariate.

WPT: Group differences in number of rounds taken to reach criterion performance, recall performance at the immediate test, and overnight change in memory performance were assessed via a series of one-way ANCOVAs with the factor Group (HC, FHR, EC), and age entered as a covariate.

2.7.3. Associations between sleep spindle density and overnight memory consolidation

We used spindle measures from the learning nights to examine relationships between sleep and overnight memory consolidation. In separate models, we regressed MST improvement and WPT change in recall against spindle density at each electrode, with Group included as a fixed effect and age added as a continuous covariate. Robust linear regression procedures were used to minimize the influence of outliers. To determine whether spindles coupled to SOs were a better predictor

than uncoupled sleep spindles, the goodness of fit of two models was compared (Mylonas et al., 2020). In one model, memory consolidation was predicted from uncoupled spindle density, and in a second model memory was predicted from coupled spindle density. The goodness of fit of each model at each electrode was compared using the Bayesian Information Criterion (BIC), where a lower value indicates a better model fit (Schwarz, 1978).

2.7.4. Relation of sleep spindles and general cognitive functioning

The relation of sleep spindles with general cognitive ability was assessed using the same robust linear regression procedure described in Section 2.7.2. Cognitive functioning was measured as the MCCB Overall Composite score.

2.7.5. Associations between sleep spindles and symptomatology

Relationships between sleep spindles and measures of symptomatology (PANSS scores, EC only, Chapman scales all participants) were assessed using the same robust linear regression procedure described in Section 2.7.2.

2.7.6. Multiple comparisons correction

To control for multiple comparisons across electrodes, and to take into account the spatial correlation of the EEG data, we used a cluster-based permutation method (Maris and Oostenveld, 2007). For each term in the model, clusters were formed from adjacent electrodes that met an uncorrected threshold of $p < .05$. Permutation distributions were created by randomly shuffling the labels (Group, Visit, Session, Age) 1000 times at each electrode and retaining the cluster with the maximum statistic for each permutation (Mylonas et al., 2020). A cluster-corrected $p < .05$ was deemed significant. Follow-up pairwise estimated marginal means tests were used as post-hoc comparisons. Pairwise tests were performed on data averaged across significant electrodes in the overall cluster, with age included as a covariate. To examine whether any observed deficits in EC were driven by schizophrenia patients, pairwise estimated marginal means tests compared ECsz and ECnsz groups for cluster averaged values.

3. Results

3.1. No group differences in sleep quality and architecture

There were no significant group differences in sleep quality or architecture (Table 2 and Table S3). Total sleep time (TST), sleep onset latency, sleep efficiency, and wake after sleep onset did not significantly differ among groups (all p's > 0.13). A borderline main effect of group was seen for time spent in REM sleep ($p = .051$), with lower REM time in FHR and EC compared to HC (Table 2). No other main effects of group were observed.

Table 2
Sleep architecture across groups averaged across the four experimental nights.

	HC	FHR	EC	*F*	*p*
Total sleep time (min)	508 ± 74	486 ± 67	507 ± 54	1.79	0.18
Sleep onset latency (min)	25 ± 29	33 ± 36	20 ± 20	1.18	0.32
Sleep efficiency (%)	86 ± 8	83 ± 11	85 ± 9	2.06	0.14
Wake after sleep onset (min)	52 ± 41	57 ± 48	65 ± 49	1.72	0.19
N1 (min)	31 ± 23	28 ± 23	34 ± 40	0.18	0.84
N2 (min)	262 ± 54	251 ± 63	259 ± 57	1.34	0.27
N3 (min)	102 ± 31	111 ± 46	121 ± 47	1.66	0.20
REM (min)	113 ± 33	96 ± 36	93 ± 42	3.17	0.05
N1 (% of TST)	6.1 ± 4.7	5.7 ± 4.3	6.9 ± 8.2	0.14	0.87
N2 (% of TST)	51.5 ± 6.7	51.6 ± 8.5	51.1 ± 10	0.30	0.74
N3 (% of TST)	20.5 ± 6.5	23.4 ± 9.2	23.8 ± 8.6	2.52	0.09
REM (% of TST)	21.9 ± 5.1	19.3 ± 5.8	18.1 ± 7.6	3.01	0.06

Note. F statistic corresponds to the main effect of group on sleep architecture. For the borderline main effect of REM (min), effects were driven by reduced REM time in FHR and EC relative to HC (p's < 0.001). The same trend emerged for REM (% of TST); p's < 0.005).

3.2. Early course patients show selectively reduced spectral power in the sigma (sleep spindle) frequency band

The N2 power spectrum, averaged across nights and electrodes, is displayed in Fig. 2**A**. Topographical differences between groups in canonical frequency bands are shown in Fig. 2**B**. We observed a significant main effect of group for Sigma ($F_{sum} = 153.26$, $p = .007$), reflecting a reduction in EC (p's ≤ 0.004). There was no difference between ECsz and ECnsz ($p = .97$). No other group differences emerged in any other canonical frequency band (Fig. 2**B**), demonstrating a selective spindle-band deficit in EC.

