PERSPECTIVE

Temporal imprecision of phase coherence in schizophrenia and psychosis—dynamic mechanisms and diagnostic marker

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Schizophrenia (SCZ) is a complex disorder in which various pathophysiological models have been postulated. Brain imaging studies using EEG/MEG and fMRI show altered amplitude and, more recently, decrease in phase coherence in response to external stimuli. What are the dynamic mechanisms of such phase incoherence, and can it serve as a differential-diagnostic marker? Addressing this gap in our knowledge, we uniquely combine a review of previous findings, novel empirical data, and computational-dynamic simulation. The main findings are: (*i*) the review shows decreased phase coherence in SCZ across a variety of different tasks and frequencies, e.g., task- and frequency-unspecific, which is further supported by our own novel data; (*ii*) our own data demonstrate diagnostic specificity of decreased phase coherence for SCZ as distinguished from major depressive disorder; (*iii*) simulation data exhibit increased phase offset in SCZ leading to a precision index, in the millisecond range, of the phase coherence relative to the timing of the external stimulus. Together, we demonstrate the key role of temporal imprecision in phase coherence of SCZ, including its mechanisms (phase offsets, precision index) on the basis of which we propose a phase-based temporal imprecision model of psychosis (PTP). The PTP targets a deeper dynamic layer of a basic disturbance. This converges well with other models of psychosis like the basic self-disturbance and time-space experience changes, as discussed in phenomenological and spatiotemporal psychopathology, as well as with the models of aberrant predictive coding and disconnection as in computational psychiatry. Finally, our results show that temporal imprecision as manifest in decreased phase coherence is a promising candidate biomarker for clinical differential diagnosis of SCZ, and more broadly, psychosis.

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INTRODUCTION

Schizophrenia (SCZ) is a complex disorder featured by a variety of different symptoms, including positive and negative symptoms [1], among others [2]. EEG/MEG studies in SCZ have reported changes in the amplitude in neural activity, as measured by event-related potentials (ERPs) [3]. Recent observations suggest going beyond the amplitude by focusing on other EEG/MEG markers, such as event-related spectral perturbation (ERSP), which hold the promise that neural oscillations, and their related measurements, can serve as a biomarker [4–6].

One feature of neural oscillations are phase fluctuations. These fluctuations can be measured by the phase coherence at each time and frequency datapoint over trials, so over the repeated presentation of the same stimulus. Called intertrial phase coherence (ITPC, or sometimes called intertrial phase clustering), consistent evidence [7–11] has shown that temporal regularity of the phase activity over trials is decreased in SCZ, e.g., decreased phase coherence resulting in decreased ITPC.

In addition to the many ITPC findings in SCZ, there have been several other related findings concerning phase irregularities. In the spontaneous neural activity of the resting state, the lack of phase consistency has been measured by the PDI [12], which supports the idea of temporal imprecision as an underlying characteristic of SCZ [13]. Finally, such temporal imprecision can also be found in the amplitude of neural activity over trials as measured by computing a transfer function [14].

Given this increasing evidence for phase-related changes in EEG/MEG of SCZ, we here raise the following questions. Is decreased phase coherence (ITPC) specific for particular tasks and frequencies? Is decreased ITPC specific for SCZ or does it also occur in other mental disorders like major depressive disorder (MDD)? What are the mechanisms of the decreased phase coherence in SCZ? Addressing these questions is the goal of our paper. For that purpose, we combine a review of existing studies with novel empirical data and computational simulation.

Our main findings show an ITPC decrease in SCZ over a variety of different tasks and frequencies in the reviewed studies. This is further supported by our own data. Moreover, presenting novel data, we demonstrate diagnostic specificity of decreased ITPC for SCZ as distinct from MDD. Finally, employing computational simulation, we show phase offsets with temporal imprecision to be a key mechanism of decreased ITPC in SCZ, and measure this with a precision index (PI) in the millisecond range. Following these observations, we develop a phase-based temporal model of psychosis (PTP), which converges with and enriches other models of psychosis, such as corollary discharge [15], source monitoring [16, 17], the dopamine hypothesis [18], the NMDA-hypothesis [19, 20], the disconnection hypothesis [21–23], and predictive coding [24–28].

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Table 1. Scientific journal articles and their relevant findings related to schizophrenia and intertrial phase coherence (ITPC).

Year	Authors	Title	Journal	Findings
2010	Shin et al.	Increased Temporal Variability of Auditory Event Related Potentials in Schizophrenia and Schizotypal Personality Disorder	Schizophrenia Research	In the deviant tones of an auditory oddball task, ITPC was significantly lower in the SCZ group in the delta and theta bands
2012	Kirihara et al.	Hierarchical Organization of Gamma and Theta Oscillatory Dynamics in Schizophrenia	Biological Psychiatry	In an ASSR stimulation, the SCZ group had significantly reduced gamma ITPC
2015	Shin et al.	Intra-individual neurophysiological variability in ultra-high-risk for psychosis and schizophrenia patients: single-trial analysis	Npj Schizophrenia	In an auditory oddball task, the SCZ group displayed lower alpha/theta ITPC compared with ultra-high-risk participants and healthy controls
2016	Ludwig et al.	Spectral EEG abnormalities during vibrotactile encoding and quantitative working memory processing in schizophrenia	NeuroImage: Clinical	In response to periodic tactile stimuli in the primary somatosensory cortex, the SCZ group had significantly reduced ITPC
2016	Tada et al.	Differential Alterations of Auditory Gamma Oscillatory Responses Between Pre-Onset High-Risk Individuals and First-Episode Schizophrenia	Cerebral Cortex	In ASSR task at 40 Hz, FES group had significantly lower ITPC at electrode FCz
2018	Koshiyama et al.	Electrophysiological evidence for abnormal glutamate-GABA association following psychosis onset	Translational Psychiatry	In ASSR stimulation at 40 Hz, recent-onset SCZ group had significantly reduced ITPC
2019	Kim et al.	Cortical volume and 40-Hz auditory-steady-state responses in patients with schizophrenia and healthy controls	NeuroImage: Clinical	In ASSR stimulation at 40 Hz, SCZ group showed significantly higher ITPC at electrode Cz
2019	Parker et al.	Auditory Steady-State EEG Response Across the Schizo-Bipolar Spectrum	Schizophrenia Research	In ASSR at 40- and 80 Hz, SCZ group had greater reduction in ITPC compared to SAF
2020	Dias et al.	Impaired Fixation-Related Theta Modulation Predicts Reduced Visual Span and Guided Search Deficits in Schizophrenia	Cerebral Cortex	In visual fixations, significantly lower ITPC in SCZ group in theta
2020	Hamilton et al.	Impaired Potentiation of Theta Oscillations During a Visual Cortical Plasticity Paradigm in Individuals with Schizophrenia	Frontiers in Psychiatry	SCZ group didn't show significant increases in theta ITPC relative to baseline in a visual task
2021	Roach et al.	Theta Phase Synchrony Is Sensitive to Corollary Discharge Abnormalities in Early Illness Schizophrenia but Not in the Psychosis Risk Syndrome	Schizophrenia Bulletin	When speaking vowel, early illness SCZ group had lower ITPC in theta
2021	Zheng et al.	Impaired interaural correlation processing in people with schizophrenia	European Journal of Neuroscience	In auditory binaural stimulation, SCZ group had decreased ITPC in theta at electrode FCz
2022	Valt et al.	Reduced magnetic mismatch negativity: A shared deficit in psychosis and related risk	Psychological Medicine	In auditory oddball task, SCZ group had reduced theta ITPC

ITPC intertrial phase coherence, *SCZ* schizophrenia, *ASSR* auditory steady-state response, *FES* first episode schizophrenia, *SAF* schizoaffective disorder.

RESULTS

Intertrial phase coherence (ITPC) in schizophrenia—Unspecific for tasks, frequencies, regions, and modalities/domains, but specific for diagnosis

Auditory and visual oddball paradigms—decreased ITPC reflects increased phase incoherence. Event-related potentials (ERPs) measure the mean baseline corrected amplitude over trials elicited by a particular stimulus or task after the stimulus is presented. Though ERPs are commonly measured in EEG/MEG studies, there is a second component in the electrophysiological signal that has shown promise in SCZ research, namely the phase.

The phase concerns the periodic fluctuating cycles of neural activity—including peak/trough, rise/fall—which can be featured by different phase angles (between 0 and 2π) [29]. Importantly, the phase cycles undergo continuous fluctuations which can be described and operationalized as 'phase variance' or 'phase coherence' [30, 31]. The concept of phase variance means that the phase angle fluctuates over time and can be shifted ('phase jumps' [32], or 'reset' [29]) across different phase cycles and trials. Low phase variance means high coherence, so consistency in the phase over trials at the same time and frequency points. Therefore, if the phase variance over trials is low, the phase shows a high coherence, i.e., phase coherence [33].

Traditionally, phase shifts are evoked or induced [29, 34, 35] by the repetition of rhythmically presented external stimuli, like auditory oddball paradigms, with Mismatch Negativity (MMN) [36–38] or auditory steady state responses (ASSR) [5, 39, 40] (See below for details). Here, the rhythmic stochastics of the external stimuli induce the phase shift in a frequency range that

roughly corresponds to that of the stimulus input stochastics—this is often described as 'entrainment' [30]. This can be measured by intertrial phase coherence (ITPC) which measures the variance of the phase angle at each time and frequency datapoint over presentations of the same stimulus [33].

Studies have shown that deficits in phase-related changes in the auditory oddball paradigm are indeed present in SCZ (compared to ultra-high-risk participants and healthy control subjects (see Table 1)), as observed in reductions in alpha [41, 42] and theta ITPC (Shin et al., 2015a).

Moreover, Shin et al. [42] observed increased intra-subject variability in subjects' behavioral responses to standard and deviant tones. This suggests decreased temporal precision [43], or decreased consistency in their behavioral responses over trials. They therefore consider increased intra-individual variability in behavior to be closely linked to increased phase variance, i.e., increased variance is decreased ITPC, and as a candidate biomarker of SCZ (see also [13]; see below for details). Together, these findings (see Table 1) show decreased phase coherence in SCZ over a variety of different tasks and frequencies, e.g., remaining task- and frequency-unspecific.

Auditory steady state response (ASSR)—decreased ITPC reflects deficient entrainment. Another measure frequently used in SCZ research is the ASSR (see Table 1 and [5, 40, 44–50]. It is one of the most widely used paradigms for eliciting synchronization of neural activity with external stimuli, i.e., entrainment, which can be measured by either the amplitude/power and/or the phase.

ASSR is comprised of a series of successive auditory stimuli at precise frequencies (i.e., 40 Hz, usually from 20–80 Hz) that are presented to the participant. One can typically observe stimulus-evoked power changes in healthy participants, as well as an increase in phase coherence/synchronization, i.e., increased ITPC. This indicates that the frequency of the external stimulus elicits phase synchronization in a corresponding frequency of the brain's neural activity [5, 47]. The findings are relatively consistent across studies; there is a reduction in both spectral power and ITPC in response to the stimulus, especially at 40 Hz, in participants with SCZ.

In 2016, Thune et al. [5] conducted a meta-analysis of 40 Hz ASSR studies in SCZ. They found a reduction in spectral power and ITPC in 17 of the 20 studies (~606 patients with acute or chronic SCZ). Independent of stimulus conditions and methodological issues, high consistency in the findings across different studies were found (though [40] observed an increase in ITPC during 40 Hz ASSR). This suggests that ASSR ITPC may serve as a candidate biomarker of SCZ; one would expect the finding to be specific to SCZ and thus not be altered in other psychiatric disorders.

This was addressed by Zhou et al. and Parker et al. They investigated participants with SCZ [49, 51], schizoaffective (SA) [49, 51], bipolar with psychosis (BDP) [49, 51], bipolar without psychosis (BDNP) [49], and MDD [49]. Both studies found a reduction of spectral power and ITPC during the 40 Hz ASSR in the psychotic groups (SCZ, SA, and BDP) whereas no changes were observed in the non-psychotic groups (BDNP and MDD). Parker et al. [49] also investigated spectral power and ITPC in response to 20 Hz and 80 Hz ASSR. Again, the psychotic groups exhibited reduction in spectral power and ITPC. Similar to the 40 Hz findings, the SCZ group showed the strongest reductions and the BDP the weakest changes (compared to healthy controls, respectively).

