Archival Report

Biological Psychiatry: CNNI

Limited Consistency and Strength of Neural Oscillations During Sustained Visual Attention in Schizophrenia

Ian S. Ramsay, Victor J. Pokorny, Peter A. Lynn, Samuel D. Klein, and Scott R. Sponheim

ABSTRACT

BACKGROUND: Neural oscillations support perception, attention, and higher-order decision making. Aberrations in the strength or consistency of these oscillations in response to stimuli may underlie impaired visual perception and attention in schizophrenia. Here, we examined the phase and power of alpha oscillations (8–12 Hz) as well as aspects of beta and theta frequency oscillations during a demanding visual sustained attention task.

METHODS: Patients with schizophrenia (n = 74) and healthy control participants (n = 68) completed the degraded stimulus continuous performance task during electroencephalography. We used time-frequency analysis to evaluate the consistency (intertrial phase coherence) of the alpha cycle shortly after stimulus presentation (50–250 ms). For oscillation strength, we examined event-related desynchronization in a later window associated with decision making (360–700 ms).

RESULTS: Alpha intertrial phase coherence was reduced in schizophrenia, and similar reductions were observed in theta (4–7 Hz) and beta (13–20 Hz), suggesting a lack of responsiveness in slower oscillations to visual stimuli. Alpha and beta event-related desynchronization were also reduced in schizophrenia and associated with worse task performance, increased symptoms, and poorer cognition, suggesting that limited responsiveness of oscillations is related to impairments in the disorder. Individuals with lower intertrial phase coherence had slower resting-state alpha rhythms consistent with dysfunctional oscillations persisting across default and task-related brain states.

CONCLUSIONS: In schizophrenia, abnormalities in the phase consistency and strength of slower oscillations during visual perception are related to symptoms and cognitive functioning. Altered visual perception and impaired attention in the disorder may be the consequence of aberrant slower oscillations that fail to dynamically reset and modulate in response to stimuli.

https://doi.org/10.1016/j.bpsc.2023.02.001

Cycling of neural activity is hypothesized to reflect the means by which information is passed through circuits of the brain (1). These cycles are thought to be reflected in oscillations of brain activity, wherein the coherent synchronization of neuronal populations determine the opening and closing of windows for transmission of information through brain circuits. There is growing evidence that oscillations in neurophysiological recordings (electroencephalography [EEG] and magnetoencephalography) reflect neural functions that are crucial for the processing of visual stimuli (2). For instance, researchers have shown that posterior alpha oscillations (approximately 10 Hz) are important to the sensitivity of perception to external visual stimuli (3,4), which may influence broader attentional (5) and decision-making functions (6).

Schizophrenia is associated with impairments in sustained attention (7) that are characterized by aspects of poor cognitive control (8) and aberrant perception (9). Our recent work revealed that the pace of endogenous alpha oscillations (i.e., individual alpha peak frequency [IAPF]) in part explains deficits in perceptual vigilance noted in people with schizophrenia (10). Specifically, we showed that IAPF was not only reduced in participants with schizophrenia compared with control participants but also was related to impaired cognition by way of impaired performance on a visual sustained attention task. However, previous findings suggest that the point of the neural oscillatory cycle when a visual stimulus arrives (also known as phase) influences the likelihood the stimulus will be perceived (11,12) and attended (13). Subsequently, enhanced perception and attention toward a stimulus is purportedly driven by neural populations aligning in their phases of activity allowing for the successful transmission of information through brain circuits (14).

Here, we report on an examination of the phase and strength of oscillations recorded over occipital/parietal brain regions in people with schizophrenia while they performed a visual target detection task designed to tap sustained attention. We characterized the consistency of oscillatory phase across trials following the onset of a stimulus to assess whether there was poor alignment of neural responses after

ISSN: 2451-9022

visual input in schizophrenia. We also tested whether the amplitude (i.e., strength) of oscillations after stimulus onset (which can reflect synchronization of neural populations) was aberrant in people with schizophrenia. Although the degraded stimulus continuous performance task (DS-CPT) has been widely used to assess visual sustained attention, we are unaware of published reports of oscillatory dynamics that may support perceptual functions and allow differentiation of targets and nontarget stimuli.

The discrimination of visual stimuli in healthy individuals relies on early phase locking (15,16) and later desynchronization of alpha (17,18) that reflect aspects of attention and alertness. In patients with schizophrenia, reductions in intertrial phase coherence (ITPC) have been observed during passive viewing of visual stimuli (19) as well as during a visual learning task (20). Stimulus-induced shifts in alpha synchronization (i.e., amplitude or strength) have also been examined in schizophrenia. These studies have revealed blunted alpha desynchronization during a perceptually demanding visual task (21) and similar impairments during a facial discrimination task (22). However, it is unclear whether such effects are present in sustained visual attention that is central to global cognitive impairments in the disorder (23).

In the current study, we measured alpha band ITPC and event-related desynchronization (ERD) during the DS-CPT in patients with schizophrenia and healthy control participants. We hypothesized that patients with schizophrenia would show 1) impairments in stimulus discrimination that relate to reduced alpha ITPC shortly after stimulus presentation consistent with disrupted perceptual processes and 2) reduced ERD during a later period of stimulus processing consistent with impairments in attention allocation and/or cognitive control. To understand the functional significance of these oscillatory processes, we examined interrelationships between alpha ITPC and ERD as well as their associations with task performance, IAPF measured from resting EEG, and indices of clinical and cognitive functioning. Finally, we determined whether oscillatory abnormalities were specific to alpha by examining oscillations of nearby frequencies (e.g., theta and beta).

METHODS AND MATERIALS

Participants

Patients with schizophrenia (n = 91) and control participants (n = 76) 18 to 60 years of age performed the DS-CPT as part of 4 separate study protocols. All participants completed a diagnostic interview performed by trained research staff using the Structured Clinical Interview for DSM-IV-TR and the Diagnostic Interview for Genetic Studies. Diagnostic interviews were reviewed by 2 or more PhD-level clinicians or advanced graduate students to establish consensus diagnoses for each research participant. All participants with schizophrenia were required to have a clinical diagnosis of either schizophrenia or schizoaffective disorder and were largely stable outpatients. Control participants were required to have no diagnosis of a psychotic or mood disorder (including bipolar disorder) and no first-degree relatives with psychotic or mood disorders. Participants with substance abuse in the past month or substance dependence in the last 6 months were excluded. Participants with compromised hearing or vision (i.e., legally blind or unable to hear without a hearing aid), an estimated IQ $<$70, epilepsy or recurrent seizures in adulthood, or any other medical condition that might preclude participation were excluded. A total of 72 participants with schizophrenia were receiving a stable dose of an antipsychotic medication. All participants completed a written informed consent process before participation, and all procedures were approved by the institutional review boards of the Minneapolis Department of Veterans Affairs Medical Center and the University of Minnesota.

Participants also completed clinical and cognitive assessments. The Brief Psychiatric Rating Scale (24) was administered to both control and schizophrenia participants to measure a broad set of mental disorder symptoms. Cognition was measured using 4 subtests from the Wechsler Adult Intelligence Scale, Third Edition: block design to measure perceptual reasoning, digit span to measure working memory, digit-symbol coding to measure processing speed, and vocabulary to measure verbal reasoning. Age-normed scores across all 4 subtests were averaged to derive a measure of global cognition.

