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The infraslow fluctuation of sigma power during sleep in young individuals with schizophrenia

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ABSTRACT

A well-replicated finding in schizophrenia is a reduction in sleep spindles, a major electrophysiological characteristic of Non-Rapid Eye Movement sleep. However, recent evidence indicates that even in healthy individuals, sleep spindles are not uniformly distributed throughout the night. Rather, they fluctuate rhythmically on an infraslow ~50-second timescale, alternating between periods of high and low spindle activity. This fluctuation is referred to as the infraslow fluctuation of sigma power (10–16 Hz EEG activity, ISFS), which is modulated by noradrenergic activity from the locus coeruleus and seems to organize periods of arousability and periods of memory reactivation processes during sleep. Given the known deficit in sleep spindles, dysregulation of noradrenergic activity, and impairments in sleep maintenance and memory in schizophrenia, this study investigates the ISFS in sleep EEG data from individuals with either Childhood-Onset Schizophrenia (COS; N = 17) or Early-Onset Schizophrenia (EOS; N = 11), aged 9 to 21 years, alongside age- and sex-matched healthy controls (N = 56). The ISFS strength was reduced in both COS and EOS groups compared to controls, particularly in central-parietal electrodes. No significant difference in the ISFS strength was found between the two clinical groups, nor were there correlations between the ISFS strength and clinical characteristics or spindle density. These findings suggest that the ISFS is detectable but attenuated in young patients with schizophrenia, underscoring the value of considering spindle timing when probing disease mechanisms and designing interventions.

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1. Introduction

A reduction in sleep spindles—brief oscillatory bursts characteristic of Non-Rapid Eye Movement (NREM) sleep—has been consistently reported in schizophrenia (Castelnovo et al., 2018; Ferrarelli, 2024; Ferrarelli et al., 2007; Manoach et al., 2016). Over the past two decades, spindle deficits in schizophrenia have been understood to reflect disruptions in thalamocortical connectivity, with evidence implicating both impaired glutamatergic signaling and altered GABAergic control within the thalamic reticular nucleus (Benson, 2006; Ferrarelli and Tononi, 2011; Manoach et al., 2016; Vukadinovic, 2011; Zhang et al., 2020). The reduction in sleep spindles is observed in adult-onset schizophrenia when compared to both healthy and clinical controls and appears independent of medication status (Castelnovo et al., 2018). Sleep spindle deficits have been observed even in young individuals with schizophrenia, including those with Childhood-Onset Schizophrenia (COS; diagnosis before age 13) and Early-Onset Schizophrenia (EOS; diagnosis between ages 13 and 18) (Dimitriades et al., 2023; Gerstenberg et al., 2020; Markovic et al., 2020). COS and EOS are neurobiologically and phenomenologically continuous with adult-onset schizophrenia (Driver et al., 2013; Gogtay, 2008). However, COS is often considered a more severe form of the disorder, frequently associated with pronounced developmental deviations and structural brain anomalies that precede or accompany symptom onset. Importantly, first studies assessing spindles deficits showed a robust and widespread reduction in individuals with COS, whereas individuals with EOS exhibit only circumscribed and localized reductions (Dimitriades et al., 2023; Gerstenberg et al., 2020; Markovic et al., 2020).

Recently, growing interest has shifted beyond the number of sleep spindles to their precise timing (Champetier et al., 2023; Dimitriades et al., 2024; Lázár et al., 2019; Lecci et al., 2017; Osorio-Forero et al., 2021). Rather than occurring evenly throughout NREM sleep, sleep spindles fluctuate over an approximately 50-s timescale, alternating between phases of high and low spindle activity (Lecci et al., 2017; Watson, 2018). This variation in the timing of sleep spindle activity has been observed in rodents as well as humans, spanning from childhood to late adulthood, and is referred to as the infraslow fluctuation of sigma power (ISFS) (Champetier et al., 2023; Dimitriades et al., 2024; Lecci et al., 2017). In rodents, the ISFS has been found to be driven by locus coeruleus noradrenergic activity, a key modulator of arousal in the brain (Hayat et al., 2020; Osorio-Forero et al., 2021). Interestingly, arousals during sleep—as well as markers of memory reactivation—occur at specific phases of the ISFS in both rodents and humans (Dimitriades et al., 2024; Lecci et al., 2017), suggesting that there may be coordinated periods of increased environmental responsiveness and periods for memory consolidation processes during sleep. These findings have sparked interest in examining the ISFS in clinical populations, where such processes are often disrupted.

Young individuals with schizophrenia have not been well studied with respect to arousals during sleep or memory reactivation, whereas adults with chronic schizophrenia exhibit more frequent arousals (Bagautdinova et al., 2023) and reduced or absent overnight improvements in procedural learning tasks, when compared to healthy controls (Genzel et al., 2015; Manoach et al., 2004; Seeck-Hirschner et al., 2010). Moreover, while predominant hypotheses on the pathomechanisms of schizophrenia focus on disruptions in glutamatergic and dopaminergic signaling (Howes et al., 2015; Kitzinger and Arnold, 1949; Lieberman et al., 1987), there is also evidence pointing to dysfunction in the locus coeruleus-noradrenaline system (Mäki-Marttunen et al., 2020; Maletic et al., 2017; Yamamoto and Hornykiewicz, 2004).