The assumption of a spectrum-wide (i.e., across different frequencies) rather than frequency specific (i.e., 40 Hz) deficit in entrainment is further supported by Puvvada et al. [52]. They compared 2.5 Hz and 40 Hz ASSR paradigms in 128 participants with SCZ. Their findings show deficits in delta ITPC, specifically in 2.5 Hz ASSR, while weaker deficits were also seen in 40 Hz. These findings confirm the deficits in delta phase entrainment originally established by Lakatos et al. [53] while simultaneously showing their impact on perceptual (perceptual anomaly) and cognitive (verbal working memory) function.

Together, these findings show that SCZ participants suffer from a deficit in entrainment (phase synchronization) which manifests in a high degree of phase variance over stimuli, i.e., low ITPC. Though initially observed and replicated in ASSR of 40 Hz, i.e., low gamma, this deficit in entrainment is not limited to the gamma range, but also manifests in lower frequency bands such as delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), and beta (13–30 Hz). This suggests a more fundamental, or basic, deficit in phase-related entrainment across the frequency spectrum.

Beyond ASSR and MMN—phase incoheren+ce is not specific to task or frequency. Is the observation of increased phase variance over trials task specific? Is it only present in ASSR and MMN? Various studies applied different experimental paradigms (visual or auditory, perceptual/cognitive tasks) to probe for temporal irregularity and related phase synchronization in SCZ. Moreover, they also tested ITPC in lower frequency bands like delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz) and beta (13–30 Hz) ranges in SCZ [7, 42, 49, 54–57]. Despite their different paradigms and frequencies, these studies show decreased ITPC in SCZ in response to the rhythmic stochastics of the external stimuli. Importantly, reduced ITPC correlated with positive symptoms in SCZ (dis-organization, delusion, and hallucination) as well as with working memory deficits (see also [12, 57]).

These studies show a clear and consistent deficit in the capacity to synchronize a participants own ongoing phase activity with the temporal structure of the external stimuli. This deficit in phase synchronization, and ultimately entrainment, does not appear to be specific for SCZ but for psychosis in general; it occurs in SA and BDP [49, 51, 58], though to a lesser degree. In contrast, participants not suffering from psychosis (BDNP, MDD) do not show this lack of phase synchronization [49].

In addition, ITPC deficits in various frequency bands have also been reported in autism ([59–66] see though [67] and [68]). Given that autism shares many features with SCZ [69, 70] and shows analogous deficits in social cognition, with predominance of

internally oriented cognition [71], these findings are not surprising. They suggest that alterations in phase variance may represent a more syndromal and dimensional biomarker of psychosis rather than a specific one for a particular diagnosis like SCZ.

Together, these findings suggest that phase synchronization and entrainment deficits are not specific to a particular task. Instead, they are present in a variety of tasks, thus are task unspecific. Likewise for the frequency. Finally, phase synchronization and entrainment deficits occur not only in SCZ, but more generally in psychosis (and autism). In contrast, they do not occur in non-psychotic subjects—this indicates a lack of disease-specificity but rather a syndrome specificity. Overall, this suggests that phase synchronization and entrainment deficits are a more fundamental, or basic, disturbance of psychosis as a syndrome (rather than specifically of SCZ as separate disease category) that resonates through all frequencies and tasks in a task- and frequency-unspecific way.

Novel data on decreased ITPC in SCZ—unspecific for region, task, and modalities, but specific for diagnosis and behaviorally relevant. As shown in our literature review (Table 1) and mentioned above, the decreased phase synchrony in SCZ occurs across different frequencies, tasks, sensory modalities, and topographical locations. To test this directly, we here measured ITPC in different sensory modalities (visual and auditory) and tasks (cost conflict, gating, and oddball), and at different topographical locations (electrode clusters in the frontal, central, and occipital lobes) across a range (1–80 Hz) of different frequencies. We hypothesized that decreased ITPC would be found in all tasks and sensory modalities in SCZ participants but not in those with MDD who serve as psychiatric controls. We also expected these differences to be found in the three topographical electrode clusters measured. Statistical analysis was done using permutation testing with extreme pixel correction.

We started with two tasks from two EEG datasets obtained in healthy controls (CON) and SCZ participants (Fig. 1). The first task was a cognitive cost conflict task which required a response (button press) by the participants, and the second was an auditory gating (P50) task in which no response was required (see methods for details). The permutation testing found a significant difference between CON and SCZ in the cost conflict task in the pre- and post-stimulus range (−50 ms to 100 ms after stimulus onset) of the theta (4–8 Hz) frequency band (Fig. 1A, permutation testing in column 3 on the right, with dotted line showing area of significance). These areas of significance were found in the frontal and central electrode clusters (top two rows), but not in the occipital cluster (bottom row). Similar results were found in the auditory gating task (Fig. 1B), with pre- and poststimulus areas of significance in the theta band in the frontal and central electrode clusters. Again, there was no area of significant ITPC difference in the occipital cluster.

In a third dataset, we tested ITPC to see if the decrease found in SCZ was specific to psychosis or also present in other psychiatric diagnoses (Fig. 2). In this dataset and auditory oddball task, participants with MDD served as the psychiatric controls. We found significant differences between CON and SCZ in the delta (1–4 Hz) and theta frequency range in all three electrode clusters (Fig. 2A, B). When the same analysis was done between CON and MDD, a significant difference was found in the delta poststimulus interval in the occipital electrode cluster only. Therefore, differences found in the frontal and central electrode clusters were specific to SCZ and not found in MDD.

In a final step, we wanted to examine if ITPC was relevant to behavior; specifically, if there was a link between temporal imprecision in neural activity and performance on a specific task. To test this, we examined the responses to two different tasks in two different datasets, the first (cognitive cost conflict task) and third (auditory oddball) datasets analyzed above (Fig. 3).

We first divided all trials in both datasets and paradigms by their reaction times. In the auditory oddball task (Fig. 3D, E, F), only trials for the deviants were used as there were no responses to the standard stimuli. All reaction times were sorted in ascending order, and the top 35% ($\mu_{cost\ conflict} = 126 \pm 13$ trials, $\mu_{oddball} = 27 \pm 4$ trials) of reaction times (longest 35% of responses) were considered the slow trials. The bottom 35% were considered the fast trials; the middle 30% of trials were discarded. From these two groups of trials for each participant, the median was calculated, and the ITPC at the frontal, central, and occipital electrodes (same as in previous analyses) was computed (Fig. 3B, E).

From the ITPC plots at the three electrode sites, a small window was extracted (400–500 ms, 2–2.5 Hz) for both the fast and slow trials. The mean of this window was Spearman correlated with the median reaction times.

In both datasets and tasks, and at all electrode sites, the Spearman correlations were significant (cognitive cost conflict dataset: $p_{front} = 4.482 \times 10^{-9}$, $p_{cent} = 5.616 \times 10^{-5}$, $p_{occip} = 4.807 \times 10^{-6}$; auditory oddball dataset: $p_{front} = 0.032$, $p_{cent} = 0.002$, $p_{occip} = 0.002$; see supplementary materials for additional results). All *p*-values were Benjamini-Hochberg False Discovery Rate (FDR) corrected for multiple comparisons. These findings show a significant relationship between behavior as measured with reaction times and temporal imprecision as measured with ITPC; were there no relationship, dividing the reaction times as we did would show no difference in the resulting ITPC calculated.

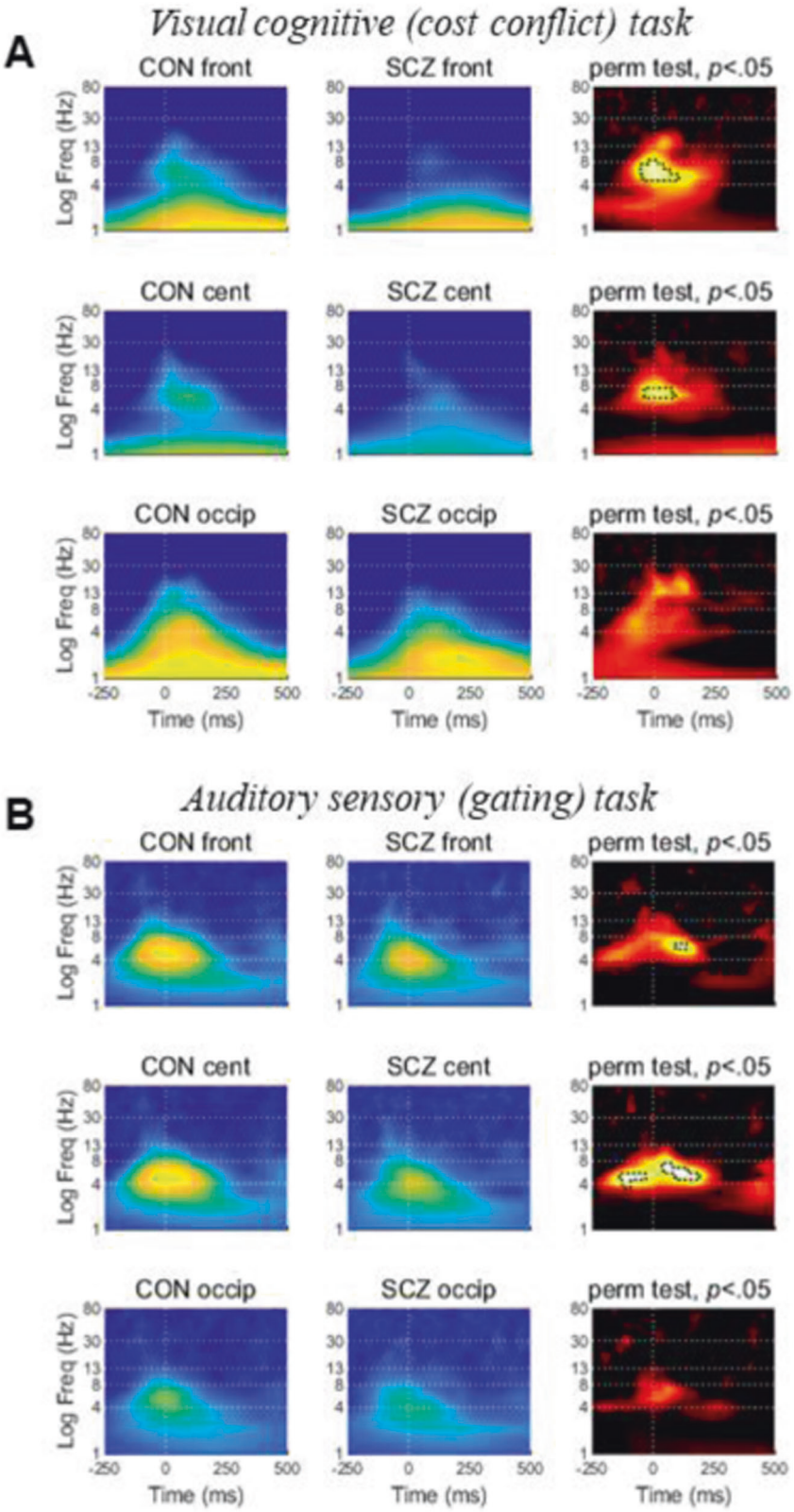
Together, the results from our own novel data analysis confirm the presence of decreased ITPC across different sensory modalities, e.g., visual, and auditory indexing modality-generality, and different domains, e.g., sensory vs cognitive indicating domain-generality. Moreover, we demonstrate that ITPC deficits can be observed in different topographical areas/electrodes including frontal, motor/central and visual-occipital electrode clusters and that it is relevant to behavior. This suggests the ITPC deficit to be a cortex-wide phenomenon rather than being restricted to specific regions. Finally, our data show diagnostic specificity of ITPC as it only occurs in SCZ but not in MDD, and it may contribute to the variability in task performance seen in SCZ.

