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Temporal imprecision and phase instability in schizophrenia resting state EEG

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ABSTRACT

Schizophrenia is characterized by temporal imprecision and irregularities on neuronal, psychological cognitive, and behavioral levels which are usually tested during task-related activity. This leaves open whether analogous temporal imprecision and irregularities can already be observed in the brain's spontaneous activity as measured during the resting state; this is the goal of our study. Building on recent task-related data, we, using EEG, aimed to investigate the temporal precision and regularity of phase coherence over time in healthy, schizophrenia, and bipolar disorder participants. To this end, we developed a novel methodology, nominal frequency phase stability (NFPS), that allows to measure stability over phase angles in selected frequencies. By applying sample entropy quantification to the time-series of the nominal frequency phase angle time series, we found increased irregularities in theta activity over a frontocentral electrode in schizophrenia but not in bipolar disorder. We therefore assume that temporal imprecision and irregularity already occur in the brain's spontaneous activity in schizophrenia.

1. Introduction

Schizophrenia has been described as a mental disorder that features temporal disruption on several levels, experiential (Johnson and Petzel, 1971; Stanghellini et al., 2016; Vogel et al., 2019; Arantes-Gonçalves et al., 2021), psychological-cognitive (Thoenes and Oberfeld, 2017; Giersch et al., 2015; Giersch et al., 2016) and neural (Andreasen et al., 1998; Wolff et al., 2022) Experiments investigating temporal disturbances mostly focus on the several-second time range. However, a few studies suggest that temporal deficits are already present in the millisecond range (Giersch et al., 2015; Giersch et al., 2016; Spencer et al., 2004; Carroll et al., 2009). Schizophrenia patients have been reported to have difficulties discerning the temporal order of separate events in an explicit way, i.e., reporting that they consciously perceive two events as separate in time – this can be observed for stimulus onset asynchronies down to 8 ms (Giersch et al., 2015; Giersch et al., 2016; Martin et al., 2014; Giersch and Mishara, 2017). The exact neuronal basis of such psychological-cognitive deficits in the millisecond range remains yet unclear, though.

Several EEG studies report abnormal timing in schizophrenia in both amplitude and phase during task-related activity. A recent study by Karanikolaou et al. (Karanikolaou et al., 2022) observed millisecond delays in the amplitude during a cognitive task in schizophrenia (Karanikolaou et al., 2022). Analogous millisecond delays in both amplitude and phase (e.g., intertrial phase coherence/ITPC) have been observed by Wolff and colleagues (Wolff et al., 2022) during an auditory oddball task. This is well in line with the observation of ITPC deficits in schizophrenia in various frequencies including delta (Lakatos et al., 2013), theta (Shin et al., 2015), alpha (Shin et al., 2015; Koh et al., 2011) and gamma bands (Sun et al., 2013) in a variety of paradigms.

Abbreviations: NFPS, Nominal frequency phase stability; SZ, Schiophrenia; BP, Bipolar disorder; HC, Healthy Controls; ITPC, Intertrial phase coherence; SNR, Signal-to-noise ratio; ERP, Event-related potential.

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Whether these timing changes in the phase are specific for schizophrenia or also occur in other disorders like Bipolar Disorder remains yet unclear (see a meta-analysis by (Jefsen et al., 2022).

Are these timing deficits in phase-related processes specific to task states-related activity? A novel direction in research of phase stability challenges this assumption by showing that phase processes are already altered in the resting state of brains of schizophrenia patients. Koshiyama and colleagues (Koshiyama et al., 2021) use a method developed by Sanders (Sanders, 2019) that measures stability in the phase in the resting state. Their "phase discontinuity index" was used to assess alpha and theta phase discontinuities in several cortical networks of schizophrenia during rest. However, one shortcoming of this method is that it introduces temporal smoothing by comparing continuity in five-second segments which does not allow for probing in the millisecond range reported in the psychological-cognitive literature (Giersch et al., 2015).

The goal of our paper is to measure phase stability, that is, phase variance in the millisecond range of the resting state of schizophrenia compared to both bipolar disorder and healthy subjects. Given the previous findings of timing deficits on both psychological-cognitive and neuronal levels, we assumed that the phase-related processes are more variable and thus unstable in schizophrenia and thus more disordered over time in the millisecond range compared to those in bipolar and healthy participants.

For that purpose, we introduce a novel method, "nominal frequency phase stability" (NFPS). The NFPS can be applied to the resting state EEG and allows for investigation of phase processes on the millisecond timescale. As the name suggests, NFPS measures the phase stability for a specific nominal frequency (for a related frequency stability method in oscillators see Li et al., 2014; Li et al., 2019). The procedure to obtain NFPS is detailed in Fig. 1. In a first step, the continuous recording is first filtered narrowly with a phase-zero filter. The frequency between the high and low pass of the filter settings is defined as the *nominal frequency* (Fig. 1, STEP 1). For example, theta NFPS uses 5 Hz as the nominal frequency and hence filters narrowly between 4 and 6 Hz. In a next step, the phase-angle time series is obtained by extracting the imaginary part of the Hilbert transformation (Fig. 1, STEP 2). Next, all indices of the beginnings of the individual phase cycles are extracted (Fig. 1, STEP 3) which gives the length of individual phase cycles.

The underlying intuition is that each phase cycle is compared to an ideal phase cycle at a specific frequency and that if individual phase cycles of a narrow frequency band resemble that ideal phase cycle, we can speak of high phase stability. For a nominal frequency of 5 Hz, the ideal phase cycle duration is 0.2 s, longer duration of an individual cycle would mean that there is a lag, shorter would mean that there is a lead. To investigate orderliness over time, the resulting time-series of phase cycle differences (difference of duration of one phase cycle and the next) can be analyzed to investigate phase stability for a desired nominal frequency (see methods section for details).