Given the known deficits in sleep spindles, alongside dysregulated noradrenergic activity and increased arousals and impairments in memory, schizophrenia presents a compelling case for investigating potential alterations in the ISFS. To explore this, electroencephalographic (EEG) sleep data were gathered from two independent clinical samples of young individuals with schizophrenia (one group with COS, one with EOS). Features of the ISFS, specifically its presence and strength, were compared between patients and healthy controls, as well as between the two patient groups, and potential associations between the ISFS strength, sleep spindle density, and clinical characteristics were examined.

2. Materials and methods

2.1. Participants

This project pooled sleep, demographic, and clinical data from two patient groups diagnosed with schizophrenia. One sample was diagnosed with Childhood-Onset Schizophrenia (COS; N = 17), implying that the age of onset occurred before 13 years. These data were recorded as a follow-up after a few years of illness (Table 1). The other sample, diagnosed with Early-Onset Schizophrenia (EOS; N = 11), had an age of onset between 13 and 18 years and was recorded shortly after diagnosis (Table 1). All individuals were aged between 9 and 21 years at the time of the sleep EEG.

The COS group was recruited nationwide at the National Institute of Mental Health in the United States between 2014 and 2017 and the EOS group at the Department of Child and Adolescent Psychiatry of the Psychiatric University Hospital Zurich in the 1.5 million catchment area of the Canton of Zurich in Switzerland between 2012 and 2016. Screening procedures and characteristics of these patient groups have been previously published (Dimitriades et al., 2023; Gerstenberg et al., 2020; Markovic et al., 2020). This research project was approved by Ethics Committee of the Canton of Zurich and Bern, Switzerland, BASEC 2021-00215. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. All study procedures were performed according to the Declaration of Helsinki. Age of illness onset (in years), duration of illness (in years), antipsychotic medication (measured as chlorpromazine equivalent), and positive and negative symptomatology were available for every individual with schizophrenia, either according to the Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS) for the COS group or to the Positive and Negative Symptoms Scale (PANSS) for the EOS group (Andreasen, 1986, 1989; Kay et al., 1987). IQ data were available from 12 patients with COS and eight with EOS.

Every individual with COS and EOS was age- and sex-matched to two healthy controls (HC). This resulted in 34 individuals in the HC group for the COS group (HC-COS) and 22 individuals in the HC group for the EOS group (HC-EOS) (Table 1). Sleep and demographic data for all HCs were collected between 2008 and 2021 in the sleep laboratory of the University Children's Hospital Zurich in Switzerland (Groch et al., 2016; Kurth et al., 2010; Leach et al., 2024; Pugin et al., 2015; Volk et al., 2018, 2019; Wehrle et al., 2017). Sex was recorded as a binary variable (female or male).

2.2. Electroencephalogram recordings and preprocessing

EEG recording systems and sleep-specific preprocessing varied between the COS group (Markovic et al., 2020) and the EOS group and all HCs (Gerstenberg et al., 2020; Groch et al., 2016; Kurth et al., 2010; Leach et al., 2024; Pugin et al., 2015; Volk et al., 2018, 2019; Wehrle et al., 2017). All-night EEG were recorded from patients with COS using a 21-channel 10–20 system (TWin or Nihon Kohden; sampling rate: 200 Hz) and from patients with EOS and all HCs using a 128-channel system (Electrical Geodesic Sensory Net; sampling rate: 500 Hz). There were 21 channels in common between all individuals, as previously reported (Dimitriades et al., 2023).

Sleep stages were scored according to standard criteria by two sleep experts (Berry et al., 2020). Each epoch was assigned a standard sleep stage, with epochs lasting 30 s for the COS group and 20 s for the EOS group and all HCs. Semi-automatic artifact rejection was applied based

Table 1
Demographic and sleep structure parameters.

Parameter	Patient group (N)	Mean (SD)	Healthy controls (N)	Mean (SD)	Cliff's delta	*p*
Demographics						
Age (years)	COS (17)	16.00 (3.64)	HC-COS (34)	16.10 (3.86)	0.02	0.90
	EOS (11)	16.38 (1.42)	HC-EOS (22)	16.46 (1.62)	0.00	1.00
Sex (N)	COS (17)	12F, 5M	HC-COS (34)	24F, 10M	0.00	1.00
	EOS (11)	4F, 7M	HC-EOS (22)	8F, 14M	0.00	1.00
All-night sleep						
WASO (%)	COS (17)	1.44 (1.47)	HC-COS (34)	6.06 (7.54)	−0.65	**<0.001**
	EOS (11)	5.31 (4.54)	HC-EOS (22)	5.52 (6.09)	−0.03	0.89
N1 (%)	COS (17)	3.59 (2.74)	HC-COS (34)	6.81 (4.31)	−0.54	**<0.01**
	EOS (11)	6.71 (3.93)	HC-EOS (22)	7.15 (5.00)	0.00	1.00
N2 (%)	COS (17)	48.50 (19.93)	HC-COS (34)	50.19 (7.05)	0.02	0.91
	EOS (11)	48.05 (10.23)	HC-EOS (22)	52.22 (4.50)	−0.21	0.33
N3 (%)	COS (17)	29.64 (24.52)	HC-COS (34)	22.50 (8.43)	0.06	0.74
	EOS (11)	26.07 (13.01)	HC-EOS (22)	20.63 (6.02)	0.20	0.37
REM (%)	COS (17)	18.27 (9.78)	HC-COS (34)	20.51 (5.18)	−0.20	0.26
	EOS (11)	19.16 (7.70)	HC-EOS (22)	20.00 (5.33)	0.04	0.86
Total sleep time (min)	COS (17)	542.62 (167.73)	HC-COS (34)	452.93 (51.83)	0.65	**<0.001**
	EOS (11)	437.85 (123.67)	HC-EOS (22)	417.26 (63.55)	0.37	0.09
Bouts of N2 sleep						
Bout number	COS (17)	13.71 (10.09)	HC-COS (34)	12.71 (3.24)	0.02	0.92
	EOS (11)	13.64 (5.82)	HC-EOS (22)	13.00 (3.27)	0.17	0.45
Mean bout length (s)	COS (17)	450.58 (86.42)	HC-COS (34)	588.37 (121.86)	−0.68	**<0.0001**
	EOS (11)	531.96 (96.48)	HC-EOS (22)	576.95 (104.70)	−0.24	0.28
Mean relative location (%)	COS (17)	52.23 (13.34)	HC-COS (34)	54.16 (7.16)	−0.08	0.67
	EOS (11)	54.10 (7.50)	HC-EOS (22)	51.09 (7.05)	0.25	0.26
Total duration of bouts (min)	COS (17)	110.35 (91.19)	HC-COS (34)	127.21 (47.00)	−0.20	0.26
	EOS (11)	123.06 (55.57)	HC-EOS (22)	123.98 (34.86)	0.14	0.54
Proportion of all N2 (%)	COS (17)	38.23 (23.40)	HC-COS (34)	55.07 (15.71)	−0.41	**0.02**
	EOS (11)	56.01 (15.43)	HC-EOS (22)	56.68 (11.29)	−0.02	0.95