Dynamic mechanisms of decreased intertrial phase coherence (ITPC)—phase offsets and precision error in the millisecond range

Computational simulation—phase offsets in the millisecond range at single trials. From the studies outlined above and our own analysis, lower ITPC in SCZ participants compared to healthy controls is a robust finding. What ITPC cannot tell us directly, however, are the phase characteristics of the individual trials. How can we go from a measure like ITPC that is computed over all trials to infer to the mechanisms occurring at individual trials? We posited that the difference in ITPC between groups was due to more phase shifting in individual trials in the SCZ participants.

To demonstrate this relationship between phase shifting on the single trial level and ITPC as measured across all trials, and to quantify the phase shifting associated with varying levels of ITPC, we decided to do a computational simulation (see methods for details). This simulation only varied the degree of phase shifting in individual trials (see methods). We therefore simulated a set of data with multiple trials in which there was no phase shifting (negative control), a set with complete phase shifting (positive control), and 98 linearly spaced intervals between the two. From these simulated datasets—in which the 'ground truth' or known properties of the sine waves would be known—the ITPC was measured using the same methods as shown previously (Fig. 4).

When inspecting the simulations, the poststimulus ITPC in the theta band is highest when there was no phase shifting (Fig. 4A, far left plot) and decreases in the plots to the right. As expected, the lowest ITPC was in the far-right plot which had a phase shift of 2π.



From these simulation results, a neural network regression model mapping the relationship between the phase offsets and resulting ITPC was calculated (Fig. 4D–I). We modeled this relationship to allow us to calculate the phase offsets in individual trials from the ITPC (computed over trials) in real human data.

After fitting the model with training and validation data and testing the results (see methods for details), we then applied the model to the actual ITPC data from the auditory oddball task (results shown in Fig. 2). Based on visual inspection of the ITPC data in Fig. 2, ITPC results for each individual in the frontal

Fig. 1 Intertrial phase coherence (ITPC) in two tasks and sensory modalities. A ITPC in a visual cognitive cost conflict task from the PREDICT + online database (http://predict.cs.unm.edu/downloads.php). Two hundred randomly selected training trials were analyzed for each participant in three-electrode clusters (frontal, central, occipital, see methods). Healthy controls (left column) were compared to schizophrenic (SCZ) participants (middle column) between -250 ms and 500 ms, and between 1–80 Hz. The statistical analysis (right column, black/red/yellow plot) was done using permutation testing with extreme pixel correction at the significance level of 0.05. Areas of significance are shown with the dotted black line. In the frontal (top row) and central (middle row) electrode clusters, there was a statistically significant difference between groups around stimulus onset (just before to just after) in the theta (4–8 Hz) band. The ITPC in theta was lower in both electrode clusters in the SCZ group. **B** ITPC in auditory sensory gating task from the study Wolff et al., 2022. 65 randomly selected gating (first stimulus only) trials were analyzed for each participant in the same electrode clusters as in (**A**). As in (**A**), the statistical testing (right column, black/red/yellow plot) was permutation testing with extreme pixel correction. The results showed significant differences between groups in the frontal (top row) and central (middle row) electrode clusters in the post-stimulus (frontal) and pre- and post-stimulus (central) period in theta.

electrode cluster was extracted between 3–5 Hz and 200–300 ms. This actual data served as the input to the neural network model. The predicted phase offsets (Fig. 4I) showed a significant difference between the healthy controls and the SCZ participants ($Z_{SCZ} = -3.630$, $p_{SCZ} < 0.001$), but not between the controls and the MDD participants ($Z_{MDD} = -0.256$, $p_{MDD} = 0.798$).

Together, these results demonstrate that phase offsets in the millisecond ranges in individual trials are a key mechanism underlying the observation of decreased ITPC (as resulting from averaging the variance across trials). We, therefore, suppose that temporal imprecision in the phase coherence relative to the timing of the external stimulus characterizes task-based phase-related processes in SCZ.

Empirical data on ITPC—phase-based precision index in the millisecond range. Similar to our data analyses in multiple datasets, we next developed a measure of the phase precision over trials. Termed the precision index (PI), it measures the precision of all the phase angles over trials (Fig. 5A), similar to the ITPC but with subtle differences. ITPC measures variability with the normalized standard deviation of phase angles over trials at each time and frequency point. In contrast, PI measures variability with the normalized interquartile range (IQR) which measures the middle 50% (from the 25th to the 75th percentile) of phase angles in all trials, and only in a window of 2 Hz and 100 ms which varies according to the stimulus. Finally, the normalized IQR at each time and frequency point in this window is calculated, and then the mean of these is subtracted from 1 (see methods for equation). Like the ITPC, the PI (a) is measured at each electrode so has no spatial component, unlike the phase-locking value which calculates the phase difference between electrodes; (b) can range from 0 (no precision in phase) to 1 (perfect precision in phase); (c) quantifies the phase variability over trials. However, the PI differs from the ITPC in that (a) it Measures the middle 50% of trials thus, unlike the ITPC, is insensitive to outliers or extreme values, and (b) it is the mean of a specified time interval and frequency range rather than, as the ITPC, being calculated at each timepoint and frequency.

We calculated the PI in three different tasks (visual cost conflict, auditory gating, auditory oddball) and datasets at three electrode clusters (frontal, central, occipital) to see if there was a difference between the CON and SCZ groups, or between them and the MDD group.

In the first task and dataset (Fig. 5B), the Mann-Whitney U test found significant differences in the frontal ($Z_{front} = 3.313$, $p_{front} = 0.002$) and central ($Z_{cent} = 2.551$, $p_{cent} = 0.003$) electrode clusters, but not in the occipital cluster ($Z_{occip} = 1.329$, $p_{occip} = 0.098$). In the second dataset and task (Fig. 5C), a significant difference between groups was found in all three (frontal, central, occipital) electrode clusters ($Z_{front} = 4.105$, $p_{front} < 0.001$; $Z_{cent} = 4.388$, $p_{cent} < 0.001$; $Z_{occip} = 4.331$, $p_{occip} < 0.001$).

In the last task and dataset, we found results that support our above ITPC results (Fig. 5D). We found a significant difference between CON and SCZ in all three electrode clusters ($Z_{front} = 4.110$, $p_{front} < 0.001$; $Z_{cent} = 3.970$, $p_{cent} < 0.001$; $Z_{occip} = 3.270$, $p_{occip} = 0.001$). In contrast, no significant difference between CON and MDD was found ($Z_{front} = 0.861$, $p_{front} = 0.453$; $Z_{cent} = 0.971$, $p_{cent} = 0.453$; $Z_{occip} = 0.751$, $p_{occip} = 0.453$) which shows that the low PI measure in this window is specific to SCZ and does not extend to MDD. Note that there was quite high inter-individual differentiation between psychotic and non-psychotic data in our PI data.

In sum, in all three datasets and tasks, the PI was found to be significantly lower in the SCZ group at the frontal and central electrodes clusters, and significantly lower in the occipital electrode cluster in the two auditory tasks. No such difference was found between the healthy controls and MDD group. This, although not completely, was also observed to large degrees on the individual level; this hints upon the potential utility of the combined simulation-empirical PI as clinical marker for the differential diagnosis of psychosis.

DISCUSSION

Phase-based temporal imprecision model of psychosis (PTP)

Combining review, novel empirical data, and computational simulation, we demonstrate the following: (i) decreased phase coherence in SCZ is unspecific for task, frequency, modality/domain, and topographical region; (ii) decreased phase coherence is specific for SCZ albeit in a dimensional way, that is for psychosis, rather than being specific for SCZ as diagnostic category; (iii) decreased ITPC is driven by phase offsets in individual trials which can be measured by a PI in the millisecond range.

Considering our first finding of the lack of specificity in various features, we suppose decreased phase coherence to reflect a basic disturbance that, as such, affects all functions, regions, and frequencies. Specifically, decreased phase coherence implies temporal imprecision in the millisecond range of 2–10 ms. This is supported by our phase data on the neural level but also by millisecond deficits (8–10 ms) in time perception on the psychological level [72, 73]. Since such temporal imprecision can be traced to phase-related processes, we speak of a phase-based temporal imprecision model of psychosis (PTP). The PTP supposes that temporal imprecision in the millisecond range is a basic disturbance of SCZ/psychosis which underlies its deficits in various sensory and cognitive functions. How can we further support the assumption of such phase-based temporal imprecision in psychosis? This leads us to the MMN and phase discontinuity.

Mismatch negativity (MMN) and temporal imprecision

Besides the above ITPC findings, one of the most consistent findings in SCZ are deficits in the MMN [12, 74, 75]. The MMN is calculated from an auditory (or visual) oddball paradigm in which a high proportion of the stimuli are standard tones, and a low proportion are deviant tones (target stimuli). When the mean amplitude over trials of the standard tones is subtracted from that of the deviant tones, the MMN in EEG/MEG is calculated.

SCZ typically shows reduction in MMN amplitude, with a reduced ability to detect deviant tones. As its one of the most consistent findings in both acute and chronic SCZ, as well as