EEG Acquisition

Three different EEG collection systems and montages were used across the 4 studies. Forty-five (patients with schizophrenia: n = 21; control participants: n = 24) recordings were obtained using a BioSemi 64-channel ActiveTwo AgCl electrode system (BioSemi Inc.), and 89 (patients with schizophrenia: n = 47; control participants: n = 42) recordings were obtained using a BioSemi 128-channel ActiveTwo AgCl electrode system. In both cases, recordings were sampled at 1024 Hz and referenced after collection to an average ears signal. A further 33 (patients with schizophrenia: n = 23; control participants: n = 10) recordings were collected using a BrainVision 128-channel actiCHamp active electrode EEG system (Brain Products GmbH) sampled at 1000 Hz and referenced online to Cz.

DS-CPT procedures have been described in detail elsewhere (25–27). Briefly, white single-digit numerals (0–9; 4.3° × 3.4° visual angle) were presented for 29 ms on a black background followed by a white display for 971 ms. Both the digits and the black background were degraded, such that 40% of white pixels were switched to black, and 40% of black pixels were switched to white. Participants were asked to respond with a button press to target stimuli (“0”) presented 25% of the time and withhold a response to nontarget stimuli (“1–9”). After 160 practice trials, participants completed 320 trials over 4 separate blocks (80 trials/block) presented in pseudorandom order (Figure 1). Additionally, all participants underwent resting EEG procedures, which are described in detail elsewhere (10). Briefly, participants alternated between 45-second periods of keeping their eyes open or closed. Each state was repeated at least 3 times, for a minimum of 135 seconds of recorded EEG. Participants had a mean (SD) 119.80 (21.49) seconds of analyzed data with no differences between groups (p = .45). Only data from the eyes-closed period were used in the current

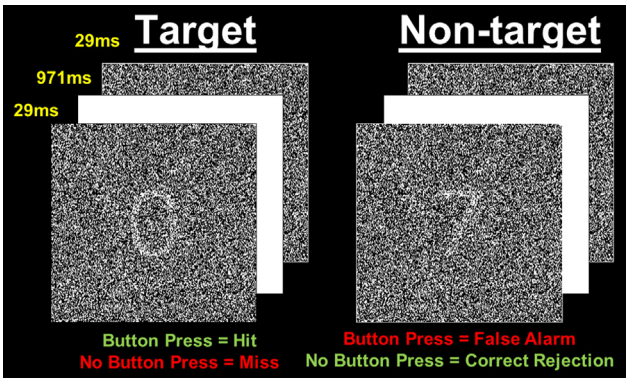

Figure 1. White single-digit numerals (0–9; 4.3° × 3.4° visual angle) were presented for 29 ms on a black background followed by a white display for 971 ms. The digits and black background were degraded, such that 40% of white pixels were switched to black, and 40% of black pixels were switched to white. Participants were asked to respond with a button press to target stimuli ("0") presented 25% of the time and withhold a response to nontarget stimuli ("1–9"). (Original stimulus images were provided courtesy of Keith H. Nuechterlein.)

analysis with IAPF calculated as the frequency with maximum power between 7 and 13 Hz.

EEG Preprocessing

EEG signals were digitized, high-pass filtered at 0.5 Hz, and downsampled to 256 Hz using the resample function in MATLAB (R2020a, The MathWorks, Inc.) (which includes an anti-aliasing filter). Recordings were then divided into epochs that extended from 200 ms before the stimulus onset to 1000 ms after the stimulus onset. Next, epoched data were submitted to independent component analysis for the removal of ocular, muscular, and cardiac artifacts (28). This method combined both automated and manual inspection of the independent components as well as visual examination of the time series to exclude contaminated epochs. Last, the denoised data were reconstituted for each subject, and electrodes that were deemed noisy were interpolated using spherical splines before re-referencing to the average signal across all electrodes. After denoising, the BioSemi 128-channel data and BrainVision 128-channel data were interpolated to reflect the 64 channels of the BioSemi 64-channel montage (in part because the BioSemi electrodes conformed to a radial montage). Therefore, all datasets shared a common montage before further analysis. Only correct trials were included in the ensuing analyses.

Measurement of ITPC and ERD

Time-frequency analysis was implemented via complex morlet wavelet convolution. Due to a relatively short task intertrial interval, each trial was reflected forward and backward to help reduce spectral leakage (i.e., the trial values were flipped left to right and then concatenated to both the beginning and the end of the original trial) (29). Baseline for power normalization was defined as −175 ms prestimulus to −25 ms prestimulus. This was done to maximize the signal-to-noise ratio of the baseline while avoiding contamination by 1) event-related activity that bleeds into the prestimulus time window due to temporal smearing (a by-product of wavelet convolution) and 2) slight spectral leakage from reflected trial before baseline. Wavelet cycles were logarithmically spaced from 3 to 8 for a 1- to 40-hz frequency window. Power values were baseline normalized and converted to decibels. ITPC was calculated from the phase angle time series produced by the Morlet wavelet convolution over the specified window for each participant. ERD (effectively total event-related spectral power perturbation) was quantified by averaging power across frequency and time for each specified time-frequency window for each participant.

Planned Analyses

Based on previous work, we included only subjects with a sufficient number of artifact-free correct trials in the analysis [at least 20 trials based on guidelines suggesting that ITPC metrics stabilize at this point (29)]. Included participants had a mean (SD) of 53.61 (18.27) target trials with no differences between groups (t_{140} = 0.03, p = .98) and 205.89 (39.62) nontarget trials with no differences between groups (t = −0.55, p = .58). Based on visual inspection of grand averaged surface plots and scalp topographies collapsed across groups, the investigators (ISR and VJP) chose to measure early alpha (8–12 Hz) ITPC 50 to 250 ms after stimulus onset over occipital electrodes Oz, O1, O2, POz, PO3, and PO4 and alpha (8–12 Hz) ERD 360 to 700 ms after stimulus onset over posterior parietal electrodes O1, O2, PO3, PO4, PO7, and PO8. For both dependent variables, we used a 2 × 2 repeated-measures analysis of variance covarying for age, gender, and study montage to test the effects of group (schizophrenia vs. control), trial type (target vs. nontarget), and a group × trial type interaction.

We followed up with exploratory linear models (neural measures predicting clinical/cognitive outcomes and covarying for age, gender, and study montage) to examine the relationship between ITPC/ERD and task performance (d'), psychiatric symptoms (Brief Psychiatric Rating Scale total score), and global cognition (Wechsler Adult Intelligence Scale, Third Edition composite scores) as well as between ITPC/ERD and IAPF measured during resting EEG. Initial linear models included an interaction term with group to determine whether schizophrenia and control participants showed significant slope differences. In cases where slopes differed, we examined relationships with clinical/cognitive variables in schizophrenia and control participants independently. In cases where slopes did not differ, we examined common slope relationships across groups. Finally, though we did not hypothesize lateralized effects, we performed post hoc analyses to determine laterality in ERD over posterior parietal electrodes (see the Supplement).