3.3. Reduced sleep spindle activity in early course patients

There was a significant main effect of group on spindle density ($F_{sum} = 249.12$, $p = .009$; Fig. 3**A**, Row 1). EC exhibited lower spindle density than both HC ($t(63) = 3.02$, $p = .004$) and FHR ($t(63) = 3.08$, $p = .003$; Fig. 3**B**, Left). There was no evidence of a spindle deficit in FHR compared to HC ($t(63) = 0.13$, $p = .90$). Within EC, there was significantly lower spindle density in ECsz compared with ECnsz ($t(14) = 2.39$ $p = .03$; Fig. 3**C**, Right) who did not differ from HC ($p = .17$).

A significant main effect of group on spindle amplitude was observed ($F_{sum} = 309.80$, $p = .002$; Fig. 3**A**, Row 2) with significant amplitude reduction in EC (Fig. 3**B**, Center) compared to both HC ($t(63) = 3.49$, $p < .001$) and FHR ($t(63) = 3.51$, $p < .001$). Spindle amplitude did not differ between HC and FHR ($t(63) = 0.08$, $p = .94$) or between ECsz and ECnsz (t(14) = 1.34, $p = .21$; Fig. 3**C**, Center). There was no difference between the groups with regards to spindle duration (no cluster formed; Fig. 3**A**, Row 3). With regards to spindle energy (ISA), results mirrored those found for spindle amplitude. A significant main effect of group was found ($F_{sum} = 286.82$, $p = .012$; Fig. 3**A**, Row 4), driven by significantly lower spindle energy in EC (Fig. 3**B**, Right) relative to HC ($t(63) = 3.46$, $p < .001$) and FHR ($t(63) = 3.21$, $p = .002$). There was no difference in spindle energy between HC and FHR ($t(63) = 0.22$, $p = .83$, or between ECsz and ECnsz ($t(14) = 0.40$, $p = .70$; Fig. 3**C**, Right).

To summarize, compared with HC and FHR, EC showed reduced N2 spindle density, amplitude, and energy. In the case of spindle density, the group differences were driven by ECsz. There were no interactions between group and either visit or session (TableS4). Similar results were found for N3 sleep (Fig. S2).

3.4. Increased SO-spindle coupling consistency in early course patients and first-degree relatives

There were no group differences in either the density or peak-to-peak amplitude of detected SOs (Fig. 4**A**; TableS4). Of all detected spindles, 11.6 % ± 5.4 % were coupled to an SO. Across participants and at all electrodes, we found significant non-uniformity in the preferred phase of the SO to which spindles were coupled (all Z ≥8.65, all p < .001). Sleep spindles preferentially coupled to the rising phase of the SO, close to the positive peak (M = -28.7° ± 19.7°) at electrode Cz; Fig. 4**B**). There were no group differences in the average coupling phase of sleep spindles to SOs (Table S4) or with the percent of spindles coupled to SOs at any of the electrodes (Table S4).

There was a significant group effect on coupling consistency ($F_{sum} = 277.61$, $p = .005$; Fig. 4**C**; Table S4) corresponding to significantly *lower* SO-spindle coupling consistency in HC compared with both EC (t(63) = 2.98, $p = .004$) and FHR (t(63) = 2.37, $p = .021$; Fig. 4**D**). There were no differences between EC and FHR (t(63) = 0.84, $p = .40$), or between ECsz and ECnsz (t(14) = 1.17, $p = .26$). Across all participants, the consistency of SO-spindle timing correlated with SO amplitude, with a