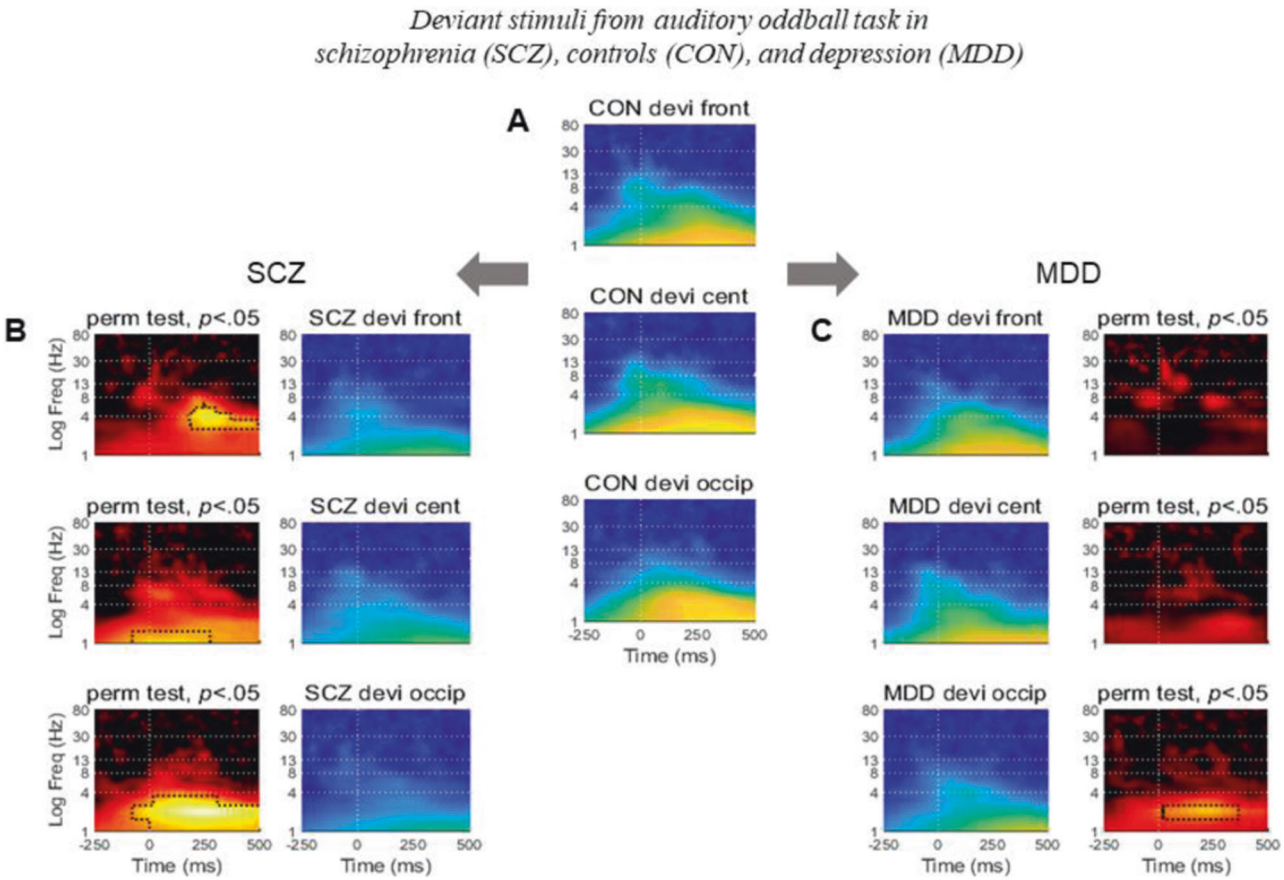


Fig. 2 Intertrial phase coherence (ITPC) decrease in deviant stimuli from an auditory oddball is specific to schizophrenia (SCZ) and not found in depression (MDD). A ITPC (blue and yellow plots) in healthy controls (CON). Fifty randomly selected deviant trials were analyzed in three electrode clusters (frontal, central, occipital, see methods). Healthy controls in (**A**) were then compared to schizophrenic (SCZ) participants ((**B**) shown to the left of the healthy controls) and finally to depressed participant ((**C**) shown to the right of the healthy controls) between -250 ms and 500 ms, and between 1–80 Hz. Statistical analysis (red, black, and yellow plots to far left and right columns, next to the data from the SCZ and MDD groups in blue and yellow) between CON and SCZ (statistical plots on the far left) and CON and MDD (statistical plots on the far right) was done via permutation testing with extreme pixel correction (red, black, and yellow plots). Areas of significance were shown with black dotted line in statistical plots. **B** A significant difference was found between SCZ and CON in all three electrode clusters, in the post-stimulus high delta/low theta in the frontal cluster (top row), and in delta around stimulus onset in the central (middle row) and occipital (bottom row) clusters. **C** In contrast, there was no significant difference between MDD and CON in the frontal (top row) and central (middle row) clusters. There was, however, a significant difference in the post-stimulus delta in the occipital cluster. The results here support previous evidence that decreased ITPC is specific to SCZ/psychosis.

high-risk and first-episode subjects, MMN may serve as a biomarker [12, 74, 75]. Is the MMN deficit related to temporal mechanisms and, more specifically, phase-related changes resulting in temporal imprecision?

Horacek et al. [76] compared the effect of regular and irregular temporal intervals of the deviant tone on the MMN. SCZ participants showed no reduction in MMN in the regular intervals (every seventh tone was a deviant) but did so in the temporally irregular intervals (deviant tones were randomly interspersed among the standard tones). According to the authors, this suggests that SCZ participants have no deficit in prediction per se, as there was no reduction in the regular intervals. Their impairments appear when there is temporal irregularity in the external stimuli—their deficit in prediction, including the empirical prior, may thus be primarily temporal.

The assumption of temporal mechanisms driving MMN changes is further supported by the observation of MMN changes in paradigms where standard and deviant stimuli differ in their temporal duration. Higuchi et al. [77] observed a significant decrease in amplitude in the dMMN (d = duration), especially in chronic SCZ. This reduction was weak in first-episode psychosis participants and those at risk (but still reduced when compared to healthy controls). In a later study, they tested whether the dMMN is predictive of the outbreak of psychosis in those at risk. This was done by following them from a pre-psychotic to a later state (psychotic or non-psychotic). At risk participants who later developed psychosis exhibited lower dMMN compared to those who failed to develop psychosis [78]. That further underlines the importance of temporal mechanisms driving the MMN deficits in SCZ. Accordingly, the impact of temporal irregularity on deviant stimulus prediction and detection strongly suggest that phase-related changes underlie and drive the changes in the MMN amplitude of SCZ.

Together, the findings show consistent deficits in the MMN amplitude (see supplementary materials for addition variance of amplitude analysis), with their close relationship to temporal regularity/irregularity and increased phase variability over trials in SCZ. Recent findings suggest that this may be related to impairment, specifically in deviant detection of conditional probability on the neuronal level (rather than adaptation or tone processing) [12] and temporal imprecision on the behavioral level [13, 42, 43]. Rather than reflecting a general prediction deficit, these findings are compatible with the idea of changes in the temporal underpinnings of prediction, i.e., predictive coding. This

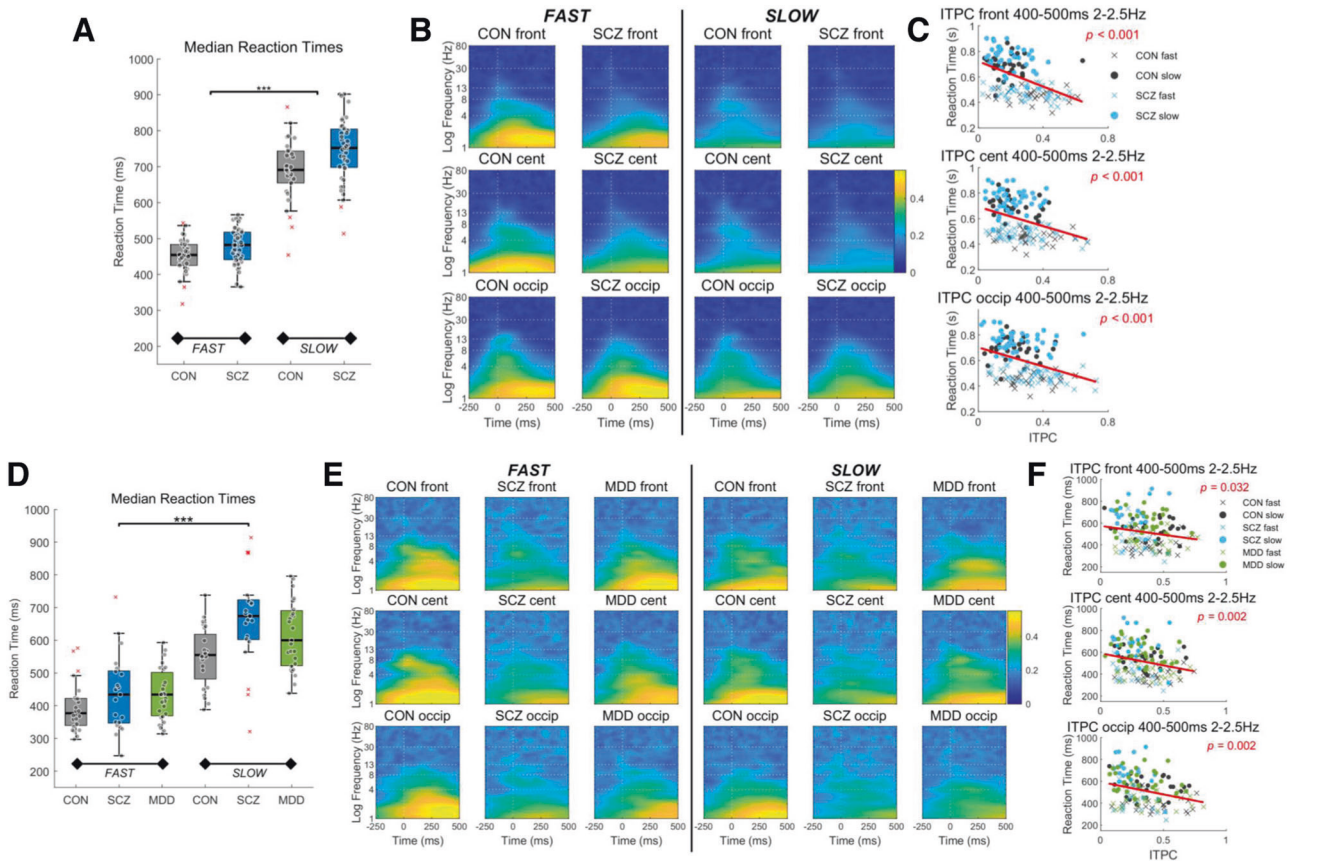


Fig. 3 Intertrial phase coherence (ITPC) is behaviorally relevant. To test the relationship between ITPC measured in neural activity and behavior, we examined the responses to two different tasks in two different datasets. The data shown here in (**A**), (**B**), and (**C**) was a cognitive visual task (same as shown in Fig. 1A) while the data shown here in (**D**), (**E**) and (**F**) was an auditory sensory task (same as shown in Fig. 2). We first divided all trials into both datasets and paradigms by their reaction times. In the auditory sensory task (**D**, **E**, **F**) only trials for the deviants were used as there were no responses to the standard stimuli. **A**, **D** All reaction times were sorted in ascending order, and the top 35% of reaction times (longest 35% of responses) were considered the slow trials. The bottom 35% were considered the fast trials; the middle 30% of trials were discarded. From these two groups of trials for each participant, the median was calculated, and the ITPC at the frontal, central, and occipital electrodes (same as in previous analyses) was computed (**B**, **E**). From the ITPC plots at the three electrode sites, a small window was extracted (400–500 ms, 2–2.5 Hz) for both the fast and slow trials. **C**, **F** The mean of this window was Spearman correlated with the median reaction times seen in (**A**) and (**D**). In both datasets and tasks, and at all electrode sites, the Spearman correlations were significant. All p-values were Benjamini-Hochberg False Discovery Rate corrected for multiple comparisons.

may be related to phase-based temporal imprecision as manifest in increased phase variance.

Spontaneous activity and its phase fluctuations—Increased phase variance

We so far reported increased phase variance during different task states. Is this variability in phase also evident in the ongoing spontaneous neural activity?

Koshiyama et al. [12] investigated the phase discontinuity in the resting state of SCZ. Relying on a recently introduced method by Sanders [32] who speaks of a phase-jump index, Koshiyama calculate the phase discontinuity index (PDI) in continuous, not event-related, activity. The PDI measures the proportion of large ('non-trivial') phase jumps or discontinuities relative to small ('trivial') phase discontinuities. It is measured in large temporal windows (10 s) of continuous activity for each frequency.

In a larger SCZ sample (mainly chronic patients; $n = 100$), during a 3 min resting state they observed increased phase discontinuity in the alpha band of the temporal cortex, which is accompanied by a decrease in alpha peak frequency in roughly the same regions. Phase discontinuity in theta is decreased in temporal regions, FFA and posterior cingulate cortex. Those rather localized changes in phase discontinuity contrast with more widespread changes in power over several regions, which is related to deficits in verbal memory and working memory. The reasons for this discrepancy - local circumscribed changes in phase discontinuity and more global widespread changes in power- remain unclear.

The assumption of phase discontinuity in the spontaneous activity of SCZ is further supported by a recent EEG study [79]. Investigating spontaneous phase variability in the millisecond range at specific frequencies in EEG, they observe not only increased phase variability in SCZ but also increased entropy, e.g., disorder in the phase changes. Together, these findings demonstrate abnormally increased phase variability in the resting state, showing increased disorder, that is, temporal irregularity and imprecision in SCZ. That further supports the idea of the PTP with phase-related temporal imprecision serving as a basic disturbance of SCZ.