RESULTS

A total of 142 participants (schizophrenia: n = 74; control: n = 68) had enough artifact-free target and nontarget trials to be included in the full analysis. Participant demographics are presented in Table 1. Patients with schizophrenia were younger (t_{140} = −2.13, p = .03), had less education (t_{140} = 4.70, p < .001), were more symptomatic (t_{140} = 11.22, p <

Table 1. Demographics

	SCZ Group, *n* = 74, Mean (SD)	CON Group, *n* = 68, Mean (SD)	*t* Value (*df*)	*p* Value	Effect Size, *d*
Age, Years	42.64 (10.76)	46.52 (10.7)	−2.13 (140)	.03	0.36
Education, Years	13.47 (2.23)	15.13 (1.9)	−4.7 (140)	<.001	0.80
DS-CPT *d′*	2.2 (0.97)	2.46 (1.07)	−1.49 (140)	.14	0.25
WAIS-III Composite Score[a]	9.42 (2.37)	11.14 (2.12)	−3.99 (140)	<.001	0.76
BPRS Total Score	44.48 (10.62)	28.77 (4.52)	11.22 (140)	<.001	1.84
CPZ Equivalent Dosage	595.84 (541.24)	–	–	–	–

The schizophrenia (SCZ) (males: *n* = 54) and control (CON) (males: *n* = 41) groups did not differ on the number of male and female participants (χ^2_1 = 1.14, *p* = .29).

BPRS, Brief Psychiatric Rating Scale; CPZ, chlorpromazine; *d′*, task performance; DS-CPT, degraded stimulus continuous performance task; WAIS-III, Wechsler Adult Intelligence Scale, Third Edition.

[a]WAIS-III composite scores reflect the average from 4 age-normed scaled scores.

.001), and had worse global cognition (t_{140} = −3.99, *p* = .001) than control participants, but the groups were similar in gender composition (χ^2_1 = 1.14, *p* = .29). Patients with schizophrenia as a group failed to show significant impairment on the DS-CPT task performance measured by the signal detection index *d′* when age and gender were included as covariates ($F_{1,140}$ = 2.60, *p* = .11; Cohen's *d* = 0.25).

Intertrial Phase Coherence

ITPC measured 50 to 250 ms after stimulus onset over occipital electrodes (Oz, O1, O2, POz, PO3, and PO4) in the alpha range (8–12 Hz) was reduced in patients with schizophrenia compared with control participants ($F_{1,136}$ = 9.41, *p* = .003; these results were confirmed when additionally including number of trials as a covariate, *p* = .002) (Figure 2). There was no effect of trial type ($F_{1,140}$ = .40, *p* = .53) or a group × trial

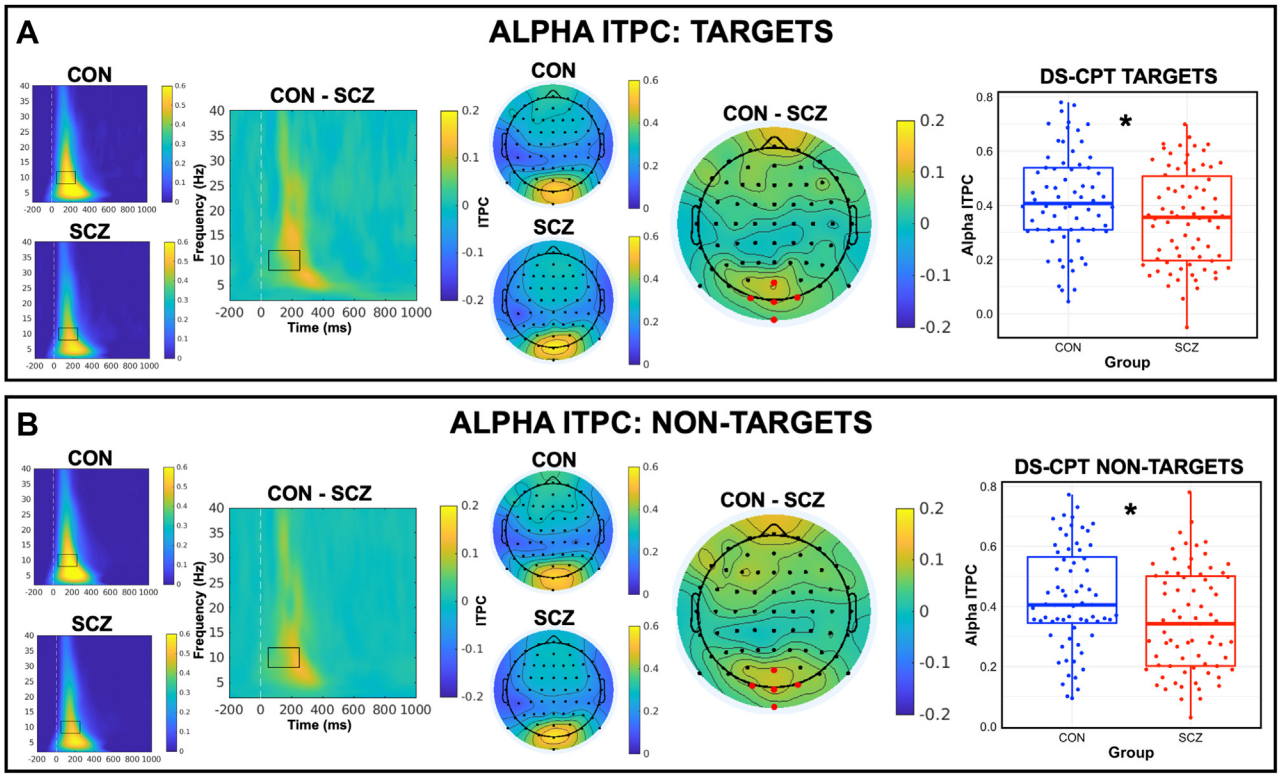

Figure 2. Alpha intertrial phase coherence (ITPC) during the degraded stimulus continuous performance task (DS-CPT). Alpha ITPC (i.e., the consistency across trials of the phase of alpha activity after stimulus presentation) was compared between schizophrenia (SCZ) and control (CON) groups for target and nontarget trials during the DS-CPT. **(A)** ITPC during target trials was examined in the alpha band (8–12 Hz) 50–250 ms after stimulus onset (depicted by black boxes on the surface plots) over posterior electrodes (depicted in red on the topographies). Alpha ITPC was reduced in patients with SCZ compared with CON participants for target trials (t_{140} = −2.21, *p* = .03). **(B)** ITPC during nontarget trials also examined alpha 50–250 ms over posterior electrodes. ITPC for nontargets was reduced in patients with SCZ compared with CON participants (t_{140} = −2.60, *p* = .01). A 2 × 2 analysis of variance comparing groups and trial types confirmed that ITPC was reduced in patients with SCZ for both target and nontarget trials ($F_{1,136}$ = 9.41, *p* = .003) but revealed no effect of trial type or a group × trial type interaction. *$p < .05$.