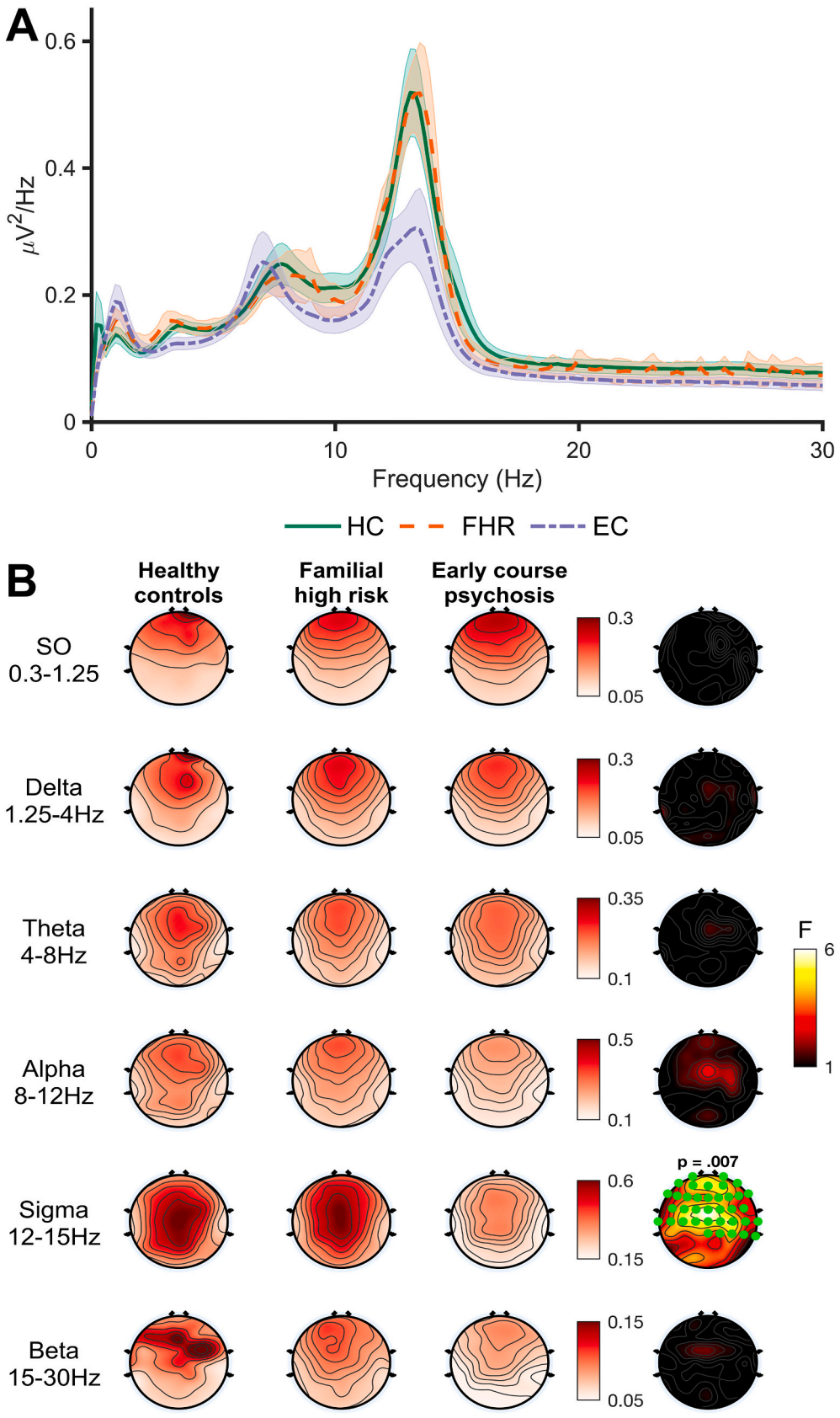

Fig. 2. N2 sleep spectral power. **A** - Global power spectral density (PSD) in frequencies from 0 to 30 Hz, collapsed across electrodes and nights. Shaded area around lines indicates the between-subject standard error. **B** - Main effect of group on PSD in canonical frequency bands. Topographies averaged across all four nights are shown for each group separately. Right hand topoplots show F values at each electrode for the main effect of group. Significant electrodes (cluster-corrected) are highlighted in green. Significant cluster *p* values displayed above plot. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