COS: Childhood-Onset Schizophrenia; EOS: Early-Onset Schizophrenia; HC-COS: Healthy Controls for COS; HC-EOS: Healthy Controls for EOS; SD: standard deviation; F: female; M: male; WASO: Wake After Sleep Onset; Non-Rapid Eye Movement Sleep Stages (N1, N2, N3); REM: Rapid Eye Movement; min: minutes; s: seconds; %: percent. Sex is reported as a binary variable (female or male), with the number of females and males indicated in the table. Bout: N2 sleep data lasting at least 300 s without transitions to other vigilance states or artifacts. Mean Relative Location: Mean of all bout midpoints divided by the total recording length, expressed as a percentage. Proportion of all N2: Total duration of N2 bout data relative to total N2 sleep duration. Statistically significant *p*-values are shown in bold.

on power in the delta and beta frequency bands, following previously established methods (Huber et al., 2000; Leach et al., 2023). Only artifact-free epochs across all channels were included in further analyses. Channels with poor signal quality were interpolated from neighboring channels. Further, all EEG data were low-pass filtered (−3 dB cut-off: 39.25 Hz; Hamming Window Finite Impulse Response (FIR) filter; filter order: 184; *pop_eegfiltnew* from EEGLAB) (Delorme and Makeig, 2004), downsampled (200 Hz; for the EOS group and all HCs; *pop_resample* from EEGLAB), and high-pass filtered (−3 dB cut-off: 0.27 Hz; Kaiser Window FIR filter; filter order: 2390; custom implementation in MATLAB). The data were re-referenced to the mean of the mastoids.

2.3. Analyses of the infraslow fluctuation of sigma power and sleep spindles

Uninterrupted NREM Stage N2 (N2) sleep, free from artifacts or transitions to other vigilance states, was isolated. This procedure followed Dimitriades et al. (2024), with the exception that N2 sleep bouts were required to last at least 300 s (instead of 280), to account for differences in sleep staging epoch lengths between groups (20 versus 30 s). N2 sleep bout parameters were compared between patients and HCs. These parameters include: the number of bouts, the mean bout length (in seconds), the mean relative location of the bouts (the mean across all bout midpoints divided by the total length of the recording; in percent), the total duration of the bouts (in minutes), and the proportion of all N2 (the duration of the N2 bout data is divided by the total duration of N2 sleep and multiplied by 100; in percent). The subsequently explained ISFS and sleep spindle analyses were performed on the aforementioned N2 sleep bouts.

The ISFS was analyzed as previously described (Dimitriades et al., 2024). In brief, the sigma power was extracted over time from N2 sleep bouts using a Gabor-Morlet wavelet (4 cycles, 0.2 Hz resolution) across a broad sigma range (10–16 Hz) to capture frontal and central sleep spindle activity (Fernandez and Lüthi, 2020; Kwon et al., 2023). The sigma power over time was then centered around zero by subtracting the mean, and the Fast Fourier Transform (FFT) was applied. To account for varying N2 sleep bout lengths (≥300 s), the spectral power was adjusted by dividing the FFT output by the given bout duration. Spectral power was averaged across all N2 bouts. To account for potential intra- and interindividual differences, the average spectral power was normalized by dividing spectral power in each frequency bin by the mean spectral power across all frequency bins (0–0.1 Hz). A horizontal baseline correction was further applied by subtracting the mean power from 0.06 to 0.1 Hz. The frequency range for the ISFS peak detection was set between 0.01 and 0.04 Hz, where the infraslow spectral peak typically occurs (Lecci et al., 2017). This procedure was performed on every channel and participant separately.