Table 2. Post Hoc Relationships Between Neural and Clinical/Cognitive Outcomes

	Slope Difference						Common Slopes					
	Task Performance		Symptoms		Cognition		Task Performance		Symptoms		Cognition	
Measure	*t* (*df*)	*p*	*t* (*df*)	*p*	*t* (*df*)	*p*	*t* (*df*)	*p*	*t* (*df*)	*p*	*t* (*df*)	*p*
Alpha ITPC, All Trials	2.60 (134)	.01[a]	−0.43 (134)	.67	−0.79 (134)	.43	0.78 (136)	.44	−1.42 (136)	.16	1.90 (136)	.06
Broadband ITPC, All Trials	2.44 (134)	.02[a]	−0.16 (134)	.87	−0.76 (134)	.45	0.82 (136)	.42	−1.59 (136)	.11	−1.97 (136)	.05
Alpha ERD, All Trials	0.41 (134)	.68	0.52 (134)	.60	−1.75 (134)	.08	−2.90 (136)	.004[a]	2.99 (136)	.003[a]	−3.17 (136)	.002[a]
Later Alpha ERD, Targets	0.90 (134)	.37	−0.37 (134)	.72	−1.08 (134)	.28	−1.52 (136)	.13	2.47 (136)	.01[a]	−2.55 (136)	.01[a]
Later Alpha ERD, Nontargets	−0.25 (134)	.80	0.72 (134)	.47	−1.52 (134)	.13	−4.26 (136)	<.001[a]	2.58 (136)	.01[a]	−2.42 (136)	.02[a]
Beta ERD, Targets	0.51 (134)	.61	−0.25 (134)	.81	−0.11 (134)	.91	−2.25 (136)	.03[a]	2.27 (136)	.02[a]	−2.28 (136)	.02[a]
Beta ERD, (Nontargets)	0.64 (134)	.52	0.66 (134)	.51	−1.25 (134)	.21	−5.47 (136)	<.001[a]	2.96 (136)	.004[a]	−2.13 (136)	.04[a]

	SCZ Group						CON Group					
	Task Performance		Symptoms		Cognition		Task Performance		Symptoms		Cognition	
	t (*df*)	*p*	*t* (*df*)	*p*	*t* (*df*)	*p*	*t* (*df*)	*p*	*t* (*df*)	*p*	*t* (*df*)	*p*
Alpha ITPC, All Trials	1.98 (68)	.05	0.26 (68)	.80	−0.03 (68)	.98	−1.04 (62)	.30	1.53 (62)	.13	1.07 (62)	.29
Broadband ITPC, All Trials	1.89 (68)	.06	0.35 (68)	.73	0.11 (68)	.91	−0.98 (62)	.33	0.82 (62)	.42	1.18 (62)	.25
Alpha ERD, All Trials	−1.24 (68)	.22	0.71 (68)	.48	−2.80 (68)	.007[a]	−1.95 (62)	.06	0.19 (62)	.85	−0.50 (62)	.62
Later Alpha ERD, Targets	0.11 (68)	.92	−0.18 (68)	.86	−1.73 (68)	.09	−1.19 (62)	.24	0.02 (62)	.99	−0.30 (62)	.77
Later Alpha ERD, Nontargets	−2.72 (68)	.008[a]	0.76 (68)	.45	−2.28 (68)	.03	−2.50 (62)	.02[a]	−0.08 (62)	.94	−0.27 (62)	.79
Beta ERD, Targets	−0.82 (68)	.41	−0.39 (68)	.70	−0.86 (68)	.38	−1.49 (62)	.14	−0.48 (62)	.64	−0.93 (62)	.36
Beta ERD, Nontargets	−2.86 (68)	.006[a]	0.90 (68)	.37	−1.72 (68)	.09	−4.05 (62)	<.001[a]	0.35 (62)	.72	−0.24 (62)	.81

All exploratory linear models included covariates for age, gender, and study montage to examine the relationship between ITPC/ERD and task performance (*d'*), psychiatric symptoms (Brief Psychiatric Rating Scale total score), and global cognition (Wechsler Adult Intelligence Scale, Third Edition composite scores). Slope difference models included an interaction term for group to determine whether the schizophrenia (SCZ) and control (CON) groups showed significant differences in their relationships. We also examined common slope relationships across groups as well as relationships in the SCZ and CON groups independently.

ERD, event-related desynchronization; ITPC, intertrial phase coherence.

[a]Significant difference ($p < .05$).

type interaction ($F_{1,140} = .72$, $p = .40$). Next, ITPC averaged across both trial types was entered into separate linear models to predict task performance (*d'*), clinical (Brief Psychiatric Rating Scale), and cognitive outcomes (Wechsler Adult Intelligence Scale, Third Edition). These results are fully reported in Table 2. ITPC predicting task performance revealed slope differences between groups ($t_{134} = 2.60$, $p = .01$), but did not show significant relationships within groups (*p*s > .05). Neither clinical nor cognitive scores showed significant relationships with ITPC. Antipsychotic medication dosage (chlorpromazine equivalents) was also unrelated to ITPC for the subset of patients with schizophrenia taking medications (*p*s > .63).

Next we examined relationships between alpha ITPC and IAPF. Groups did not show slow slope differences ($t_{134} = 1.38$, $p = .17$); therefore, we examined patterns across schizophrenia and control groups. IAPF across groups predicted ITPC across both trial types ($b = 0.22$, $t_{136} = 2.78$, $p = .006$), suggesting that faster endogenous cycling of alpha oscillations is related to greater consistency in the phase of the alpha band after stimulus presentation. This is consistent with a greater pace of the alpha rhythm facilitating better reset of the cycle with sensory input. However, within groups, this relationship was observed only in patients with schizophrenia ($b = 0.26$, $t_{68} = 2.52$, $p = .01$) and not control participants ($b = 0.05$, $t_{62} = 0.43$, $p = .67$) (Figure 3A).

Based on examination of the time and frequency plots in Figure 2, we performed follow-up tests on frequency bands near alpha to determine whether ITPC effects were specific to the alpha range (Figure S1). Patients with schizophrenia showed reduced early ITPC (50–250 ms) over occipital electrodes in the lower beta band (13–20 Hz) compared with control participants ($F_{1,136} = 7.95$, $p = .006$), which did not differ by trial type ($F_{1,140} = 0.59$, $p = .44$), and group did not interact with trial type ($F_{1,140} = 1.04$, $p = .31$). A similar, though longer, phase consistency period (50–450 ms) was also observed in the theta band (4–7 Hz), where ITPC was greater in control participants compared with patients with schizophrenia ($F_{1,136} = 8.04$, $p = .005$), with no trial type ($F_{1,140} = 0.41$, $p = .52$) or group × trial type effects ($F_{1,140} = 1.26$, $p = .26$). We examined broadband ITPC averaged from 4 to 20 Hz over 50 to 250 ms and across both target and nontarget trial types in relation to task performance, symptoms, and cognition (Table 2). The relationship between broadband ITPC and task performance showed slope differences between groups ($t_{134} = 2.44$, $p = .02$), but no significant relationships within groups (*p*s > .05). Relationships between broadband ITPC and both symptoms and cognition were also not observed (*p*s > .11). Together, these findings indicate that schizophrenia is associated with less consistency in the reset of oscillations with visual stimulus input, but only marginally relate to performance impairments on a sustained visual attention task.