PTP reflects a basic disturbance of psychosis—relationship to other models

What exactly is meant by basic disturbance? Our behavioral data clearly show relationship of ITPC to behavior with decreasing ITPC being related to longer reaction times. This shows the behavioral relevance of ITPC. On the other hand, we could not demonstrate direct relationship of ITPC with clinical symptom severity which, again, is in line with other findings. Accordingly, there is strong evidence for the ITPC being decreased in psychosis as distinct

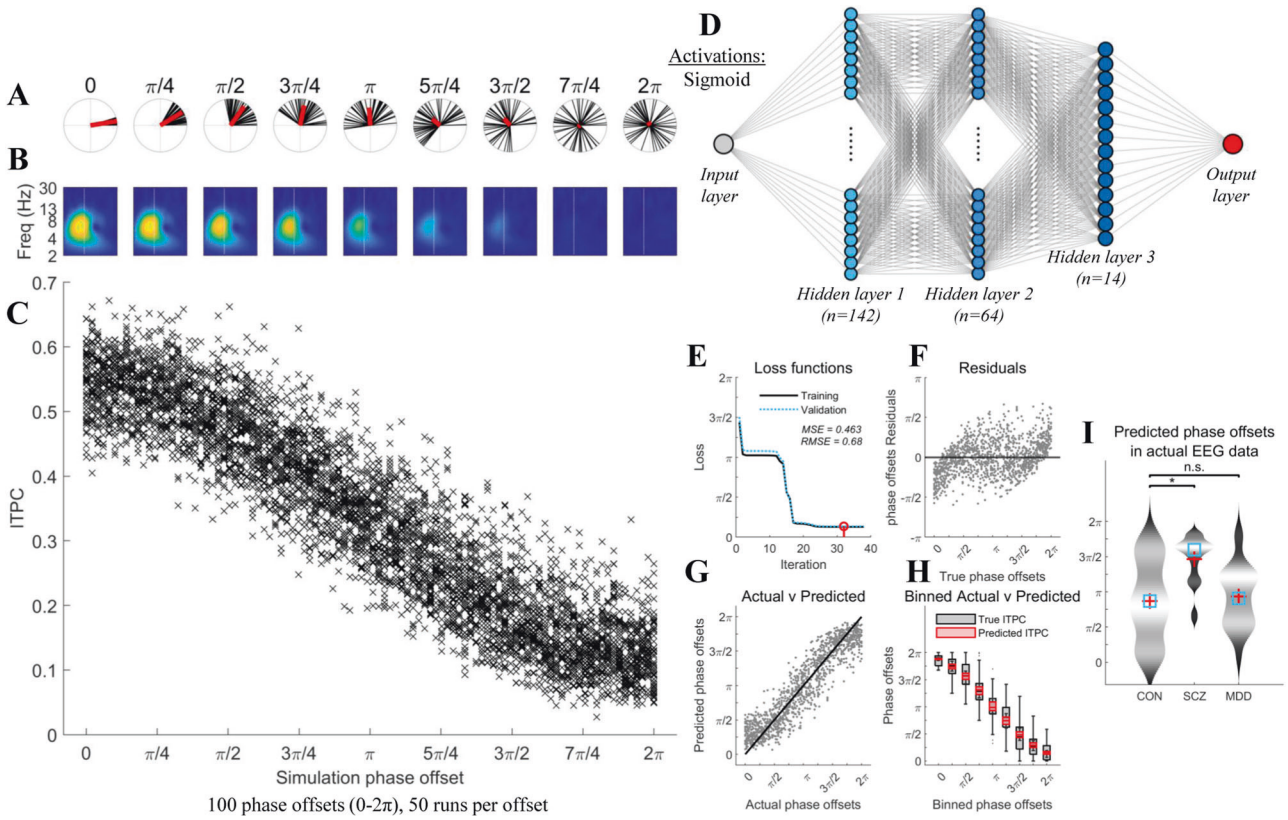


Fig. 4 Computational simulation of varying phase offsets in individual trials and their relationship to intertrial phase coherence (ITPC) computed over all trials. A Polar plots of phase offsets at 9 of the 100 linearly spaced intervals in the simulation. Each black line in the polar plot shows the phase angle at one individual trial while the thick red line shows the preferred phase angle over all trials. Moving from left to right, the phase is very consistent in all trials and becomes less consistent as we move right, with higher phase offsets in individual trials. In the right most polar plot, the phase angles occur throughout the circle, and the preferred phase is very small showing low intertrial phase consistency. **B** The ITPC plots from 9 of the linearly spaced 100 phase offset intervals. The ITPC level is linearly spaced from dark blue to bright yellow. As in **A**, moving from left to right shows a decrease in the ITPC, so showing less consistency over trials. **C** The results of the simulation. As each of the 100 phase offsets, 50 simulated participants (black crosses) each had 50 simulated trials with the specified phase offset (see methods). Once the 50 simulation trials were created, the ITPC over these trials was computed and the mean between 0–122 ms and 4–8 Hz was calculated. **D** Structure of the regression neural network model built to map the relationship between the ITPC over trials and the phase offsets in individual trials in the computational simulation. **E** Loss functions for the training (black line) and validation (blue dotted line) iterations. The model was trained on 32 iterations (red circle and line). **F** Residuals from the test set. **G** Actual phase offsets from the test set compared to predicted phase offsets. The datapoints fall roughly along the reference line which indicates a good model fit. **H** Comparing the predicted and actual phase offsets in bins (9 linearly spaced bins). The difference between predicted and actual was fairly evenly distributed across the phase offsets. **I** Using the real ITPC data from the SCZ, MDD and CON participants in the auditory oddball task, the phase offsets in individual trials were predicted using the neural network model. Wilcoxon rank sum nonparametric tests found a significant difference between CON and SCZ, but no difference between CON and MDD. Red cross = mean; Blue box = median.

from other disorders like MDD, BD and anxiety while, on the other hand, no direct relation to symptom severity can be observed.

This resembles the situation in basic self-disturbances in psychosis as measured by the Experience of Anomalies of self experience (EASE) where, similarly, no direct relationship with symptom severity can be observed (Nordgaard et al. [80], Sandsten et al. [81]). Albeit tentatively, we therefore assume that the ITPC operates on a deeper layer that, just like insulin in the case of diabetes (Northoff [82]) and analogous to the basic self-disturbance in SCZ, constitutes a basic disturbance (Northoff and Hirjak [83, 84]). One would consequently predict that the decreased ITPC should be directly related to the basic self-disturbance as measured by the EASE. We thus assume that the deficit in ITPC reflects a basic disturbance at a deeper level of the pathophysiology that is only indirectly but not directly, e.g., in a one-to-one way, connected with the severity of symptoms at a more superficial level. This would suggest strong proximity of the PTP with phenomenological psychopathology.

Moreover, the decrease in ITPC is also in line with the phenomenological description of a "loss of dynamic contact with reality" as basic disturbance of SCZ (Minkowski [69]): if one cannot synchronize with the external rhythm as in case of a reduced ITPC, one loses the dynamic contact with the outer reality. One would consequently assume disturbances in time (and space) experience in SCZ focusing on temporal disconnection and fragmentation; these can indeed be observed (Stanghellini et al. [85, 86]) and have recently been operationalized by the Scale for time-space experience in psychosis (STEP) (Arantes-Goncalves et al. [70]). Together, this suggests strong convergence of the dynamic model of the PTP with Spatiotemporal psychopathology (see also Hirjak et al. [87]).

Other convergences of the PTP hold with other models of psychosis like the predictive coding (Sterzer et al. [88], Heinz et al. [27], Friston and Stephan 2016) and the disconnection models (Stephan et al. [89], Friston and Stephan [21]). Temporal imprecision and specifically our PI may be closely related to the constitution of abnormal priors as typically observed in psychosis (Sterzer et al. [88], Heinz et al. [27], Friston and Stephan [21]); if so, there may be a dynamic phase- and thereby precision-based underpinning and shaping of the empirical priors which may then be characterized primarily by decreased temporal precision relative to the external

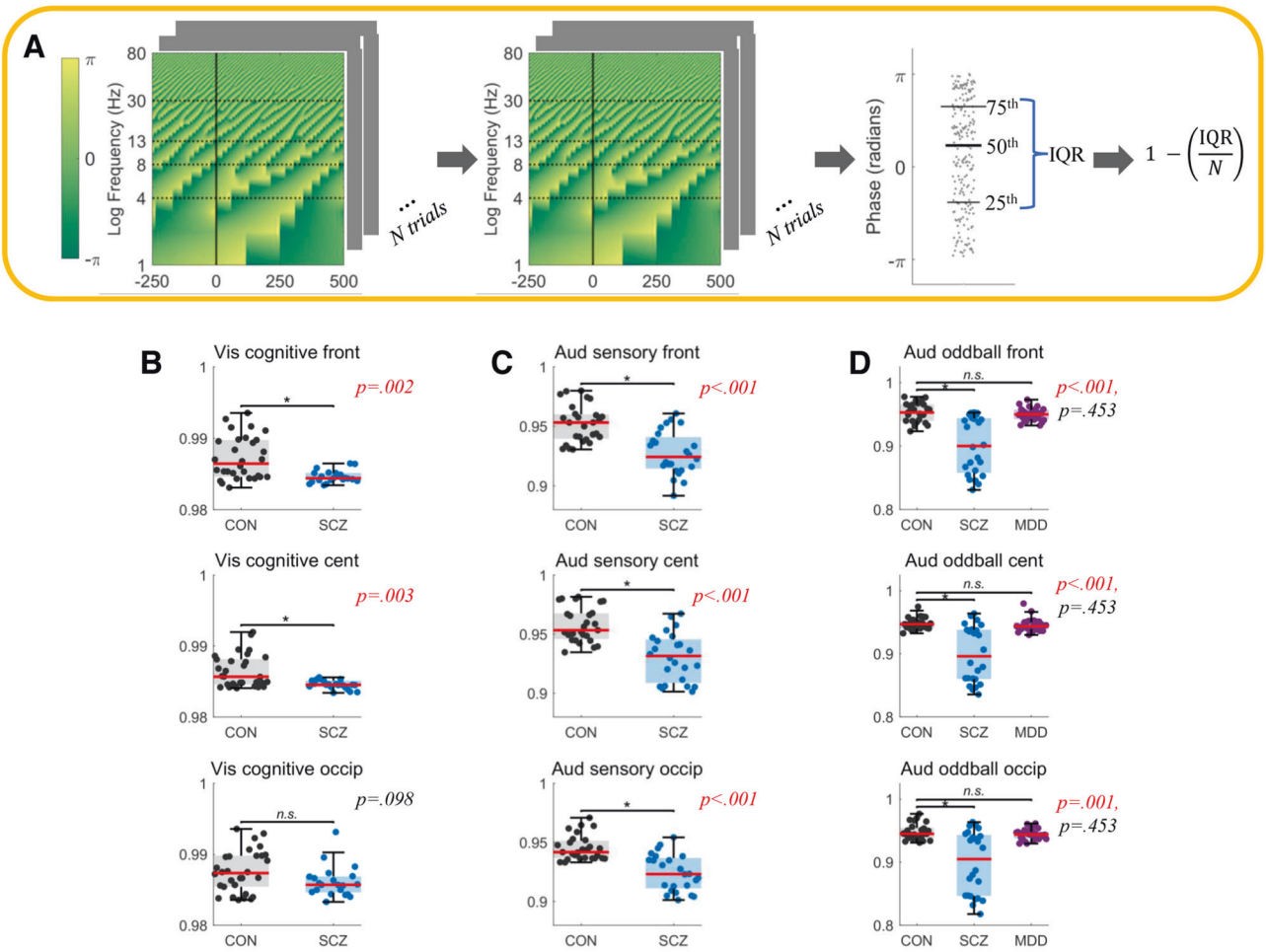


Fig. 5 Precision index (PI) in three different datasets and tasks. A The PI was computed from the Morlet wavelet data in individual trials. A window of time and frequency (specific to each dataset, according to the permutation statistics shown in Figs. 1 and 2) that covered 2 Hz and 100 ms (red rectangle) was extracted from the phase data in each trial. For each time and frequency point in this window (i.e., 5 Hz and 100 ms), the phase angles for all trials were extracted and the interquartile range (IQR) was computed (scatter plot 3rd from left). The IQR is the distance between the 25th and 75th percentile (middle 50% of datapoints). Once the IQR was calculated for the specified time and frequency point, it was divided by the number of trials, and this was subtracted from 1. As stated, this was done for each time and frequency point, then the median across both the time and frequency points was computed as the overall PI for that window. **B** The PI in a visual cognitive cost conflict task from the PREDICT+ online database (http://predict.cs.unm.edu/downloads.php). The time and frequency interval for the calculation of the PI was 5–7 Hz and −50 to 50 ms. A significant difference between groups was found in the frontal and central electrode clusters, with the SCZ being lower. **C** The PI in an auditory gating task was computed for the interval 5–7 Hz and 100–200 ms. The difference between groups was significant for all electrode clusters, and again the SCZ group had lower values. **D** The PI in the deviant stimuli of an auditory oddball task was computed for the interval 3–5 Hz and 250–350 ms. There was a significant difference between the healthy controls (CON) and the SCZ group, with lower values in the SCZ group for all electrodes. There was no difference between the controls and the MDD group. The red line in the boxplots is the median. The p-values for all statistical tests are FDR Benjamini-Hochberg corrected.

event they aim to predict—this may result in high prediction error as manifest in decreased ITPC. Future computational models may thus want to connect the dynamics of the decreased ITPC and our PI to the dynamics of the empirical prior, e.g., dynamical prior (Friston 2017) and the prediction error. The same applies to the disconnection model (Stephan et al. [89], Friston and Stephan [21]): the disconnection between different regions may be related to their decreased synchronization as mediated by another phase-based measure, the phase locking index (PLI) which, again, is also abnormal, e.g., decreased in psychosis (Gomez-Pillar et al. [57]). Taken together, one may be inclined to hypothesize that reduced synchronization, manifest in decreased ITPC and PLI, may drive both aberrant predictive coding and disconnection.