Subsequently, two features of the ISFS, the presence and the strength, were calculated for each channel and participant. To assess the ISFS presence, two criteria were applied: 1) a Gaussian function was attempted to be fit on the spectral power and 2) if a Gaussian was fit, a threshold (1.5 times the standard deviation (SD) of the Gaussian) was defined that the peak power must surpass. If both criteria were met, the ISFS presence was confirmed in that given channel and participant (Dimitriades et al., 2024). To complement this binary classification, the coefficient of determination (R^2) was also calculated for each fit. This provided a continuous measure of how well the Gaussian model captured the spectral power profile. To assess the ISFS strength, the area

under the curve of the spectral power was calculated using the MATLAB function *trapz*, which approximates the integral of the spectral power. Spectral powers between 0.01 and 0.04 Hz were considered (Lecci et al., 2017; Osorio-Forero et al., 2021). Unlike the presence and R^2, which rely on fitting assumptions, the strength measure is agnostic to signal shape and thus provides an estimate of the total infraslow power regardless of spectral peak structure.

Sleep spindles were detected using an amplitude-based thresholding approach (Ferrarelli et al., 2007). N2 sleep bout data were first extracted and processed with a band-pass filter (−3 dB cut-offs: 9.96 and 17.5 Hz; Chebyshev Type II IIR filter; filter order: 6; using the MATLAB function *filtfilt*). Sleep spindles were further identified as periods when the signal amplitude exceeded the upper threshold and continued until it dropped below the lower threshold. The upper threshold corresponded to five times the channel-specific mean amplitude and the lower threshold to two times the channel-specific mean amplitude. Only events lasting at least 0.3 s were considered sleep spindles (Warby et al., 2014). Sleep spindle density was calculated as the number of detected sleep spindles divided by the total time of the N2 sleep bout data in minutes.

2.4. Statistical analyses

All statistical analyses were performed in MATLAB R2022a. Data normality was evaluated using quantile-quantile plots and Shapiro-Wilk tests. Group differences in age and sleep structure parameters were assessed using Mann-Whitney *U* tests for non-parametric data, with effect sizes estimated via Cliff's delta, while sex differences were assessed using Fisher's exact test. The percent of electrodes showing the ISFS presence was compared between patient and HC groups using an unpaired *t*-test, while the ISFS presence at each electrode was compared between patient and HC groups using a z-test for proportions. Differences in the ISFS strength and sleep spindle density were analyzed with unpaired *t*-tests. To account for multiple comparisons across 19 channels, non-parametric cluster-based statistical mapping was applied. Pearson correlations were used to examine relationships between symptomatology and the ISFS strength in patients (extracted from a cluster of central-parietal channels: C3, Cz, C4, P3, Pz, P4) and sleep spindle density and the ISFS strength in all groups (compared in one central channel: C4). If not otherwise specified, values are expressed as the mean ± SD.

3. Results

3.1. Demographic and sleep structure parameters

Demographic and all-night sleep structure parameters have been previously published (Dimitriades et al., 2023). Age and sex were not significantly different between the patient groups and their respective HC groups (Table 1). All-night sleep structure and N2 bout sleep parameters were not significantly different for the EOS and HC-EOS groups (Table 1).

The COS and HC-COS groups did not differ significantly in the percentage of time spent in N2, N3, or rapid eye movement sleep (Table 1). However, the COS group showed less wake after sleep onset ($p < 0.001$), less N1 sleep ($p < 0.01$), and longer total sleep time ($p < 0.001$). While both groups had comparable numbers of bouts, mean relative bout location, and total bout duration, the COS group exhibited shorter mean bout lengths ($p < 0.0001$) and spent less of their total N2 sleep time in N2 bouts ($p < 0.05$).

3.2. The infraslow fluctuation of sigma power presence and strength are reduced in patients with schizophrenia compared to healthy controls

In a first step, the ISFS presence was quantified for each electrode and participant. As expected (Dimitriades et al., 2024), HCs showed that the ISFS was present in most electrodes (percent of electrodes with the ISFS: HC-COS: 73.99 ± 27.64 %; HC-EOS: 82.54 ± 19.79 %). The ISFS presence was also detectable in the COS and EOS groups, however the percent of electrodes with the ISFS presence was significantly lower in the COS (54.49 ± 28.76 %; $t(49) = 2.34$, $p < 0.05$) and EOS (59.33 ± 34.12 %; $t(31) = 2.48$, $p < 0.05$) groups compared to their respective HC group. Topographical analyses of the ISFS presence and coefficient of determination are reported in Supplementary Fig. 1.

To complement the strict ISFS presence criterion, the ISFS strength was quantified for each electrode and participant, providing a continuous measure of the ISFS power that does not depend on fitting assumptions. In both HC groups, the topography of the ISFS strength was maximal over central-parietal regions (specifically C3, Cz, C4, P3, Pz, P4). The EOS group exhibited a similar topography to HCs but with a lower magnitude, whereas the COS group showed no discernible topographical pattern. The ISFS strength was significantly reduced in the COS group compared to the HC-COS group and in the EOS group compared to the HC-EOS group, primarily in central-parietal regions (Fig. 1).

To assess the consistency of these findings across individuals, the ISFS strength was plotted for each patient with schizophrenia alongside their age- and sex-matched HCs (Fig. 2). Most HCs exhibited local maxima in the previously identified central-parietal cluster, a pattern that was less pronounced in the schizophrenia groups.