Event-Related Desynchronization

Alpha (8–12 Hz) ERD was measured over posterior parietal electrodes (O1, O2, PO3, PO4, PO7, and PO8) 360 to 700 ms

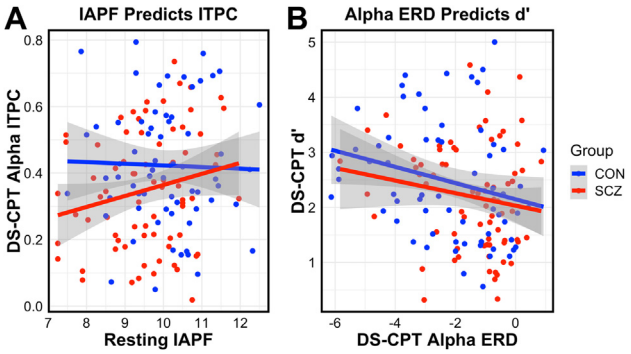

Figure 3. Relationships with alpha intertrial phase coherence (ITPC) and event-related desynchronization (ERD). **(A)** Lower individual alpha peak frequency (IAPF) measured from eyes-closed resting electroencephalography was predictive of less consistency in the phase of the alpha band response across trials (ITPC) (b = 0.22, t_{136} = 2.78, p = .006). Within groups, this relationship was observed only in patients with schizophrenia (SCZ) (b = 0.26, t_{68} = 2.52, p = .01) and not control (CON) participants (b = 0.05, t_{62} = 0.43, p = .67). **(B)** Less reduction in alpha band power after stimulus presentation (alpha ERD, where stronger ERD reflects lower values) predicted worse differentiation between degraded stimulus continuous performance task (DS-CPT) targets and nontargets as measured by the signal detection index d' (b = −0.25, t_{136} = −2.90, p = .004). This effect was observed independently in both SCZ (b = −0.32, t_{68} = −2.72, p = .001) and CON (b = −0.32, t_{62} = −2.50, p = .02) participants.

after stimulus onset. ERD was weaker in patients with schizophrenia (less reduction in alpha power) compared with control participants ($F_{1,136}$ = 9.06, p = .003) (Figure 4), with an effect of trial type ($F_{1,140}$ = 108.59, p < .001) where target stimuli were followed by stronger ERD compared with nontargets. There was no group × trial type interaction ($F_{1,140}$ = 2.04, p = .16). Stronger ERD across trial types was predictive of better task performance (d', b = –0.25, t_{136} = –2.90, p = .004) (Figure 3B), though neither group alone showed a significant relationship (ps > .06). Stronger ERD across trial types and groups was predictive of fewer psychiatric symptoms (b = 0.26, t_{136} = 2.99, p = .003) and better cognition (b = −0.30, t_{136} = −3.17, p = .002). However, for patients with schizophrenia, stronger ERD predicted better cognition (b = −0.35, t_{68} = −2.80, p = .007), while ERD was not predictive of cognition in control participants. ERD was unrelated to resting IAPF, occipital ITPC, and antipsychotic dosage for patients with schizophrenia taking medications (all ps > .24). Together, these results suggest that while alpha ERD across groups is related to the strength of visual sustained attention and the severity of symptoms and cognitive deficits, it is independent of diminished alpha phase consistency after stimulus onset.

On examination of the time and frequency plots in Figure 4, we sought to follow up on posterior parietal ERD within briefer time windows to better capture effects of the task demands (Figure S2). Similar to previous work (21), we conducted post hoc analyses on an early (360–530 ms) and a late (531–700 ms) alpha ERD window. Early ERD showed main effects of group ($F_{1,136}$ = 6.52, p = .01) and an effect of trial type ($F_{1,140}$ = 67.20, p < .001), but no group × trial type interaction ($F_{1,140}$ = 0.26, p = .61). Later ERD also showed main effects of group ($F_{1,136}$ = 12.08, p = .001) and trial type ($F_{1,140}$ = 127.90, p < .001) as well as a group × trial type interaction ($F_{1,140}$ = 4.07, p = .046). The interaction effect was driven by stronger group differences in target ERD (t_{140} = 3.32, p = .001) compared with nontarget ERD (t_{140} = 2.74, p = .007).

Because the later window revealed a group × trial type interaction, we separately examined the relationships of performance and clinical variables with ERD for targets and nontargets (Table 2). Task performance showed no relationship with target ERD (ps > .13). However, better task performance across groups was related to stronger nontarget ERD (b = −0.35, t_{136} = −4.26, p < .001). This effect was observed independently in both patients with schizophrenia (b = −0.32, t_{68} = −2.72, p = .001) and control participants (b = −0.32, t_{62} = −2.50, p = .02). Individuals with better global cognition exhibited stronger target (b = −0.25, t_{136} = −2.56, p = .01) and nontarget ERD (b = −0.23, t_{136} = −2.42, p = .02), though, again, only patients with schizophrenia showed this relationship with nontarget ERD (b = −0.29, t_{68} = −2.28, p = .03; all other relationships p > .10). No relationships were observed between later ERD and symptoms in the schizophrenia group.

Based on visual inspection of the surface plot, we also performed post hoc analyses on beta (13−20 Hz) ERD across the 360- to 700-ms window (Figure S2). We observed weaker ERD in patients with schizophrenia than control participants ($F_{1,136}$ = 12.48, p < .001) and less ERD for target than nontarget trials. We also observed a significant effect of trial type ($F_{1,140}$ = 87.75, p < .001). There was a group × trial type interaction ($F_{1,140}$ = 3.96; p = .048) driven by stronger group differences in target ERD (t_{140} = 3.64, p < .001) compared with nontarget ERD (t_{140} = 2.47; p = .01). Both stronger target ERD (b = −0.20, t_{136} = −2.25, p = .03) and nontarget ERD (b = −0.44, t_{136} = −5.47, p < .001) were related to better task performance (Table 2), though these relationships were observed independently only for nontargets in schizophrenia and control participants (schizophrenia: b = −0.33, t_{68} = −2.86, p = .006; control: b = −0.48, t_{62} = −4.05, p = .0002). Better cognition was associated with stronger target ERD (b = −0.22, t_{136} = −2.50, p = .01) and nontarget ERD (b = −0.20, t_{136} = −2.29, p = .02); neither group showed these effects independently (all ps > .09).

DISCUSSION

Neural oscillatory dynamics are disrupted in schizophrenia (30) and have been found to drive impairments in visual perception and attention (10,21,31). Consistent with our hypotheses, patients with schizophrenia showed reduced early alpha ITPC in response to both target and nontarget stimuli on the DS-CPT, perhaps reflecting compromised perceptual processing regardless of stimulus salience. Interestingly, ITPC was related to IAPF measured during an eyes-closed resting state, suggesting that alpha phase reset in response to visual stimuli may be dependent on the pace of endogenous oscillatory activity. We also found that alpha ERD was impaired in schizophrenia, with weaker ERD during a later cognitive processing time window relating to impaired task performance across groups. The relationship between ERD and task performance was most prominent during nontarget trials and was evident separately in schizophrenia and control groups.