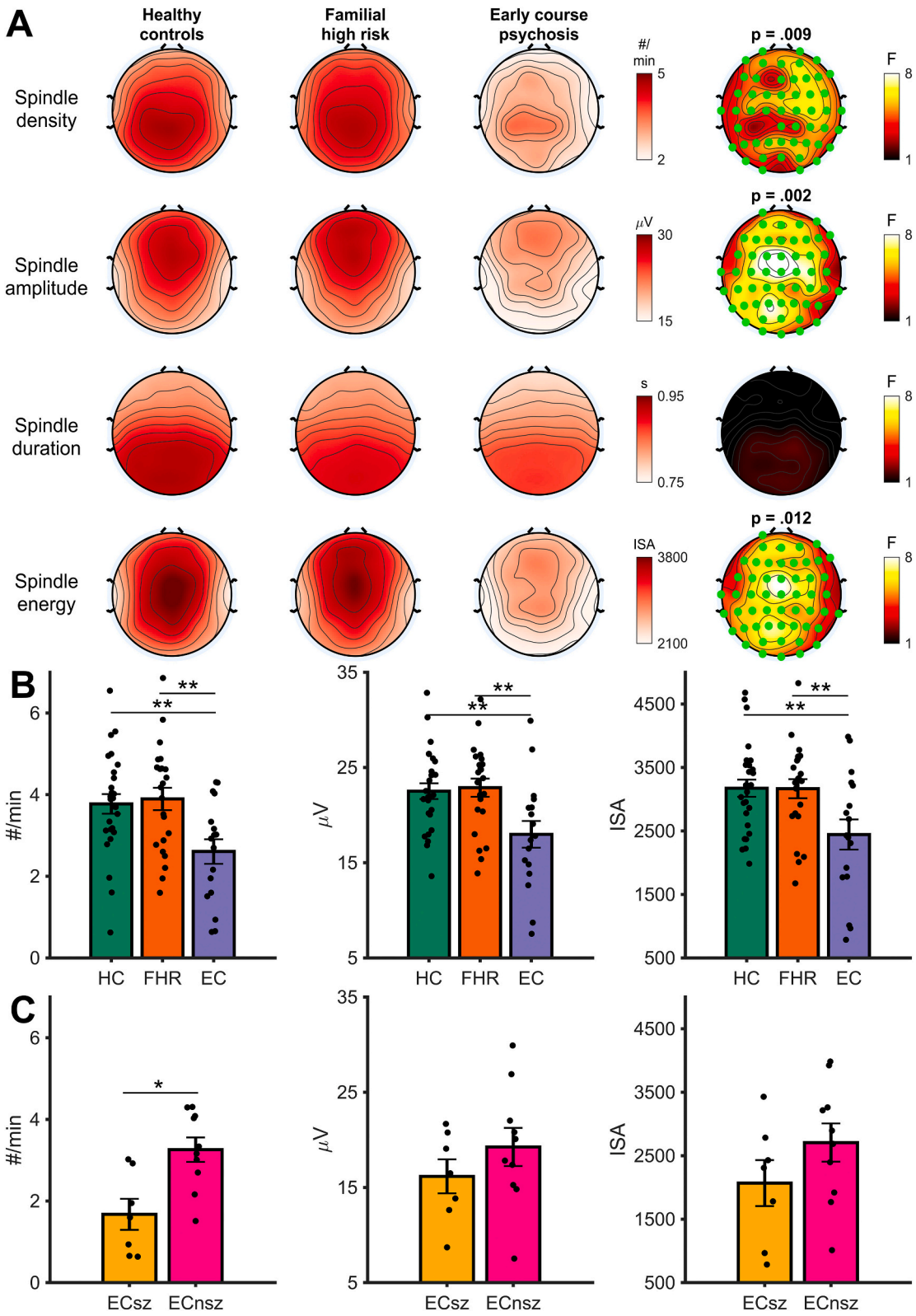

Fig. 3. N2 sleep spindles. **A** - Topographies showing the main effect of group on N2 spindle density (Row 1), amplitude (Row 2), duration (Row 3), and energy (Row 4). The right-most column shows F values at each electrode for the main effect of group. Significant electrodes (cluster-corrected) are highlighted in green. Cluster *p*-value displayed above plot. **B** - Pairwise tests for the main effect of group on N2 spindle density (left), amplitude (center), and energy (ISA; right) with spindle activity averaged over significant electrodes in the cluster highlighted in **A**. **C** – Same as **B**, but shows differences between schizophrenia and non-schizophrenia psychosis patients. ISA = Integrated spindle activity, HC = Healthy controls, FHR = First degree relatives, EC = Early course psychosis; calculated as the integral of the spindle envelope over its duration ECsz = Early course schizophrenia, ECnsz = Early course non-schizophrenia psychosis. Error bars indicate the standard error. *** = $p < .001$, ** = $p < .01$, * = $p < .05$ from pairwise estimated marginal means tests. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