To ensure that differences in sleep data between the COS and HC-COS groups (reported in Section 3.1) did not account for the observed ISFS reduction, we assessed correlations between altered sleep parameters and ISFS strength (Supplementary Analysis 1) and repeated all key analyses on sleep-matched data (Supplementary Table 1); results remained consistent (Supplementary Fig. 2).

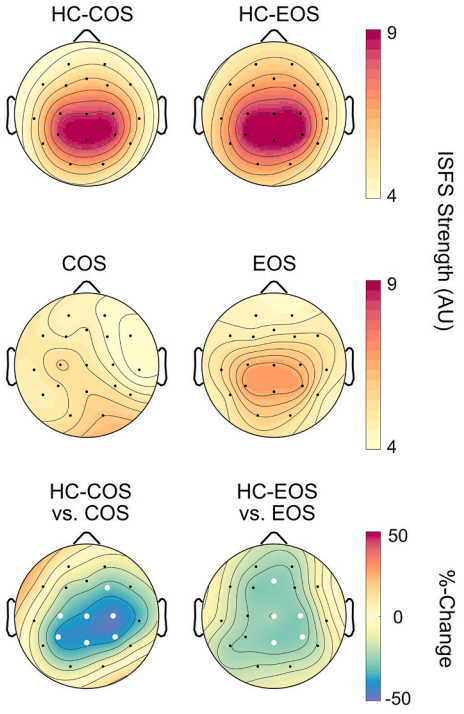

Fig. 1. Individuals with schizophrenia show a reduction in the infraslow fluctuation of sigma power strength compared to healthy controls.
Topographical distribution of the infraslow fluctuation of sigma power (ISFS) strength in patient groups (middle row: COS: Childhood-Onset Schizophrenia; EOS: Early-Onset Schizophrenia) and their respective healthy control groups (top row: HC-COS: Healthy Controls for COS; HC-EOS: Healthy Controls for EOS) is presented. ISFS strength was compared using an unpaired *t*-test (electrodes showing significant group differences are marked with a white dot) and is presented as the percent change between groups (bottom row).

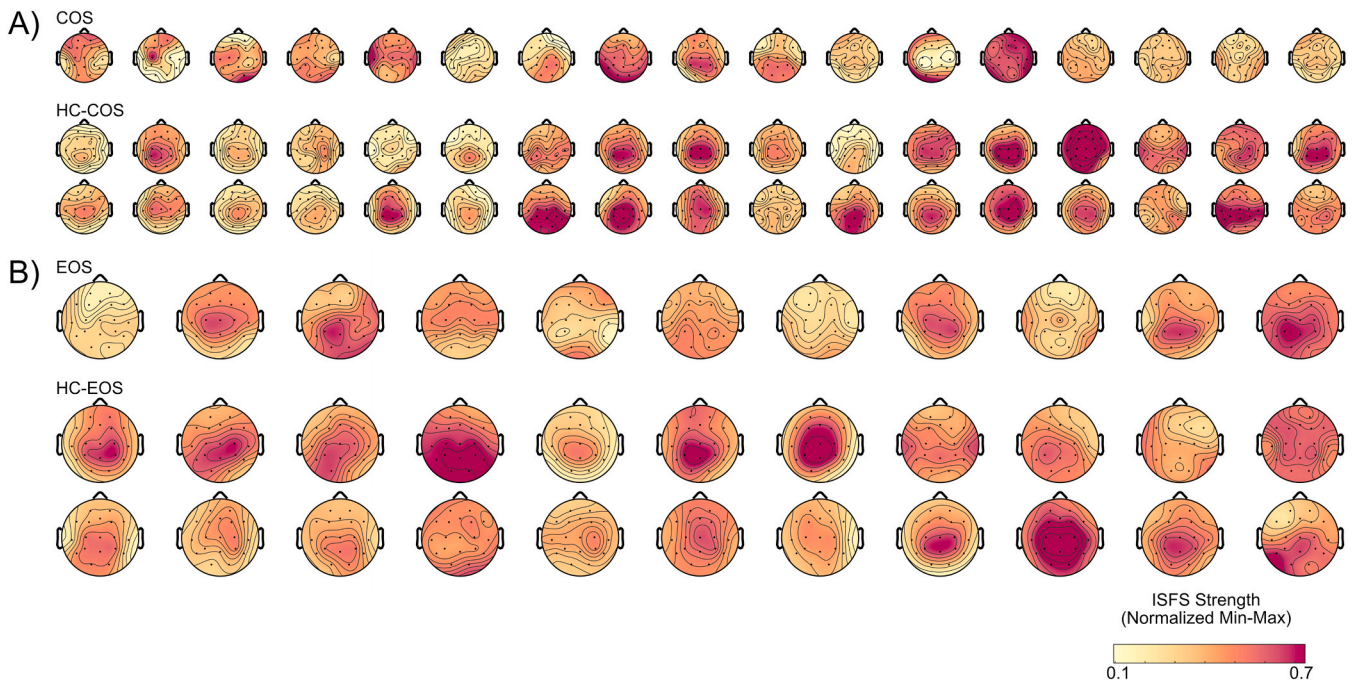

Fig. 2. Individual topoplots of the infraslow fluctuation in sigma power strength for all patients with schizophrenia and healthy controls.
Topographical distribution of the infraslow fluctuation of sigma power (ISFS) strength is shown A) for every individual with Childhood-Onset Schizophrenia (COS; top) and their two age- and sex-matched healthy controls (HC-COS; bottom) and B) for every individual with Early-Onset Schizophrenia (EOS; top) and their two age- and sex-matched controls (HC-EOS; bottom). The ISFS strength values were normalized using Min-Max scaling, rescaling each value to a range of 0 to 1 based on the global minimum and maximum values across groups. Individuals are plotted by age (youngest on the left, oldest on the right).