Limitations

As with all analyses, our results shown here have several limitations. First, the size of the datasets were modest, so future studies would benefit from datasets with more participants. Second, in our psychiatric disease control analysis, we only compared the SCZ participants to one other diagnosis (MDD). Broadening of this analysis would include several other diagnoses (i.e., bipolar disorder, generalized anxiety, etc.) in order to determine with greater confidence that the decreased ITPC we see is specific only to SCZ/psychosis and not to other diagnoses not involving psychosis.

CONCLUSION

We reviewed recent findings in phase-related changes in SCZ in particular and psychosis in general. Increased phase variance, e.g., reduced phase coherence can be observed across a variety of different task states in a frequency- and task-unspecific way, as well as across different sensory modalities and domains. This is in line with the observation of abnormal phase variance in the

spontaneous activity, e.g., rest or prestimulus. Mechanistically, we show phase offset at single trials as key dynamic mechanism of decreased ITPC as measured by a PI. Summing the various findings, we postulate a basic dynamic disturbance in psychosis at a deeper spatiotemporal level. Specifically, such dynamic disturbance is described by our phase-based temporal imprecision model of psychosis (PTP) where temporal imprecision in the millisecond range leads to reduced neural synchronization with the timing of any kind of external stimuli.

This converges well with other models of psychosis. For instance, through the PI results in our dynamic simulation, the PTP suggests future convergence with both predictive coding and disconnection models of psychosis, as in Computational psychiatry. There is also convergence of our PTP with Phenomenological Psychopathology and, specifically, the basic self-disturbance and time-space experience. Together, the PTP may ultimately be able to bridge the gap between neuronal and experiential levels as postulated in Spatiotemporal Psychopathology (Northoff and Hirjak [83, 84] Hirjak and Northoff [90]). Finally, the data, especially our dynamic simulations with the high differentiation of psychotic and non-psychotic subjects, suggest that such phase-based temporal imprecision in the millisecond range could serve as a strong biomarker candidate of the clinical differential diagnosis of SCZ, e.g., psychosis [91–100].

METHODS

EEG datasets and preprocessing

All relevant info and explanations of the datasets included in the analysis and their tasks appears in the supplementary materials. This is also the case for the preprocessing details.

Intertrial phase coherence (ITPC) analysis

ITPC was computed using complex Morlet wavelets according to:

$$ITPC_{tf} = \left| n^{-1} \sum_{r=1}^{n} e^{ik_{tfr}} \right|$$

where n is the number of trials, r is the trial number, e^{ik} is Euler's formula providing the complex polar representation of a phase angle k on trial r at time-frequency point tf. The absolute value bars indicate the length of the average vector. Complex Morlet wavelets were computed for the full epoch length (−800 to 1100 ms) between 1 and 80 Hz. The wavelets were composed of 3–10 logarithmically spaced cycles and 158 points in the frequency range (80–1 Hz is 79 Hz, and two points per Hz = 158 points).

Phase offset simulation

To determine the link between ITPC and phase offsets in individual trials, a computational simulation was done [101]. The method of the actual simulation itself was identical to that done in [13], with one difference: here we used 100 linearly spaced phase offsets while in the previous publication, only 5 were used.

The ITPC simulations were based on a simple sinewave, which would replicate the ERSP results common to both groups and datasets. As this increase in theta power lasted only several hundreds of milliseconds (was not continuous), we decided that our simulations would have a transient oscillation with peaks in the theta range of 4–8 Hz (see [13] for details). The base sinewave is

$$\sim_{base} = A \sin(2\pi ft + \Delta\theta r),$$

where A is the amplitude of the wave (here equal to 1), f is the frequency of the transient oscillation (4–8 Hz in increments of 1 Hz), and t is the timepoint in the trial. $\Delta\theta$ is the phase shift, which is the independent factor being varied in these simulations. The phase shifts ranged from 0 (no phase shift) to 2π (complete phase shift) with five levels (0, π/2, π, 3π/2, 2π). Finally, r, which is multiplied by the phase shift, is a number between 0 and 1, which is randomly generated for each trial. This creates some differences between trials for each phase shift. For a transient oscillation, a Gaussian kernel in the time domain is applied to the sinewave, thereby allowing for the sinewave during a specified time window rather than continuously. The Gaussian kernel (Γ) is defined as

$$\Gamma = e^{\frac{-(t-p)^2}{2s^2}}$$

where t is the timepoint, p is the peak time of the Gaussian kernel, and s is its width. In our simulations, the Gaussian kernel had a peak at 175 ms after stimulus onset and a full width at half-maximum (FWHM) of 150 ms. It was applied to the sinewave, and so the combination of these two components results in a transient increase of theta power after stimulus onset. Finally, we added two types of noise to the sinewave in order to make the simulations more realistic:

(1) pink noise, which has a 1/f power spectrum with an exponential decay of 50

(2) white noise, which has a flat power spectrum [102–104].

To approximate the actual EEG data which we compared to the simulation, 50 single channels (one channel represents one participant) and 50 trials were simulated.

Model fit to simulated data

To model the relationship between the phase offsets in the individual trials of the computational simulation and the resulting ITPC measured over all trials, we fit the data to a neural network regression model. This fit was done in MATLAB using the function *fitrnet*.

The data from the simulation (100 phase offsets × 50 runs per phase offset = 5000 examples) was divided into three subsets, training (1875 examples, 37.5%), validation (1875 examples, 37.5%), and testing (1250 examples, 25%). In the training of the model, the data was standardized.

The following were the model parameters: there were three hidden layers with 142 neurons in the first layer, 64 in the second and 14 in the third; the activations were sigmoid; the iteration limit was 1000; lambda was 3.737×10^{-6}.

V. Precision Index (PI) calculation

The PI measures the variability of phase angles over trials, similar to the ITPC. In contrast to the ITPC, however, the PI is (i) calculated in a defined time (100 ms) and frequency (2 Hz) window (see Table 2); (ii) measures variability with the normalized IQR which measures the middle 50% (from the 25th to the 75th percentile) of phase angles in all trials rather than the standard deviation; (iii) is subtracted from 1.

The equation for the PI is shown here:

$$PI = \frac{1}{N} \sum_{i=1}^{N} 1 - \left(\frac{\varsigma_i}{n}\right)$$

Table 2. Precision Index (PI) time and frequency windows for the three datasets.

Dataset	Precision Index window	
	Time (ms)	Frequency (Hz)
Visual Cost Conflict task	0–100	5–7
Auditory Gating task	100–200	5–7
Auditory Oddball task	250–350	3–5

where ς_i is the IQR of phase angles over trials at time-frequency point i in the specified window, n is the number of trials over which the IQR is calculated, and N is the number of time-frequency points in the specified window.

Statistics

The statistics in this study were of two types: (i) permutation tests with extreme pixel correction; (ii) the nonparametric Wilcoxon rank sum test. The permutation testing was used to determine the areas of significance between groups in the ITPC plots, free of an a priori hypothesis as to the time and frequency interval. Previous studies [13] have shown a significant difference in ITPC in SCZ in the delta and theta frequency bands, but as we were testing multiple datasets and paradigms, we wanted more of an exploratory analysis that included all datapoints in the time and frequency range. The permutation tests with the correction were computed using a custom MATLAB script. To correct for multiple comparisons, however, the extreme pixel correction was applied to all the datapoints in the permutation tests.

The second statistical test used was the nonparametric Wilcoxon rank sum test. A nonparametric test was used as the data were not normally distributed, so a parametric test would have been inappropriate. To calculate these tests, the MATLAB function *ranksum* was used. Finally, to correct for multiple comparisons, the FDR Benjamini-Hochberg correction [105] was applied to all rank sum tests.

For all statistical tests, a significance level of 0.05 was used.