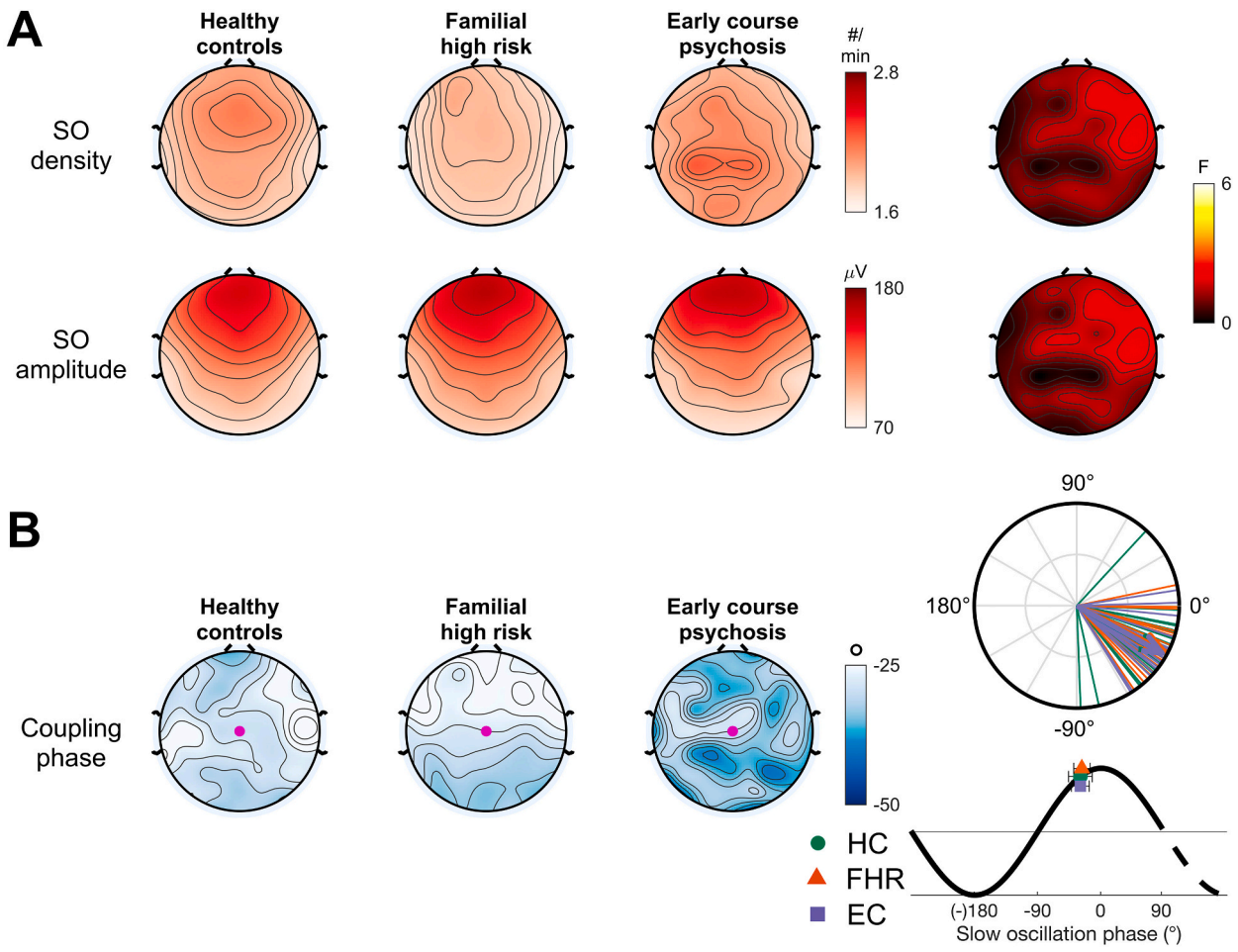

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Fig. 4. N2 SO-spindle coupling. **A** - Slow oscillation density (top row) and peak-to-peak amplitude (bottom row) in each group, averaged across the four nights. Rightmost topoplots display F values for the main effect of group. **B** - Preferred coupling phase of spindles to slow oscillations (SOs) in each group, averaged across the four nights. Right: circular phase plot displaying phase distributions across participants for each group at electrode Cz (highlighted electrode in topography). Each line indicates the preferred coupling phase of an individual participant. The direction of the arrow indicates the average phase across participants, separately for each group. A coupling of phase of 0° indicates preferential coupling of spindles at the positive peak of the slow oscillation. A coupling phase of 180° indicates preferential spindle coupling at the negative trough of the slow oscillation. Mapping of SO phase to topographical and circular plots is below the circular phase plot. **C** - Topographies showing the main effect of group on coupling consistency. Coupling consistency (measured as the mean vector length) topographies (averaged across all four nights) are shown for the three groups separately. The right hand plot shows F values at each electrode for the main effect of group. Significant electrodes (cluster-corrected) are highlighted in green. Cluster *p* value displayed above plot. **D** - Pairwise tests for the main effect of group on coupling consistency, with coupling consistency averaged over significant electrodes in cluster.. HC = Healthy controls, FHR = First degree relatives, EC = Early course psychosis, ECsz = Early course schizophrenia, ECnsz = Early course non-schizophrenia psychosis. Error bars indicate the standard error. ** = $p < .01$, * = $p < .05$ from pairwise estimated marginal means tests. **E** – Robust linear regression between slow oscillation amplitude and spindle coupling consistency. Insert shows significant electrodes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

higher SO amplitude predicting more consistent coupling ($r = 0.37$, p = .002; Fig. 4**E**).

Except for the greater consistency of the SO phase at which spindles peaked in both EC and FHR groups, EC and FHR groups did not differ from controls in spindle-SO coupling. The same pattern was seen for N3 sleep (Fig. S3).

3.5. N2 spindle density predicted overnight procedural but not declarative memory consolidation

3.5.1. MST

MST learning curves are displayed in Fig. 5**A-B**. Although EC typed fewer correct sequences overall, there were no group differences in improvement during training ($F(2, 63) = 1.54$, $p = .22$), including between ECsz and ECnsz patients ($F(1,14) = 0.14$, $p = .79$). For overnight improvement, there was no overall main effect of group ($F(2,63) = 0.75$, $p = .48$). However, a planned contrast revealed significantly less overnight improvement in ECsz ($t(64) = 2.17$, $p = .034$; Fig. 5**B-C**). In ECsz, the degree of overnight improvement (6.3 % ± 16.6 %) was not significantly different from zero ($t(6) = 1.01$, $p = .35$), whereas all other groups showed substantial improvement (18.2 % ± 13.5 %; $t(60) = 10.4$, $p < .001$).