3.3. Features of the infraslow fluctuation of sigma power are not significantly different between the schizophrenia groups

To assess potential differences in the ISFS presence and strength between the patient groups, individuals of the COS and EOS groups were one-to-one matched. Since the age range differed between groups (EOS: 13.50 to 17.92 years; COS: 9.00 to 21.00 years), the youngest three and oldest three COS participants were excluded (COS: 16.00 ± 2.37 years); all individuals from the EOS group were included. This resulted in similar age distribution while sex-matching was not applied.

This approach showed that the ISFS presence did not differ significantly between the COS and EOS groups at any electrode ($p > 0.10$). Similarly, the ISFS strength did not significantly differ between the COS and EOS groups at any electrode ($p > 0.23$).

3.4. No association between the infraslow fluctuation of sigma power strength and sleep spindle density or clinical characteristics

As previously shown (Dimitriades et al., 2023; Markovic et al., 2020), the COS group demonstrated an almost global reduction in sleep spindle density compared to the HC-COS group (Fig. 3). In contrast, the EOS group showed no significant difference in spindle density when compared to the HC-EOS group. One-to-one matching between the COS and EOS groups revealed that sleep spindle density was significantly lower in the COS group compared to the EOS group across all frontal, central, and parietal electrodes ($p < 0.05$), while no significant differences were observed in temporal and occipital electrodes ($p > 0.62$). Additionally, there was no significant correlation between the ISFS strength and spindle density at a central electrode for the COS group (rho = −0.15, $p = 0.56$) and the pooled HCs (rho = 0.07, $p = 0.59$); the EOS group showed a positive trend-level association (rho = 0.53, $p = 0.09$).

Comparison of clinical characteristics between the COS and EOS groups at the time of the sleep EEG showed that the COS group had a longer duration of illness ($p < 0.0001$), higher amount of antipsychotic medication ($p < 0.001$), and per definition, a lower age of onset when compared to the EOS group ($p < 0.0001$) (Table 2). No significant difference was found for IQ between the COS and EOS group.

Correlations between the ISFS strength from a central-parietal cluster (C3, Cz, C4, P3, Pz, P4) and clinical characteristics were assessed separately for the COS and EOS groups due to group differences in clinical characteristics and the use of different clinical interviews. In the COS group, the ISFS strength showed a negative trend-level association with positive symptomatology (SAPS: rho = −0.47, $p = 0.06$). No other clinical characteristic was significantly correlated with the ISFS strength in either the COS (Age of onset: rho = 0.17, $p = 0.51$; Duration of illness: rho = −0.33, $p = 0.19$; Antipsychotic equivalent: rho = −0.07, $p = 0.80$; SANS: rho = −0.25, $p = 0.34$; IQ: rho = 0.32, $p = 0.30$) or the EOS (Age of onset: rho = 0.19, $p = 0.57$; Duration of illness: rho = 0.07, $p = 0.84$; Antipsychotic equivalent: rho = 0.28, $p = 0.41$; PANSS Positive Score: rho = 0.06, $p = 0.86$, PANSS Negative Score: rho = 0.05, $p = 0.88$; IQ: rho = −0.07, $p = 0.86$) group.

4. Discussion

This study found that the infraslow fluctuation of sigma power (ISFS) is observable in young individuals with childhood-onset schizophrenia (COS) and early-onset schizophrenia (EOS). However, the ISFS strength is reduced in central-parietal regions in schizophrenia compared to healthy controls (HCs), suggesting less clustering of sleep spindles on an infraslow time scale. These alterations in the ISFS were observed in both the COS and EOS groups, with no significant differences between the two clinical groups despite differences in sleep spindle density and clinical characteristics.

Young HCs show a high proportion of electrodes where the ISFS is present, exhibiting a pronounced central-parietal topographical pattern. This aligns with recent findings showing that the ISFS is present from childhood to young adulthood, with its strength peaking in central-parietal regions (Dimitriades et al., 2024; Lecci et al., 2017). While the ISFS is observable in the schizophrenia groups, its presence and

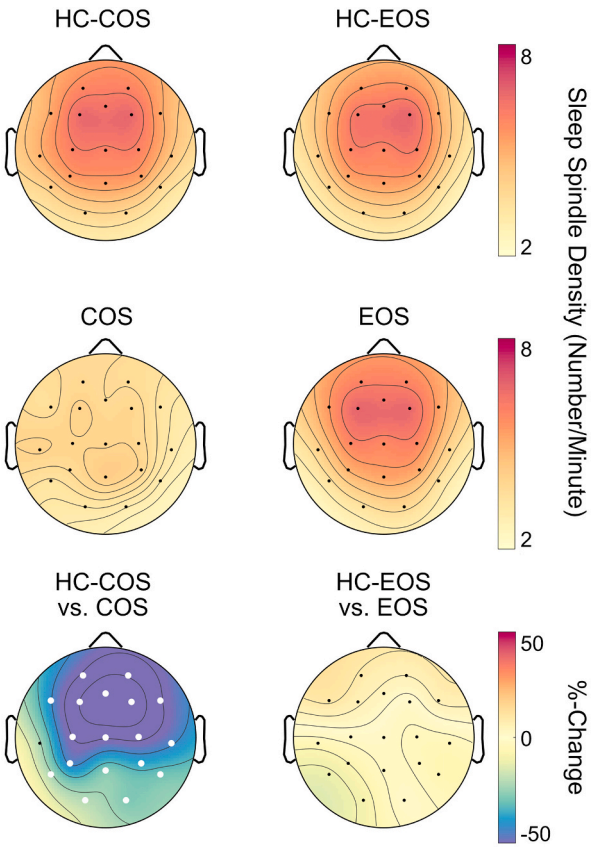

Fig. 3. Sleep spindle density in non-rapid eye movement stage N2 sleep bout data.