REFERENCES

1. McCutcheon RA, Marques TR, Howes OD. Schizophrenia—an overview. JAMA Psychiatry. 2020;77:201–10. https://doi.org/10.1001/jamapsychiatry.2019.3360.
2. Amadeo MB, Esposito D, Escelsior A, Campus C, Inuggi A, Silva BPD, et al. Time in schizophrenia: a link between psychopathology, psychophysics and technology. Transl Psychiatry. 2022;12. https://doi.org/10.1038/s41398-022-02101-x.
3. Turetsky BI, Dress EM, Braff DL, Calkins ME, Green MF, Greenwood TA, et al. The utility of P300 as a schizophrenia endophenotype and predictive biomarker: clinical and socio-demographic modulators in COGS-2. Schizophr Res. 2015;163:53–62. https://doi.org/10.1016/j.schres.2014.09.024.
4. Northoff G, Gomez-Pilar J. Overcoming rest-task divide-abnormal temporospatial dynamics and its cognition in schizophrenia. Schizophr Bull. 2021;47:751–65. https://doi.org/10.1093/schbul/sbaa178.
5. Thune H, Recasens M, Uhlhaas PJ. The 40-Hz auditory steady-state response in patients with schizophrenia. JAMA Psychiatry. 2016;73:1145 https://doi.org/10.1001/jamapsychiatry.2016.2619.
6. Javitt DC, Siegel SJ, Spencer KM, Mathalon DH, Hong LE, Martinez A, et al. A roadmap for development of neuro-oscillations as translational biomarkers for treatment development in neuropsychopharmacology. Neuropsychopharmacology. 2020;45:1411–22. https://doi.org/10.1038/s41386-020-0697-9.
7. Dias EC, Voorhis ACV, Braga F, Todd J, Lopez-Calderon J, Martinez A, et al. Impaired fixation-related theta modulation predicts reduced visual span and guided search deficits in schizophrenia. Cereb Cortex. 2020;30:2823–33. https://doi.org/10.1093/cercor/bhz277.
8. Hamilton HK, Boos AK, Mathalon DH. Electroencephalography and event-related potential biomarkers in individuals at clinical high risk for psychosis. Biol Psychiatry. 2020;88:294–303. https://doi.org/10.1016/j.biopsych.2020.04.002.
9. Ludwig S, Spitzer B, Jacobs AM, Sekutowicz M, Sterzer P, Blankenburg F. Spectral EEG abnormalities during vibrotactile encoding and quantitative working memory processing in schizophrenia. NeuroImage Clin. 2016;11:578–87. https://doi.org/10.1016/j.nicl.2016.04.004.
10. Roach BJ, Ford JM, Loewy RL, Stuart BK, Mathalon DH. Theta phase synchrony is sensitive to corollary discharge abnormalities in early illness schizophrenia but not in the psychosis risk syndrome. Schizophr Bull. 2021;47:415–23. https://doi.org/10.1093/schbul/sbaa110.
11. Valt C, Quarto T, Tavella A, Romanelli F, Fazio L, Arcara G, et al. Reduced magnetic mismatch negativity: a shared deficit in psychosis and related risk. Psychol Med. 2023;53:6037–45. https://doi.org/10.1017/s003329172200321x.
12. Koshiyama D, Miyakoshi M, Tanaka-Koshiyama K, Joshi YB, Sprock J, Braff DL, et al. Abnormal phase discontinuity of alpha- and theta-frequency oscillations in schizophrenia. Schizophr Res. 2021;231:73–81. https://doi.org/10.1016/j.schres.2021.03.007.
13. Wolff A, Gomez-Pilar J, Zhang J, Choueiry J, de la Salle S, Knott V, et al. It's in the timing: reduced temporal precision in neural activity of schizophrenia. Cereb Cortex. 2022;32:3441–56. https://doi.org/10.1093/cercor/bhab425.
14. Karanikolaou M, Limanowski J, Northoff G. Does temporal irregularity drive prediction failure in schizophrenia? temporal modelling of ERPs. Schizophrenia. 2022;8. https://doi.org/10.1038/s41537-022-00239-7.
15. Ford JM, Mathalon DH, Heinks T, Kalba S, Faustman WO, Roth WT. Neurophysiological evidence of corollary discharge dysfunction in schizophrenia. Am J Psychiatry. 2001;158:2069–71.
16. Nelson B, Lavoie S, Gawęda Ł, Li E, Sass LA, Koren D, et al. The neurophenomenology of early psychosis: an integrative empirical study. Conscious Cogn. 2020;77:102845. https://doi.org/10.1016/j.concog.2019.102845.
17. Nelson B, Whitford TJ, Lavoie S, Sass LA. What are the neurocognitive correlates of basic self-disturbance in schizophrenia?: Integrating phenomenology and neurocognition. Part 1 (Source monitoring deficits). Schizophr Res. 2014;152:12–19. https://doi.org/10.1016/j.schres.2013.06.022.
18. Maia TV, Frank MJ. An integrative perspective on the role of dopamine in schizophrenia. Biol Psychiatry. 2017;81:52–66. https://doi.org/10.1016/j.biopsych.2016.05.021.
19. Balu DT. The NMDA Receptor and Schizophrenia. From pathophysiology to treatment. Adv Pharmacol. 2016;76:351–82. https://doi.org/10.1016/bs.apha.2016.01.006.
20. Gilmour G, Dix S, Fellini L, Gastambide F, Plath N, Steckler T, et al. NMDA receptors, cognition and schizophrenia—Testing the validity of the NMDA receptor hypofunction hypothesis. Neuropharmacology. 2012;62:1401–12. https://doi.org/10.1016/j.neuropharm.2011.03.015.
21. Friston KJ, Brown HR, Siemerkus J, Stephan KE. The dysconnection hypothesis (2016). Schizophr Res. 2016;176:83–94. https://doi.org/10.1016/j.schres.2016.07.014.
22. Stephan KE, Friston KJ, Frith CD. Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophr Bull. 2009;35:509–27. https://doi.org/10.1093/schbul/sbn176.
23. Stephan KE, Baldeweg T, Friston KJ. Synaptic plasticity and dysconnection in schizophrenia. Biol Psychiatry. 2006;59:929–39. https://doi.org/10.1016/j.biopsych.2005.10.005.
24. Corlett PR, Horga G, Fletcher PC, Alderson-Day B, Schmack K, Powers AR. Hallucinations and strong priors. Trends Cogn Sci. 2019;23:114–27. https://doi.org/10.1016/j.tics.2018.12.001.
25. Friston KJ. Does predictive coding have a future? Nat Neurosci. 2018;21:1019–21. https://doi.org/10.1038/s41593-018-0200-7.
26. Griffin JD, Fletcher PC. Predictive processing, source monitoring, and psychosis. Annu Rev Clin Psychol. 2017;13:265–89. https://doi.org/10.1146/annurev-clinpsy-032816-045145.
27. Heinz A, Murray GK, Schlagenhauf F, Sterzer P, Grace AA, Waltz JA. Towards a unifying cognitive, neurophysiological, and computational neuroscience account of schizophrenia. Schizophr Bull. 2019;45:1092–100. https://doi.org/10.1093/schbul/sby154.
28. Sterzer P, Adams RA, Fletcher P, Frith C, Lawrie SM, Muckli L, et al. The predictive coding account of psychosis. Biol Psychiatry. 2018;84:634–43. https://doi.org/10.1016/j.biopsych.2018.05.015.
29. Canavier CC. Phase-resetting as a tool of information transmission. Curr Opin Neurobiol. 2015;31:206–13. https://doi.org/10.1016/j.conb.2014.12.003.
30. Lakatos P, Gross J, Thut G. A new unifying account of the roles of neuronal entrainment. Curr Biol. 2019;29:R890–905. https://doi.org/10.1016/j.cub.2019.07.075.
31. Buzsaki G. Rhythms of the Brain.; 2006. https://doi.org/10.1093/acprof:oso/9780195301069.001.0001.
32. Sanders TH. Phase discontinuities underlie increased drowsiness and diminished sleep quality in older humans. *bioRxiv*. Published online 2019. https://doi.org/10.1101/696658.
33. Diepen RMV, Mazaheri A. The Caveats of observing inter-trial phase-coherence in cognitive neuroscience. *Sci Rep*. 2018;8. https://doi.org/10.1038/s41598-018-20423-z.
34. Bolt T, Anderson ML, Uddin LQ. Beyond the evoked/intrinsic neural process dichotomy. Netw Neurosci. 2018;2:1–22. https://doi.org/10.1162/netn_a_00028.
35. David O, Kiebel SJ, Harrison LM, Mattout J, Kilner JM, Friston KJ. Dynamic causal modeling of evoked responses in EEG and MEG. NeuroImage. 2006;30:1255–72. https://doi.org/10.1016/j.neuroimage.2005.10.045.
36. Fitzgerald K, Todd J. Making sense of mismatch negativity. Front Psychiatry. 2020;11. https://doi.org/10.3389/fpsyt.2020.00468.
37. Javitt DC, Lee M, Kantrowitz JT, Martinez A. Mismatch negativity as a biomarker of theta band oscillatory dysfunction in schizophrenia. Schizophr Res. 2018;191:51–60. https://doi.org/10.1016/j.schres.2017.06.023.
38. Rentzsch J, Shen C, Jockers-Scherübl MC, Gallinat J, Neuhaus AH. Auditory mismatch negativity and repetition suppression deficits in schizophrenia