Higher spindle density predicted better overnight improvement ($F_{sum} = 341.95$, $p = .008$; Fig. 5**D**). Averaging spindle density across all significant electrodes resulted in a cluster averaged correlation coefficient of $r = 0.43$. The strength of association between spindle density and overnight improvement did not significantly differ among groups, although the correlation was numerically stronger in HC when averaged over the significant cluster (HC: $r = 0.51$, FHR: $r = 0.38$; EC: $r = 0.37$; ECsz: $r = 0.19$, ECnsz: $r = 0.32$). Although coupled spindle density also correlated with overnight improvement ($r = 0.44$, $p < .001$), coupled spindle density was not a better predictor of memory consolidation than uncoupled spindle density ($t(57) = 1.01$, $p = .32$).

3.5.2. WPT

EC took more trials to reach criterion than FHR, and numerically more than HC (main effect of group: $F(2, 59) = 5.45$, $p = .007$). However, immediate recall accuracy did not differ between the groups ($p = .127$), and there was no difference in overnight change in recall ($p = .696$). There was no difference between ECsz and ECnsz patients in the number of trials taken to reach criterion, immediate recall accuracy, or overnight change in memory (all $p \geq 0.28$). Neither spindle density, amplitude, nor SO-spindle coupling predicted overnight change in WPT. Exploratory analyses of N3 sleep revealed a positive correlation between N3 coupled spindle density and overnight retention of word pairs in the EC group only ($r = 0.60$, $p = .022$; see Supplement for details).

3.6. Spindle density correlated with better general cognitive functioning

N2 spindle density was significantly positively correlated with MCCB overall composite score ($F_{sum} = 108$, $p = .049$; Fig. 5**E**). The cluster averaged correlation coefficient was $r = 0.30$ across the whole sample (HC: $r = 0.27$, FHR: $r = 0.06$, EC: $r = 0.44$, ECsz $r = 0.32$, ECnsz: $r = 0.10$).

3.7. Spindle amplitude correlated with fewer psychotic-like experiences

Spindles measures were not associated with either positive, negative, or general psychopathology scores as measured with the PANSS in the EC group (no clusters formed). Across all groups, spindle amplitude negatively correlated with Chapman total score ($F_{sum} = 273$, $p = .007$, cluster averaged correlation coefficients whole sample: $r = -0.37$, HC: $r = -0.28$, FHR: $r = -0.39$; EC $r = -0.07$; ECsz: $r = -0.52$, ECnsz: $r = 0.15$; Fig. 5**F**). Of the Chapman subscales, a significant cluster only emerged for the magical ideation subscale ($F_{sum} = 417$, $p = .003$, cluster averaged correlation coefficients whole sample: $r = -0.41$, HC: $r = -0.27$; FHR: $r = 0.05$; EC: $r = -0.30$; ECsz: $r = -0.60$; ECnsz: $r = -0.14$). No associations were found between chlorpromazine equivalent antipsychotic medication dosage and sleep spindle activity (see Table S1 for medications).

4. Discussion

We examined sleep oscillations in relation to sleep-dependent memory consolidation in early-course minimally medicated psychosis patients and young, non-psychotic first-degree relatives. Replicating previous work, and extending it to early course patients with schizophrenia, we found pronounced deficits in sleep spindle density and overnight procedural memory consolidation relative to controls (Demirlek and Bora, 2023; Lai et al., 2021). However, neither of these deficits extended to early course patients with other psychoses or non-psychotic first-degree relatives. Both patients and relatives showed increased consistency of SO-spindle coupling compared to controls, replicating previous findings and extending them to early course and relative groups (Mylonas et al., 2020).

Spindle deficits in chronic schizophrenia have been linked to deficits in sleep-dependent memory consolidation (Göder et al., 2015; Wamsley et al., 2012). Our earlier work demonstrated that spindle deficits in APD-naive early course patients correlate with cognition more generally (e.g., IQ, executive function; Manoach et al., 2014). Here, we replicated this finding, by showing a positive link between spindle density and general cognitive ability. As in previous work, we found that higher amplitude spindles related to fewer psychotic-like experiences, adding further evidence that spindle deficits contribute to the symptoms experienced in schizophrenia (Ferrarelli et al., 2010; Kozhemiako et al., 2022; Wamsley et al., 2012). To the best of our knowledge, the present study is the first demonstration that deficits in sleep spindles correlated with reduced sleep-dependent memory consolidation (i.e., improvement of a specific memory encoded before sleep and tested afterwards) in early course schizophrenia patients. There is abundant animal and growing human evidence of a causal role of sleep spindles in memory consolidation (Denis and Cairney, 2024, 2023). Our study provides novel evidence that deficits in sleep spindles impairs sleep-related memory consolidation early in the course of schizophrenia and are therefore not due to