Topographical distribution of sleep spindle density (the number of sleep spindles per minute) in patient groups (middle row: COS: Childhood-Onset Schizophrenia; EOS: Early-Onset Schizophrenia) and their respective healthy control groups (top row: HC-COS: Healthy Controls for COS; HC-EOS: Healthy Controls for EOS). Sleep spindle density was compared using an unpaired *t*-test (electrodes showing significant group differences are marked with a white dot) and is presented as the percent change between groups (bottom row).

Table 2

Clinical characteristics between groups with schizophrenia.

Parameter	COS (17): mean (SD)	EOS (11): mean (SD)	Cliff's delta	*p*
Age of onset (years)	9.27 (1.79)	15.33 (1.45)	1.00	**<0.0001**
Duration (years)	6.73 (3.63)	1.05 (0.92)	−0.94	**<0.0001**
Antipsychotic medication (mg)	667.65 (372.05)	172.50 (158.43)	−0.78	**<0.001**
IQ	78.00 (19.21)	95.13 (26.44)	−0.59	0.13
Positive symptom severity*	21.82 (15.29)	13.45 (4.93)		
Negative symptom severity*	39.47 (21.49)	19.18 (7.43)		

COS: Childhood-Onset Schizophrenia; EOS: Early-Onset Schizophrenia. Age of onset and duration of illness are measured in years and antipsychotic medication is measured as the chlorpromazine equivalent. IQ data were available 12 COS and for 8 EOS participants. Statistically significant *p*-values are shown in bold.

* Positive and negative symptom severity were assessed using different instruments in the two groups (Scale for the Assessment of Positive Symptoms and Scale for the Assessment of Negative Symptoms in COS; Positive and Negative Symptoms Scale in EOS) and were therefore not directly compared.

strength are notably reduced in these central-parietal regions compared to HCs. This is the first characterization of the ISFS in a patient group, limiting direct comparisons with previous human data. Evidence from rodent studies (Hayat et al., 2020; Osorio-Forero et al., 2021), along with recent human findings using pupil size as a proxy for locus coeruleus activity (Carro-Domínguez et al., 2025), suggests that the ISFS arises from the locus coeruleus-noradrenaline system, which regulates arousal and thalamocortical activity. Several lines of evidence point to dysfunction in the locus coeruleus-noradrenaline system in the pathophysiology of schizophrenia, contributing to cognitive deficits and symptomatology (Bird et al., 1980; Crow et al., 1979; Farley et al., 1978; Mäki-Marttunen et al., 2020; Maletic et al., 2017; Pelegrino et al., 2023; Steinhauer and Hakerem, 1992; Yamamoto and Hornykiewicz, 2004). In this context, the reduction in features of the ISFS in schizophrenia may stem from dysregulation of the locus coeruleus-noradrenaline system. However, the relationship between the ISFS and the pathophysiological mechanisms of schizophrenia requires further validation across species.

Markedly, both schizophrenia groups show reduced ISFS features compared to HCs, with no significant differences between the two clinical groups, despite significant differences in sleep spindle density and clinical characteristics. Spindle density was only significantly reduced in the COS group when compared to HCs and the EOS group, whereas no statistical difference was found between the EOS group and HCs. This aligns with our previous findings that the COS group shows robust, global reductions in spindles compared to HCs, while the EOS group shows circumscribed, smaller reductions (Dimitriades et al., 2023). The lack of a significant difference between the EOS group and HCs is likely due to methodological differences between our previous analysis (Dimitriades et al., 2023) and the current one, including the use of a broader spindle frequency band and continuous N2 bout data. As speculated (Dimitriades et al., 2023), the difference between schizophrenia groups is likely related to the duration of illness, which has been negatively correlated with spindle deficits in a meta-analysis (Lai et al., 2022). The absence of significant spindle deficits in the EOS group, along with no significant correlations between the ISFS strength and clinical characteristics (e.g., age of onset, duration of illness, chlorpromazine equivalent, symptom severity, and IQ), may suggest that the ISFS disruption emerges early in schizophrenia. If so, the ISFS may be more closely linked to early clinical features potentially preceding the full disorder onset, such as subjective sleep disturbances and specific verbal learning and memory deficits, which do not necessarily worsen progressively (Ruhrmann et al., 2010; Metzler et al., 2014). The ISFS is driven by noradrenergic activity in the locus coeruleus, which modulates thalamic depolarization and in turn, spindle generation (Hayat et al., 2020; Osorio-Forero et al., 2021). As schizophrenia progresses, noradrenergic dysregulation may impair thalamocortical circuits, further reducing spindle density and suggesting that the ISFS impairment precedes sleep spindle deficits. Additionally, given that sleep spindle features and thalamocortical circuits undergo dynamic changes during childhood and adolescence (Alkonyi et al., 2011; Fair et al., 2010; Kwon et al., 2023; Purcell et al., 2017), longitudinal studies are needed to disentangle the effects of these processes on one another and establish causal relationships, particularly since the cross-sectional nature of this data limits our ability to make such conclusions.