explained by irregular computation of prediction error. *PLoS ONE*. 2015;10. https://doi.org/10.1371/journal.pone.0126775.
39. Grent-'t-Jong T, Gajwani R, Gross J, Gumley AI, Krishnadas R, Lawrie SM, et al. 40-Hz auditory steady-state responses characterize circuit dysfunctions and predict clinical outcomes in clinical high-risk for psychosis participants: a magnetoencephalography study. Biol Psychiatry. 2021;90:419–29. https://doi.org/10.1016/j.biopsych.2021.03.018.
40. Kim S, Jang SK, Kim DW, Shim M, Kim YW, Im CH, et al. Cortical volume and 40-Hz auditory-steady-state responses in patients with schizophrenia and healthy controls. NeuroImage Clin. 2019;22. https://doi.org/10.1016/j.nicl.2019.101732.
41. Koh Y, Shin KS, Kim JS, Choi JS, Kang DH, Jang JH, et al. An MEG study of alpha modulation in patients with schizophrenia and in subjects at high risk of developing psychosis. Schizophr Res. 2011;126:36–42. https://doi.org/10.1016/j.schres.2010.10.001.
42. Shin KS, Kim JS, Kim SN, Hong KS, O'Donnell BF, Chung CK, et al. Intraindividual neurophysiological variability in ultra-highrisk for psychosis and schizophrenia patients: Single-trial analysis. npj Schizophrenia. 2015;1. https://doi.org/10.1038/npjschz.2015.31.
43. Thoenes S, Oberfeld D. Meta-analysis of time perception and temporal processing in schizophrenia: differential effects on precision and accuracy. Clin Psychol Rev. 2017;54:44–64. https://doi.org/10.1016/j.cpr.2017.03.007.
44. Griskova-Bulanova I, Hubl D, Swam C, van, Dierks T, Koenig T. Early- and late-latency gamma auditory steady-state response in schizophrenia during closed eyes: does hallucination status matter? Clin Neurophysiol. 2016;127:2214–21. https://doi.org/10.1016/j.clinph.2016.02.009.
45. Oribe, Hirano N, Re Y, del E, Seidman LJ, Mesholam-Gately RI, et al. Progressive reduction of auditory evoked gamma in first episode schizophrenia but not clinical high risk individuals. Schizophr Res. 2019;208:145–52. https://doi.org/10.1016/j.schres.2019.03.025.
46. Roach BJ, Ford JM, Mathalon DH. Gamma band phase delay in schizophrenia. Biol Psychiatry Cogn Neurosci Neuroimaging. 2019;4:131–139. https://doi.org/10.1016/j.bpsc.2018.08.011.
47. Sugiyama S, Ohi K, Kuramitsu A, Takai K, Muto Y, Taniguchi T, et al. The auditory steady-state response: electrophysiological index for sensory processing dysfunction in psychiatric disorders. Front Psychiatry. 2021;12. https://doi.org/10.3389/fpsyt.2021.644541.
48. Tada M, Nagai T, Kirihara K, Koike S, Suga M, Araki T, et al. Differential alterations of auditory gamma oscillatory responses between pre-onset high-risk individuals and first-episode schizophrenia. Cereb Cortex. 2016;26:1027–35. https://doi.org/10.1093/cercor/bhu278.
49. Parker DA, Hamm JP, McDowell JE, Keedy SK, Gershon ES, Ivleva EI, et al. Auditory steady-state EEG response across the schizo-bipolar spectrum. Schizophr Res. 2019;209:218–26. https://doi.org/10.1016/j.schres.2019.04.014.
50. Hamm JP, Ethridge LE, Shapiro JR, Stevens MC, Boutros NN, Summerfelt AT, et al. Spatiotemporal and frequency domain analysis of auditory paired stimuli processing in schizophrenia and bipolar disorder with psychosis. Psychophysiology. 2012;49:522–30. https://doi.org/10.1111/j.1469-8986.2011.01327.x.
51. Zhou TH, Mueller NE, Spencer KM, Mallya SG, Lewandowski KE, Norris LA, et al. Auditory steady-state response deficits are associated with symptom severity and poor functioning in patients with psychotic disorders. Schizophr Res. 2018;201:278–86. https://doi.org/10.1016/j.schres.2018.05.027.
52. Puvvada KC, Summerfelt A, Du X, Krishna N, Kochunov P, Rowland LM, et al. Delta Vs Gamma auditory steady-state synchrony in schizophrenia. Schizophr Bull. 2018;44:378–87. https://doi.org/10.1093/schbul/sbx078.
53. Lakatos P, Schroeder CE, Leitman DI, Javitt DC. Predictive suppression of cortical excitability and its deficit in schizophrenia. J Neurosci. 2013;33:11692–702. https://doi.org/10.1523/jneurosci.0010-13.2013.
54. Shin YW, Krishnan G, Hetrick WP, Brenner CA, Shekhar A, Malloy FW, et al. Increased temporal variability of auditory event-related potentials in schizophrenia and schizotypal personality disorder. Schizophr Res. 2010;124:110–18. https://doi.org/10.1016/j.schres.2010.08.008.
55. Kirihara K, Rissling AJ, Swerdlow NR, Braff DL, Light GA. Hierarchical organization of gamma and theta oscillatory dynamics in schizophrenia. Biol Psychiatry. 2012;71:873–80. https://doi.org/10.1016/j.biopsych.2012.01.016.
56. Doege K, Jansen M, Mallikarjun P, Liddle EB, Liddle PF. How much does phase resetting contribute to event-related EEG abnormalities in schizophrenia? Neurosci Lett. 2010;481:1–5. https://doi.org/10.1016/j.neulet.2010.06.008.
57. Gomez-Pilar J, Poza J, Gómez C, Northoff G, Lubeiro A, Cea-Cañas BB, et al. Altered predictive capability of the brain network EEG model in schizophrenia during cognition. Schizophr Res. 2018;201:120–29. https://doi.org/10.1016/j.schres.2018.04.043.
58. Lundin NB, Bartolomeo LA, O'Donnell BF, Hetrick WP. Reduced electroencephalogram responses to standard and target auditory stimuli in bipolar disorder and the impact of psychotic features: analysis of event-related potentials, spectral power, and inter-trial coherence. Bipolar Disord. 2018;20:49–59. https://doi.org/10.1111/bdi.12561.
59. Stefano LAD, Schmitt LM, White SP, Mosconi MW, Sweeney JA, Ethridge LE. Developmental effects on auditory neural oscillatory synchronization abnormalities in autism spectrum disorder. Front Integr Neurosci. 2019;13. https://doi.org/10.3389/fnint.2019.00034.
60. Edgar JC, Iv CLF, Berman JI, Chudnovskaya D, Liu S, Pandey J, et al. Auditory encoding abnormalities in children with autism spectrum disorder suggest delayed development of auditory cortex. Mol Autism. 2015;6. https://doi.org/10.1186/s13229-015-0065-5.
61. Milne E. Increased intra-participant variability in children with autistic spectrum disorders: evidence from single-trial analysis of evoked EEG. Front Psychol. 2011;2. https://doi.org/10.3389/fpsyg.2011.00051.
62. Milne E, Gomez R, Giannadou A, Jones M. Atypical EEG in autism spectrum disorder: comparing a dimensional and a categorical approach. J Abnorm Psychol. 2019;128:442–52. https://doi.org/10.1037/abn0000436.
63. Port RG, Edgar JC, Ku M, Bloy L, Murray R, Blaskey L, et al. Maturation of auditory neural processes in autism spectrum disorder—a longitudinal MEG study. NeuroImage Clin. 2016;11:566–77. https://doi.org/10.1016/j.nicl.2016.03.021.
64. Noordt S, van, Wu J, Venkataraman A, Larson MJ, South M, et al. Inter-trial coherence of medial frontal theta oscillations linked to differential feedback processing in youth and young adults with autism. Res Autism Spectr Disord. 2017;37:1–10. https://doi.org/10.1016/j.rasd.2017.01.011.
65. Wang X, Wang S, Fan Y, Huang D, Zhang Y. Speech-specific categorical perception deficit in autism: an event-related potential study of lexical tone processing in Mandarin-speaking children. Sci Rep. 2017;7. https://doi.org/10.1038/srep43254.
66. Yu L, Wang S, Huang D, Wu X, Zhang Y. Role of inter-trial phase coherence in atypical auditory evoked potentials to speech and nonspeech stimuli in children with autism. Clin Neurophysiol. 2018;129:1374–82. https://doi.org/10.1016/j.clinph.2018.04.599.
67. Edgar JC, Fisk CL, Liu S, Pandey J, Herrington JD, Schultz RT, et al. Translating adult electrophysiology findings to younger patient populations: difficulty measuring 40-Hz auditory steady-state responses in typically developing children and children with autism spectrum disorder. Dev Neurosci. 2016;38:1–14. https://doi.org/10.1159/000441943.
68. Kolesnik A, Ali JB, Gliga T, Guiraud J, Charman T, Johnson MH, et al. Increased cortical reactivity to repeated tones at 8 months in infants with later ASD. Transl Psychiatry. 2019;9. https://doi.org/10.1038/s41398-019-0393-x.
69. Minkowski E. La schizophrénie. Psychopathologie des schizoides et des schizophrènes. Published online 1927.
70. Arantes-Gonçalves F, Wolman A, Bastos-Leite AJ, Northoff G. Scale for space and time experience in psychosis: converging phenomenological and psychopathological perspectives. Psychopathology. 2022;55:132–42. https://doi.org/10.1159/000519500.
71. Gonzalez-Andrade A, Lopez-Luengo B, Alvarez M, Santiago-Ramajo S. Divided attention in schizophrenia: a dual task paradigm. Am J Psychol. 2021;134:187–200. https://doi.org/10.5406/amerjpsyc.134.2.0187.
72. Martin B, Franck N, Giersch A. A reflection upon methods to explore timing in patients with schizophrenia. PsyCh J. 2019;8:82–9. https://doi.org/10.1002/pchj.268.
73. Martin AMS, Bartolomeo L, Howell J, Hetrick WP, Bolbecker AR, Breier A, et al. Auditory feature perception and auditory hallucinatory experiences in schizophrenia spectrum disorder. Eur Arch Psychiatry Clin Nuerosci. 2018;268:653–61. https://doi.org/10.1007/s00406-017-0839-1.
74. Davalos DB, Kisley MA, Freedman R. Behavioral and electrophysiological indices of temporal processing dysfunction in schizophrenia. J Neuropsychiatry Clin Neurosci. 2005;17:517–25. https://doi.org/10.1176/jnp.17.4.517.
75. Umbricht D, Krljes S. Mismatch negativity in schizophrenia: a meta-analysis. Schizophr Res. 2005;76:1–23.
76. Horacek M, Kärgel C, Scherbaum N, Müller BW. The effect of deviance predictability on mismatch negativity in schizophrenia patients. Neurosci Lett. 2016;617:76–81. https://doi.org/10.1016/j.neulet.2016.02.010.
77. Higuchi Y, Sumiyoshi T, Seo T, Miyanishi T, Kawasaki Y, Suzuki M. Mismatch negativity and cognitive performance for the prediction of psychosis in subjects with at-risk mental state. PLoS One. 2013;8. https://doi.org/10.1371/journal.pone.0054080.
78. Tateno T, Higuchi Y, Nakajima S, Sasabayashi D, Nakamura M, Ueno M, et al. Features of duration mismatch negativity around the onset of overt psychotic disorders: a longitudinal study. Cereb Cortex. 2021;31:2416–24. https://doi.org/10.1093/cercor/bhaa364.
79. Lechner S, Northoff G. Prolonged intrinsic neural timescales dissociate from reduced phase coherence in schizophrenia. Brain Sci. 2023;13:695.
80. Nordgaard J, Madeira L, Shinn AK, Cermolacce M. Editorial: Psychiatric diagnoses: current state and methodological issues. Front Psychiatry. 2023;14:1194755.

81. Sandsten KE, Wainio-Theberge S, Nordgaard J, Kjaer TW, Northoff G, Parnas J. Relating self-disorders to neurocognitive and psychopathological measures in first-episode schizophrenia. Early Intervention Psych. 2022;16:1202–10.
82. Northoff, Dr Georg. Neurowaves. 1st ed. McGill-Queen's University Press; 2023.
83. Northoff G, Hirjak D. Spatiotemporal Psychopathology – An integrated brain-mind approach and catatonia. Schizophrenia Research. 2024;263:151–9.
84. Northoff G, Hirjak D. Integrating subjective and objective—spatiotemporal approach to psychiatric disorders. Mol Psychiatry. 2023. 17 May 2023. https://doi.org/10.1038/s41380-023-02100-4.
85. Stanghellini G, Ballerini M, Presenza S, Mancini M, Raballo A, Blasi S, et al. Psychopathology of Lived Time: Abnormal Time Experience in Persons With Schizophrenia. SCHBUL. 2015:sbv052.
86. Stanghellini G, Fernandez AV, Ballerini M, Blasi S, Belfiore E, Cutting J, et al. Abnormal Space Experiences in Persons With Schizophrenia: An Empirical Qualitative Study. Schizophrenia Bulletin. 2020;46:530–9.
87. Hirjak D, Brandt GA, Peretzke R, Fritze S, Meyer-Lindenberg A, Maier-Hein KH, et al. Microstructural white matter biomarkers of symptom severity and therapy outcome in catatonia: Rationale, study design and preliminary clinical data of the whiteCAT study. Schizophrenia Research. 2024;263:160–8.
88. Sterzer P, Voss M, Schlagenhauf F, Heinz A. Decision-making in schizophrenia: A predictive-coding perspective. NeuroImage. 2019;190:133–43.
89. Stephan KE, Diaconescu AO, Iglesias S. Bayesian inference, dysconnectivity and neuromodulation in schizophrenia. Brain. 2016;139:1874–6.
90. Hirjak D, Northoff G. Navigating the evolving landscape of catatonia research. Schizophrenia Research. 2024;263:1–5.
91. Albrecht MA, Waltz JA, Cavanagh JF, Frank MJ, Gold JM. Increased conflict-induced slowing, but no differences in conflict-induced positive or negative prediction error learning in patients with schizophrenia. Neuropsychologia. 2019;123:131–40. https://doi.org/10.1016/j.neuropsychologia.2018.04.031.
92. Choueiry J, Blais CM, Shah D, Smith D, Fisher D, Labelle A, et al. Combining CDP-choline and galantamine, an optimized α7 nicotinic strategy, to ameliorate sensory gating to speech stimuli in schizophrenia. Int J Psychophysiol. 2019;145:70–82. https://doi.org/10.1016/j.ijpsycho.2019.02.005.
93. Jurcak V, Tsuzuki D, Dan I. 10/20, 10/10, and 10/5 systems revisited: their validity as relative head-surface-based positioning systems. NeuroImage. 2007;34:1600–11. https://doi.org/10.1016/j.neuroimage.2006.09.024.
94. Jaworska N, Somma ED, Blondeau C, Tessier P, Norris S, Fusee W, et al. Auditory P3 in antidepressant pharmacotherapy treatment responders, non-responders and controls. Eur Neuropsychopharmacol. 2013;23:1561–69. https://doi.org/10.1016/j.euroneuro.2013.03.003.
95. Wolff A, Salle S de la, Sorgini A, Lynn E, Blier P, et al. Atypical temporal dynamics of resting-state shapes stimulus-evoked activity in depression—an EEG study on rest–stimulus interaction. Front Psychiatry. 2019;10. https://doi.org/10.3389/fpsyt.2019.00719.
96. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis.; 2004:9–21. http://www.sccn.ucsd.edu/eeglab/.
97. Bigdely-Shamlo N, Mullen T, Kothe C, Su KM, Robbins KA. The PREP pipeline: standardized preprocessing for large-scale EEG analysis. Front Neuroinform. 2015;9:1–19. https://doi.org/10.3389/fninf.2015.00016.
98. Winkler I, Haufe S, Tangermann M. Automatic classification of artifactual ICA-components for artefact removal in EEG signals. Behav Brain Funct. 2011;7. https://doi.org/10.1186/1744-9081-7-30.
99. Winkler I, Brandl S, Horn F, Waldburger E, Allefeld C, Tangermann M. Robust artifactual independent component classification for BCI practitioners. J Neural Eng. 2014;11. https://doi.org/10.1088/1741-2560/11/3/035013.
100. Carvalhaes C, de Barros JA. The surface Laplacian technique in EEG: theory and methods. Int J Psychophysiol. 2015;97:174–88. https://doi.org/10.1016/j.ijpsycho.2015.04.023.
101. Einevoll, Destexhe GT, Diesmann A, Grün M, Jirsa S, Kamps V, et al. The scientific case for brain simulations. Neuron. 2019;102:735–44. https://doi.org/10.1016/j.neuron.2019.03.027.
102. Aghababaiyan K. Improving performance of neurons by adding colour noise. IET Nanobiotechnol. 2020;14:433–39. https://doi.org/10.1049/iet-nbt.2019.0280.
103. Baker DH, Richard B. Dynamic properties of internal noise probed by modulating binocular rivalry. PLoS Comput Biol. 2019;15. https://doi.org/10.1371/journal.pcbi.1007071.
104. Erra RG, Arbotto M, Schurger A. An integration-to-bound model of decision-making that accounts for the spectral properties of neural data. Sci Rep. 2019;9. https://doi.org/10.1038/s41598-019-44197-0.
105. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple. J R Stat Soc Ser B (Methodol).1995;57:289–300.

AUTHOR CONTRIBUTIONS

AW and GN conceived of the presented idea. AW did the data analysis and performed the computations and modeling. GN wrote the sections regarding entrainment and clinical aspects, while AW wrote the methods and results. Both AW and GN wrote the introduction and discussion. Both authors discussed the results and contributed to the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

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