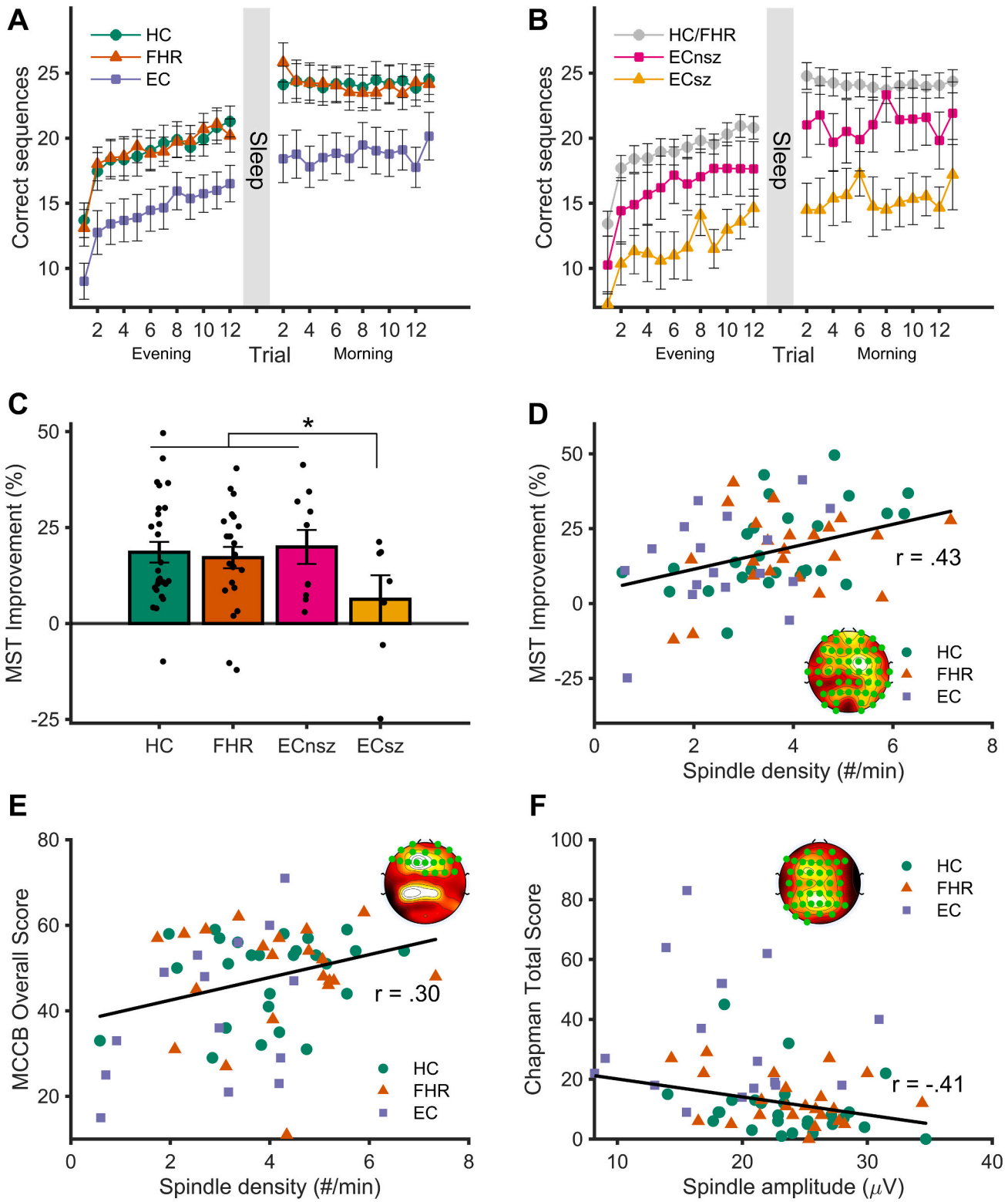

Fig. 5. Spindle correlations with overnight memory consolidation, general cognitive function, and psychotic-like symptoms. **A** - MST learning across training (evening) and test (morning) trials for each group. The Y axis represents the number of correctly typed sequences per trial. **B** - MST learning plotted separately for schizophrenia and non-schizophrenia psychosis patients. Grey circles show the combined healthy control and familial high-risk groups. **C** - Overnight MST improvement, calculated as the percent increase in correctly typed sequences from the average of the last three training trials at night to the first three test trials the following morning. * = $p < .05$, error bars reflect the standard error. **D** – Robust linear regression between N2 spindle density and overnight MST improvement (cluster averaged). Insert shows significant electrodes in the cluster. **E** – Robust linear regression between N2 spindle density and MCCB overall composite score (cluster averaged). Insert shows significant electrodes in the cluster. **F** – Robust linear regression between N2 spindle amplitude and symptomatology as assessed by the Chapman scale for psychotic-like symptoms (cluster averaged). Insert shows significant electrodes in cluster.

disease chronicity or a side-effect of prolonged medication use. Rather, spindle deficits and correlated cognitive impairments are core features of schizophrenia that should be considered as outcome measures in clinical trials.