As the ISFS and sleep spindles are both related to sigma activity, it was possible that a severe spindle deficit would render the ISFS undetectable. However, the current findings rather support the notion that while the ISFS and sleep spindles are interrelated, they capture distinct aspects of brain activity. Specifically, the ISFS reflects the temporal clustering of sleep spindles on an infraslow time scale. This distinction is supported by their differing topographical distributions—the ISFS presence and strength peak in central-parietal regions, while sleep spindle density is maximal in frontal regions in our population—and by our control analysis, which found no significant correlation between the ISFS strength and sleep spindle density at a central electrode. Moreover, reduced ISFS strength does not simply indicate fewer spindles, but rather

suggests a reduced clustering of spindles on an infraslow time scale.

Within the current framework highlighting the ISFS as a key mechanism for balancing periods of arousability and periods of memory reactivation processes, a reduced ISFS in schizophrenia may disrupt the coordination of these periods. Although not examined in this study, adult patients with chronic schizophrenia have been reported to exhibit an increased frequency of arousals and less effective procedural sleep-dependent memory reactivation (Bagautdinova et al., 2023; Genzel et al., 2015; Manoach et al., 2004; Seeck-Hirschner et al., 2010). Indeed, first studies show that arousals and markers of memory reactivation during sleep occur during specific ISFS phases in both rodents and humans, potentially linked either to spindle activity itself or to the broader neurophysiological milieu created by alternating phases of high and low noradrenaline (Dimitriades et al., 2024; Lecci et al., 2017).

There are several limitations to consider when evaluating the findings of this study. The relative rarity of access to clinical populations with schizophrenia in this age group presented a challenge which resulted in small to moderate group sizes. To enhance robustness and minimize over-interpretation of potential group differences in a population with high inter-individual variability, a two-to-one matching strategy was employed. This matching also helped control for potential sex-related effects; however, menstrual cycle phase was not recorded, and potential hormonal influences cannot be fully excluded. Furthermore, functional aspects of the ISFS could not be explored due to methodological constraints, including differing online filters affecting the slow-wave range, which prevented capturing slow wave-sleep spindle coupling (a marker of memory reactivation), as well as the lack of electromyographic data for detecting arousals, and the absence of memory readouts. Lastly, although most patients were on antipsychotic medication, previous studies suggest no direct link between spindle density and antipsychotics (Manoach et al., 2014). However, aside from the absence of a dose-dependent association between chlorpromazine equivalents and the ISFS, the impact of specific psychotropic agents could not be further assessed in this sample due to the sample size and medication heterogeneity. Larger studies including individuals at clinical high-risk for developing schizophrenia and those with adult-onset schizophrenia are needed to replicate and extend these findings. ISFS alterations may not be specific to schizophrenia; examining other psychiatric disorders—particularly those involving locus coeruleus-noradrenergic dysregulation such as Post-Traumatic Stress or Major Depression Disorders—may help determine whether impairments are specific to ISFS timing, spindle density, or both (Goddard et al., 2010; Grueschow et al., 2021; Naegeli et al., 2018; O'Donnell et al., 2004).

In summary, the current findings reveal a reduction in features of the ISFS in central-parietal regions in both young patients with schizophrenia during the early stages and those in the chronic course of the disease. This opens avenues for future research into the mechanisms, function, and extent of the ISFS reduction in schizophrenia, which could inform pathomechanistic models underlying the disorder and interventions. Current developments and strategies for novel neuromodulation techniques targeting sleep oscillations may need to address not only the quantity but also the timing of sleep spindles and other sleep oscillations. Additionally, the specificity of the ISFS reduction—whether or not accompanied by a sleep spindle deficit—requires further investigation across mental disorders with noradrenergic dysregulation.

CRediT authorship contribution statement

Maria E. Dimitriades: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Eve Schumacher:** Writing – review & editing, Methodology. **Janani Arudchelvam:** Writing – review & editing, Methodology. **Sara Fattinger:** Writing – review & editing, Data curation. **Salome Kurth:** Writing – review & editing, Data curation. **Fiona Pugin:** Writing – review & editing, Data curation. **Flavia Wehrle:** Writing – review & editing, Data curation. **Valeria Jaramillo:** Writing – review & editing, Data curation. **Carina Volk:** Writing – review & editing, Data curation. **Sven Leach:** Writing – review & editing, Data curation. **Ashura Buckley:** Writing – review & editing, Data curation. **David I. Driver:** Writing – review & editing, Data curation. **Andjela Markovic:** Writing – review & editing, Data curation. **Judith L. Rapoport:** Writing – review & editing, Data curation. **Leila Tarokh:** Writing – review & editing, Data curation. **Reto Huber:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **Miriam Gerstenberg:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

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Declaration of competing interest

The authors have no competing interests to declare.

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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.2025.09.029.

Data availability

All data supporting the findings of this study are securely stored at servers of the University Children's Hospital. Access and availability will be provided upon a material transfer agreement and after approval by the local ethics committee of the Canton of Zurich.

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