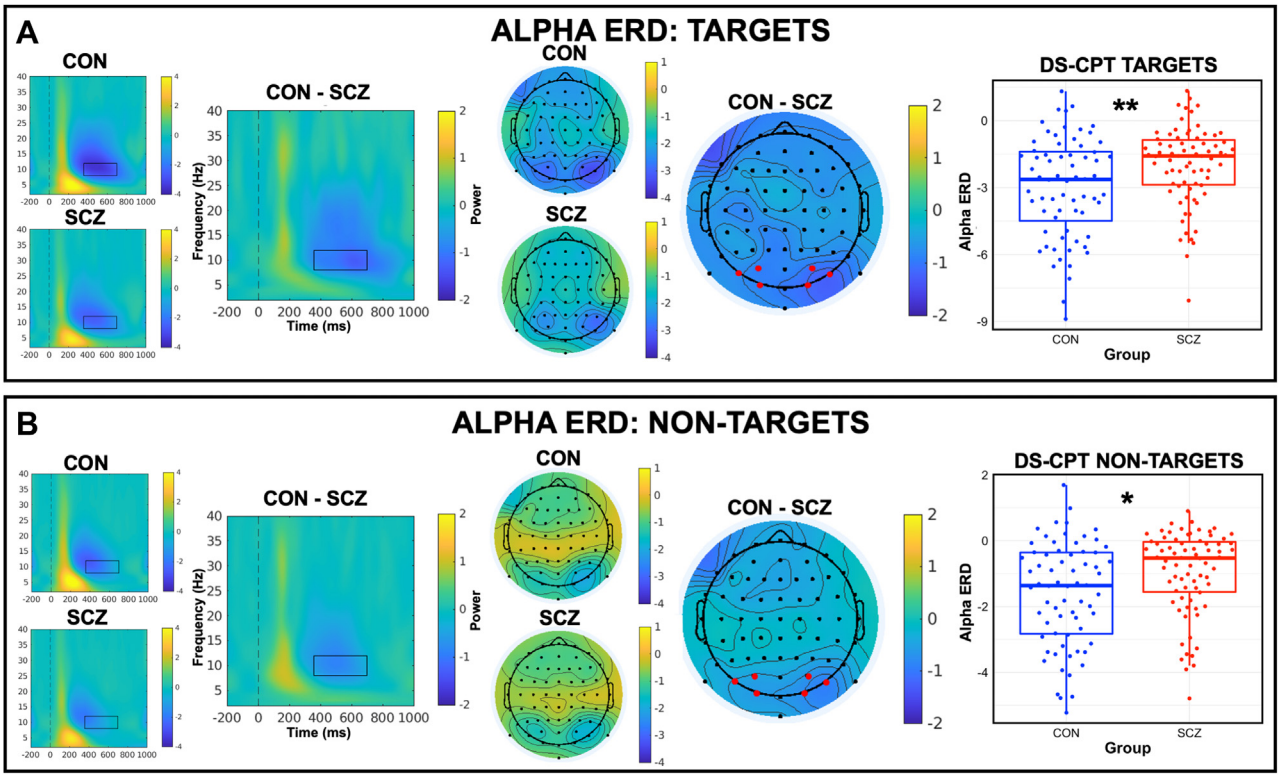

Figure 4. Alpha event-related desynchronization (ERD) during the degraded stimulus continuous performance task (DS-CPT). Alpha ERD (i.e., the decrease in alpha band power after stimulus presentation) was compared between schizophrenia (SCZ) and control (CON) groups for target and nontarget trials during the DS-CPT. **(A)** ERD during target trials was examined in the alpha band (8–12 Hz) 360–700 ms after stimulus onset (depicted by the black boxes on the surface plots) over posterior parietal electrodes (depicted in red on the topographies). Alpha ERD for targets was weaker in patients with SCZ compared with CON participants for target trials ($t_{140} = 2.92$, $p = .004$). **(B)** ERD during nontarget trials also examined alpha 360–700 ms over posterior parietal electrodes. ERD for nontargets was weaker in patients with SCZ compared with CON participants ($t_{140} = 2.70$, $p = .008$). A 2 × 2 analysis of variance comparing group and trial type confirmed weaker ERD for patients with SCZ in response to target and nontarget stimuli ($F_{1,136} = 9.06$, $p = .003$) and revealed no effect of trial type or a group × trial type interaction. *$p < .05$; **$p < .01$.

We found impaired ERD to also be related to increased psychiatric symptoms and poorer cognitive abilities. Overall, blunted alpha ERD may reflect disruptions in the allocation of attention or an inability to disengage from an inattentive default state, which likely have broader impact on clinical and cognitive functioning. Difficulty in leaving a default state may manifest in slow or unresponsive alpha rhythms. Because early alpha ITPC was unrelated to later alpha ERD, it may be that alpha phase reset after stimulus onset reflects a sensory/perceptual phenomenon, while higher-order cognitive functions are elicited later and reflect a departure from the default brain state. This is consistent with related work in an overlapping sample of subjects, who showed reduced late posterior ERPs (P3) over parietal electrodes that also related to impairments in task performance on the DS-CPT (25).

The current findings support the hypothesis that the neuropathology associated with schizophrenia can be broadly characterized by alterations in oscillatory cycles (30). Though previous work in schizophrenia has focused on the timing of higher-frequency oscillations during cognitive demands (32), our findings as well as other recent findings implicate lower-frequency oscillatory cycles as part of atypical perception (10,20,31,33). In the current study, group differences in ITPC were characterized by broadband (4–20 Hz) coherence reductions in schizophrenia, which is consistent with previous studies in schizophrenia that identified reduced ITPC in the theta band that employed visual attention (34) and visual gaze discrimination paradigms (35). It may also be consistent with evidence of greater neural noise observed in schizophrenia (36). These findings are also consistent with widely observed perceptual timing impairments in schizophrenia (37–39), which indicate that these cycles are present in behavioral data. Overall, visual perceptual disruptions appear to be a prominent feature of schizophrenia (40) and may contribute to downstream impairments in cognition (9) and functioning (41,42). Oscillatory cycles may therefore be useful treatment targets for this population.

The current findings also reveal that disruptions in alpha oscillations, and possibly beta, disrupt aspects of adaptive neuronal inhibition, as reflected in blunted ERD (i.e., reduction of oscillatory power), important during states of enhanced vigilance and cognitive control (43). Notably, both alpha and beta ERD showed evidence of group × trial type interactions, such that the control group demonstrated enhanced desynchronization during target compared with nontarget trials, while this was not observed in the schizophrenia group.

This effect is consistent with previous studies in schizophrenia that have identified impaired low-beta desynchronization in response to lateralized attention deployment (44) and weaker late window (approximately 500–700 ms) alpha desynchronization in response to salient stimuli in a cognitive control paradigm (45).