Both spindle density and memory consolidation deficits were driven by schizophrenia patients, compared with other psychoses. This is important to note as most studies of sleep do not distinguish between schizophrenia and other psychotic disorders, including schizoaffective disorder (e.g., Bagautdinova et al., 2023). The finding that the spindle density deficit was restricted to individuals with a diagnosis of schizophrenia is consistent with a large body of work showing that the presence of affective symptoms is associated with better outcomes in psychotic disorders (e.g. Arrasate et al., 2016; Harrow et al., 2000). Nevertheless, this finding should be interpreted with caution. First, the low sample size means that our findings require replication in larger samples. Second, our sample of schizophrenia vs non-schizophrenia patients were not matched on parental education or severity of psychotic symptoms, a limitation that should be addressed in future work. Finally, we note that a difference between schizophrenia and non-schizophrenia patients only emerged for spindle density, and not for other measures of spindle activity such as amplitude, duration or energy (ISA). Despite these limitations, this distinction may be an important consideration to the burgeoning field of sleep research in psychosis.

Contrary to our hypotheses, neither sleep spindles nor memory consolidation was impaired in the first-degree relatives of patients. Compared with our previous study which reported spindle deficits in relatives (Manoach et al., 2014), in the present study the relatives were older and therefore more likely to be beyond the age of maximum risk. However, work by other groups have observed spindle deficits in both young adult and middle aged samples of first-degree relatives of schizophrenia patients (D'Agostino et al., 2018) including in those without any psychopathology (Schilling et al., 2017). As relatives are hypothesised to show attenuated deficits compared to probands with schizophrenia, based on presumably lower genetic risk, larger sample sizes are necessary to evaluate group differences.

While no evidence of a spindle deficit was seen in relatives, both relatives and patients showed higher consistency in the phase of the SO at which spindles peaked (i.e., coupling consistency) compared with controls. This finding replicates a previous report in chronic medicated patients with schizophrenia, and extends it to early course patients and their first-degree relatives (Mylonas et al., 2020). In both healthy and schizophrenia samples, coupling consistency has been associated with enhanced memory consolidation, implying that higher coupling consistency is desirable (Demanuele et al., 2016; Mikutta et al., 2019). In the present study, however, coupled spindles were not a better predictor of MST consolidation than uncoupled spindles. Across participants, a higher coupling consistency correlated with larger SOs, suggesting higher amplitude SOs are better able to group spindles into their excitable upstates. Mechanistic studies are needed to understand the basis increased SO-spindle coupling consistency in people with psychosis and their first-degree relatives and its functional consequences.

Strengths of this study include the multi-night experimental protocol, high-density EEG recordings, and stringent screening and recruitment procedures. However, our sample size, especially of early course patients, was relatively small, at least in part resulting from COVID-19 pandemic related constraints which also led to a higher-than-expected drop-out rate. It is also possible that COVID-19 related dropout could have introduced a bias since those who completed the study may differ from those who dropped out. A second limitation is that, even though our sample was minimally medicated, we cannot rule out the possibility that medication use affected our outcome measures (Krystal et al., 2008). Despite this, we did not observe a spindle density deficit in the APD medicated non-schizophrenia patients, nor was there a correlation between chlorpromazine equivalent APD dosage and spindle measures in the present study. Longitudinal studies of early course patients before and at the outset of treatment with APDs would illuminate the effects of APD use on sleep spindles and sleep-dependent memory consolidation. A third limitation is that our memory tasks did not include a wake control condition. Although both tasks we used have been reliably shown to benefit from sleep (Berres and Erdfelder, 2021; Schmid et al., 2020), it was not possible to determine the magnitude of the sleep benefit compared to wake in the present sample. Finally, our cross-sectional design limits our ability to infer causal relationships between sleep spindle and ecologically valid measures of memory consolidation deficits over time (e.g., in rehabilitation and occupational settings), which is an important area for future work.

In conclusion, we found reduced sleep spindle density and a correlated deficit in overnight memory consolidation in minimally medicated, early course schizophrenia. These findings show for the first time that deficits in sleep-dependent memory consolidation in schizophrenia are not due to disease chronicity or prolonged medication use. Although we did not find spindle deficits in unaffected relatives, both relatives and patients demonstrated increased consistency in the phase coupling of spindles with SOs. This highlights the need for future research to increase our mechanistic understanding of this metric and how it relates to the risk and development of schizophrenia. We conclude that abnormal NREM sleep oscillations are a reliable finding throughout the course of schizophrenia and are a potentially tractable target for interventions to improve cognition.

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Dan Denis: Writing – review & editing, Writing – original draft, Software, Formal analysis. **Bengi Baran:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Dimitrios Mylonas:** Writing – review & editing, Software, Methodology. **Courtney Spitzer:** Investigation. **Nicolas Raymond:** Investigation. **Christine Talbot:** Investigation. **Erin Kohnke:** Investigation. **Olivia Larson:** Investigation. **Robert Stickgold:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Matcheri Keshavan:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Dara S. Manoach:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2024.10.026.

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