While ERD was modulated for targets compared with nontargets, our post hoc analyses found relationships only between better DS-CPT performance and stronger nontarget ERD in both the alpha and the beta bands. This suggests that enhanced oscillatory desynchronization during nontargets was indicative of better task performance overall and coincides with recent findings demonstrating that alpha ERD is modulated by the saliency of a distractor during working memory (46). Furthermore, our findings are consistent with evidence that alpha desynchronization reflects cognitive load or effort (47) as well as more complex cognitive control processes (48,49).

Limitations

In the current sample, groups did not statistically differ on DS-CPT performance, though a large-scale multisite study identified "medium" effect size impairments on this task in schizophrenia (50) similar to that observed in the present study (d = 0.25). While this may have blunted our observed neural effects, it does indicate that oscillatory abnormalities persist even when attention or perception is not significantly impaired. Interpretation of the ITPC findings may be limited given the triangular and broadband appearance of the task effect, suggesting that phase coherence may in part be driven by early event-related potentials (51). Also, our ERD analysis was restricted by a short baseline period, which can impact the estimate of alpha desynchronization. Because the DS-CPT does not accommodate a longer baseline period, future work may be required to use different paradigms to validate these findings. Short baseline windows also limited examination of prestimulus phase angle and synchrony that might have predicted varying levels of perception or attention from trial to trial. However, given our previous findings demonstrating that lower alpha peak frequencies are evident at rest in schizophrenia but are related to DS-CPT performance (10), it is likely that slowed oscillatory dynamics have an influential role on cognitive performance—particularly when sustained visual attention is required. Though future work may be directed at these relationships in eyes-open resting conditions. We also did not examine higher frequencies in the gamma range that may also play an important role in higher-order cognitive deficits observed in schizophrenia (30). Finally, the interpretation of these results cannot offer insights about the source of cortical dysfunction. Future work should pursue source-level analyses to identify the mechanisms underlying impairments in oscillatory coherence and synchronization in schizophrenia.

Conclusions

Individuals with schizophrenia exhibited impairments in broadband ITPC as well as blunted alpha/beta ERD during a sustained visual attention paradigm. While reduced ITPC may reflect early perceptual impairments, decreased alpha ERD likely reflects deficits in attention and cognitive control, as desynchronization was found to predict better task performance. Impaired visual perception and attention in schizophrenia could ultimately be the consequence of slowed alpha oscillations that fail to effectively respond to stimuli and inefficiently desynchronize in response to higher-order cognitive demands. Slower ITPC and alpha/beta ERD may be meaningful treatment targets for future interventions seeking to enhance perception, attention, and cognitive control in schizophrenia and related psychotic disorders.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the Department of Veterans Affairs Merit Review Award Program (Grant No. 2I01CX000227 [to SRS]) and National Institute of Mental Health (Grant No. K01MH117451 [to ISR]). This article is the result of work supported with resources and use of facilities at the Pittsburgh Department of Veterans Affairs Medical Center and Minneapolis Department of Veterans Affairs Medical Center. The contents of this article do not represent the views of the U.S. Department of Veterans Affairs or the U.S. Government.

We thank the study participants for contributions to this research and laboratory staff who carried out clinical and cognitive assessments as well as EEG acquisitions and processing.

ISR is now an employee of Akili Interactive, though the work he did supporting this manuscript was solely as an employee of the University of Minnesota. All other authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychiatry and Behavioral Sciences, University of Minnesota, Minneapolis, Minnesota (ISR, PAL, SRS); Department of Psychology University of Minnesota, Minneapolis, Minnesota (VJP, SDK, SRS); and Minneapolis Department of Veterans Affairs Medical Center, Minneapolis, Minnesota (SRS).

Address correspondence to Ian S. Ramsay, Ph.D., L.P., at ramsa045@umn.edu.

Received Sep 30, 2022; revised Dec 22, 2022; accepted Feb 2, 2023.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2022.02.001.

REFERENCES

1. Fries P (2005): A mechanism for cognitive dynamics: Neuronal communication through neuronal coherence. Trends Cogn Sci 9:474–480.
2. VanRullen R (2016): Perceptual cycles. Trends Cogn Sci 20:723–735.
3. Spaak E, de Lange FP, Jensen O (2014): Local Entrainment of alpha oscillations by visual stimuli causes cyclic modulation of perception. J Neurosci 34:3536–3544.
4. Samaha J, Sprague TC, Postle BR (2016): Decoding and reconstructing the focus of spatial attention from the topography of alpha-band oscillations. J Cogn Neurosci 28:1090–1097.
5. Jensen O, Bonnefond M, VanRullen R (2012): An oscillatory mechanism for prioritizing salient unattended stimuli. Trends Cogn Sci 16:200–206.
6. Di Gregorio F, Trajkovic J, Roperti C, Marcantoni E, Di Luzio P, Avenanti A, *et al.* (2022): Tuning alpha rhythms to shape conscious visual perception. Curr Biol 32:988–998.e6.
7. Liu SK, Chiu CH, Chang CJ, Hwang TJ, Hwu HG, Chen WJ (2002): Deficits in sustained attention in schizophrenia and affective disorders: Stable versus state-dependent markers. Am J Psychiatry 159:975–982.
8. Luck SJ, Gold JM (2008): The construct of attention in schizophrenia. Biol Psychiatry 64:34–39.
9. Butler PD, Silverstein SM, Dakin SC (2008): Visual perception and its impairment in schizophrenia. Biol Psychiatry 64:40–47.

10. Ramsay IS, Lynn PA, Schermitzler B, Sponheim SR (2021): Author Correction: Individual alpha peak frequency is slower in schizophrenia and related to deficits in visual perception and cognition. Sci Rep 11:20497.
11. Busch NA, Dubois J, VanRullen R (2009): The phase of ongoing EEG oscillations predicts visual perception. J Neurosci 29:7869–7876.
12. Mathewson KE, Gratton G, Fabiani M, Beck DM, Ro T (2009): To see or not to see: Prestimulus α phase predicts visual awareness. J Neurosci 29:2725–2732.
13. Vanrullen R, Busch NA, Drewes J, Dubois J (2011): Ongoing EEG phase as a trial-by-trial predictor of perceptual and attentional variability. Front Psychol 2:60.
14. Fries P (2015): Rhythms for cognition: Communication through coherence. Neuron 88:220–235.
15. Hanslmayr S, Klimesch W, Sauseng P, Gruber W, Doppelmayr M, Freunberger R, Pecherstorfer T (2005): Visual discrimination performance is related to decreased alpha amplitude but increased phase locking. Neurosci Lett 375:64–68.
16. Dugué L, Marque P, VanRullen R (2011): The phase of ongoing oscillations mediates the causal relation between brain excitation and visual perception. J Neurosci 31:11889–11893.
17. Klimesch W, Doppelmayr M, Russegger H, Pachinger T, Schwaiger J (1998): Induced alpha band power changes in the human EEG and attention. Neurosci Lett 244:73–76.
18. Peylo C, Hilla Y, Sauseng P (2021): Cause or consequence? Alpha oscillations in visuospatial attention. Trends Neurosci 44:705–713.
19. Corcoran CM, Stoops A, Lee M, Martinez A, Sehatpour P, Dias EC, Javitt DC (2018): Developmental trajectory of mismatch negativity and visual event-related potentials in healthy controls: Implications for neurodevelopmental vs. neurodegenerative models of schizophrenia. Schizophr Res 191:101–108.
20. Wolff A, Gomez-Pilar J, Zhang J, Choueiry J, de la Salle S, Knott V, Northoff G (2022): It's in the timing: Reduced temporal precision in neural activity of schizophrenia. Cereb Cortex 32:3441–3456.
21. Martínez A, Gaspar PA, Hillyard SA, Bickel S, Lakatos P, Dias EC, Javitt DC (2015): Neural oscillatory deficits in schizophrenia predict behavioral and neurocognitive impairments. Front Hum Neurosci 9:371.
22. Abeles IY, Gomez-Ramirez M (2014): Impairments in background and event-related alpha-band oscillatory activity in patients with schizophrenia. PLoS One 9:e91720.
23. Bismark AW, Thomas ML, Tarasenko M, Shiluk AL, Rackelmann SY, Young JW, Light GA (2018): Reverse translated and gold standard continuous performance tests predict global cognitive performance in schizophrenia. Transl Psychiatry 8:80.
24. Lukoff D, Nuechterlein KH, Ventura J (1986): Manual for the expanded brief psychiatric rating scale. Schizophr Bull 12:594–602.
25. Klein SD, Shekels LL, McGuire KA, Sponheim SR (2020): Neural anomalies during vigilance in schizophrenia: Diagnostic specificity and genetic associations. Neuroimage Clin 28:102414.
26. Sponheim SR, McGuire KA, Stanwyck JJ (2006): Neural anomalies during sustained attention in first-degree biological relatives of schizophrenia patients. Biol Psychiatry 60:242–252.
27. Nuechterlein KH, Asarnow RF (1999): Degraded Stimulus Continuous Performance Test (DS-CPT) Program for IBM-Compatible Microcomputers. Los Angeles, CA: Nuechterlein and Asarnow Version 8.12. .
28. Kang SS, Lano TJ, Sponheim SR (2015): Distortions in EEG interregional phase synchrony by spherical spline interpolation: Causes and remedies. Neuropsychiatric Electrophysiology 1:9.
29. Cohen MX (2014): Analyzing Neural Time Series Data: Theory and Practice. Cambridge, MA: MIT Press.
30. Uhlhaas PJ, Singer W (2010): Abnormal neural oscillations and synchrony in schizophrenia. Nat Rev Neurosci 11:100–113.
31. Basar-Eroglu C, Mathes B, Khalaidovski K, Brand A, Schmiedt-Fehr C (2016): Altered alpha brain oscillations during multistable perception in schizophrenia. Int J Psychophysiol 103:118–128.
32. Gonzalez-Burgos G, Cho RY, Lewis DA (2015): Alterations in cortical network oscillations and parvalbumin neurons in schizophrenia. Biol Psychiatry 77:1031–1040.
33. Rürup L, Mathes B, Schmiedt-Fehr C, Wienke AS, Özerdem A, Brand A, Basar-Eroglu C (2020): Altered gamma and theta oscillations during multistable perception in schizophrenia. Int J Psychophysiol 155:127–139.
34. Basar-Eroglu C, Schmiedt-Fehr C, Marbach S, Brand A, Mathes B (2008): Altered oscillatory alpha and theta networks in schizophrenia. Brain Res 1235:143–152.
35. Grove TB, Lasagna CA, Martínez-Cancino R, Pamidighantam P, Deldin PJ, Tso IF (2021): Neural oscillatory abnormalities during gaze processing in schizophrenia: Evidence of reduced theta phase consistency and inter-areal theta-gamma coupling. Biol Psychiatry Cogn Neurosci Neuroimaging 6:370–379.
36. Peterson EJ, Rosen BQ, Campbell AM, Belger A, Voytek B (2017): 1/f neural noise is a better predictor of schizophrenia than neural oscillations. bioRxiv. https://doi.org/10.1101/113449.
37. Ciullo V, Spalletta G, Caltagirone C, Jorge RE, Piras F (2016): Explicit time deficit in schizophrenia: Systematic review and meta-analysis indicate it is primary and not domain specific. Schizophr Bull 42:505–518.
38. Haß K, Sinke C, Reese T, Roy M, Wiswede D, Dillo W, *et al.* (2017): Enlarged temporal integration window in schizophrenia indicated by the double-flash illusion. Cogn Neuropsychiatry 22:145–158.
39. Norton D, Ongur D, Stromeyer C 3rd, Chen Y (2008): Altered "three-flash" illusion in response to two light pulses in schizophrenia. Schizophr Res 103:275–282.
40. Silverstein SM (2016): Visual perception disturbances in schizophrenia: A unified model. Nebr Symp Motiv 63:77–132.
41. Rassovsky Y, Horan WP, Lee J, Sergi MJ, Green MF (2011): Pathways between early visual processing and functional outcome in schizophrenia. Psychol Med 41:487–497.
42. Sergi MJ, Rassovsky Y, Nuechterlein KH, Green MF (2006): Social perception as a mediator of the influence of early visual processing on functional status in schizophrenia. Am J Psychiatry 163:448–454.
43. Sadaghiani S, Kleinschmidt A (2016): Brain networks and α-oscillations: Structural and functional foundations of cognitive control. Trends Cogn Sci 20:805–817.
44. Kustermann T, Rockstroh B, Kienle J, Miller GA, Popov T (2016): Deficient attention modulation of lateralized alpha power in schizophrenia. Psychophysiology 53:776–785.
45. Becske M, Marosi C, Molnár H, Fodor Z, Tombor L, Csukly G (2022): Distractor filtering and its electrophysiological correlates in schizophrenia. Clin Neurophysiol 133:71–82.
46. Fodor Z, Marosi C, Tombor L, Csukly G (2020): Salient distractors open the door of perception: Alpha desynchronization marks sensory gating in a working memory task. Sci Rep 10:19179.
47. Stipacek A, Grabner RH, Neuper C, Fink A, Neubauer AC (2003): Sensitivity of human EEG alpha band desynchronization to different working memory components and increasing levels of memory load. Neurosci Lett 353:193–196.
48. Kim S, Jung KH, Lee JH (2012): Characteristics of alpha power event-related desynchronization in the discrimination of spontaneous deceptive responses. Int J Psychophysiol 85:230–235.
49. Borghini G, Aricò P, Di Flumeri G, Cartocci G, Colosimo A, Bonelli S, *et al.* (2017): EEG-based cognitive control behaviour assessment: An ecological study with professional air traffic controllers. Sci Rep 7:547.
50. Nuechterlein KH, Green MF, Calkins ME, Greenwood TA, Gur RE, Gur RC, *et al.* (2015): Attention/vigilance in schizophrenia: Performance results from a large multi-site study of the Consortium on the Genetics of Schizophrenia (COGS). Schizophr Res 163:38–46.
51. Jones SR (2016): When brain rhythms aren't "rhythmic": Implication for their mechanisms and meaning. Curr Opin Neurobiol 40:72–80.