Finally, the search for temporal irregularities in the millisecond range must be considered in the wider framework of the recently introduced novel approach to psychiatric disorders, namely spatiotemporal psychopathology (STPP) which attempts to bridge experiential and neural features of various mental illnesses (Northoff and Hirjak, 2022; Northoff and Scalabrini, 2021; Northoff and Stanghellini, 2016; Northoff et al., 2020a). Based on historical (Minkowski, 1927) and recent (Stanghellini et al., 2016; Arantes-Gonçalves et al., 2021) phenomenological contributions, schizophrenia can be characterized by temporal fragmentation and altered time experience. STPP takes temporal imprecision in the millisecond range to be the neural equivalence of these experiential features of schizophrenia. Altered spatiotemporal

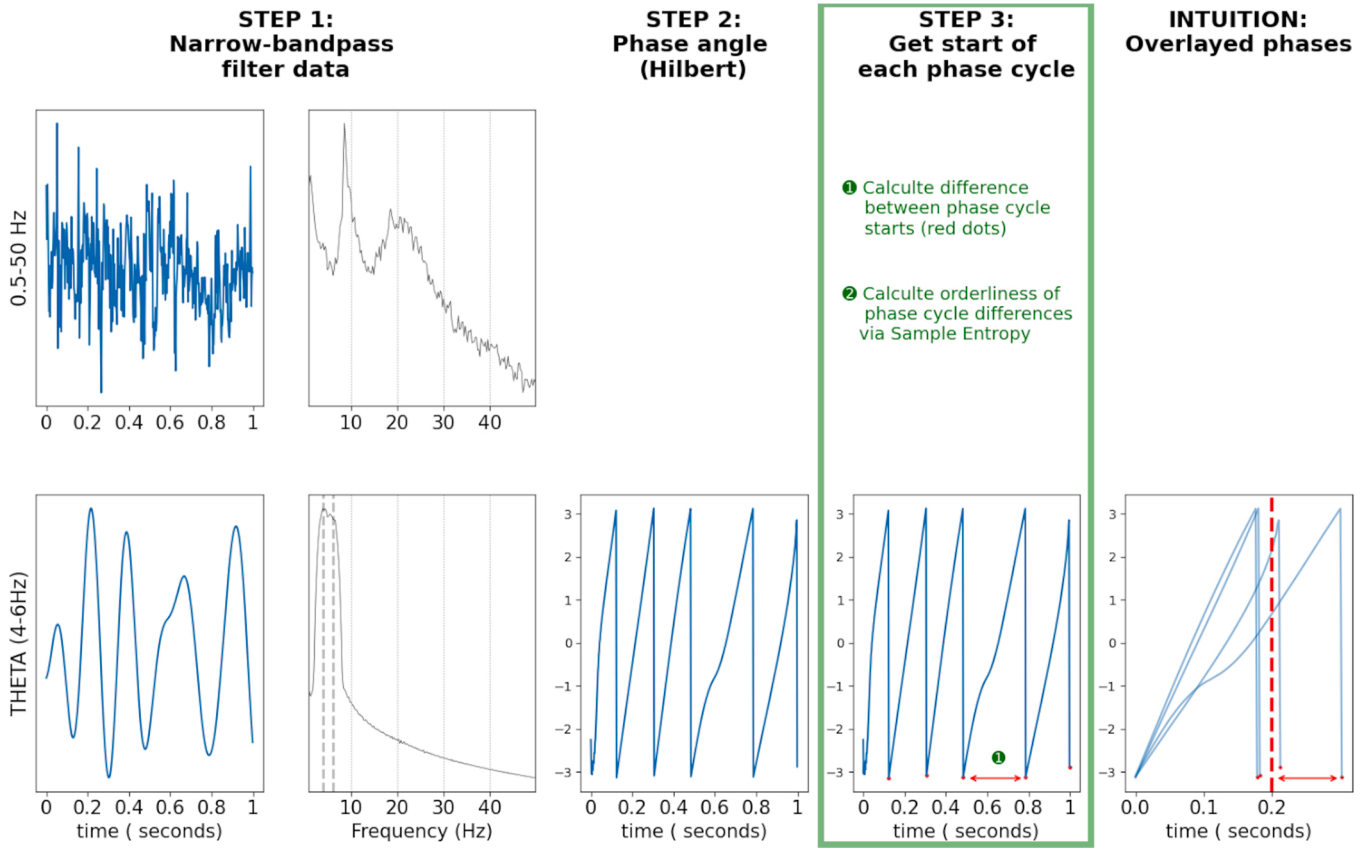

Fig. 1. Graphical representation of "nominal frequency phase stability". For a nominal frequency of 5 Hz (theta), a narrow filter of 4–6 Hz is applied to the original signal (Step 1). The phase angle time series is obtained via the Hilbert transform (Step 2). Individual phase cycles are extracted (Step 3). Individual phase cycle durations are then used for further analysis.

dynamics might then be conceived of as the basic or generative disorder (Minkowski, 1927) that underlies the plethora of symptoms in cognitive, affective, and motor domains. Furthermore, STPP gives explanatory priority to the brain's spontaneous activity suggesting that deficits are already present in the resting state dynamics of the disordered brain and are carried over to task-related deficits. We here therefore ask whether these timing deficits in phase-related processes are present already in the resting state. Moreover, by comparing schizophrenia with bipolar disorder, we probe whether timing deficits in phase-related processes are specific for schizophrenia possibly reflecting its basic or generative disorder (see also (Wolff et al., 2022)).

2. Material and methods

2.1. Subjects

For this study, 79 subjects were recruited from the Bipolar & Schizophrenia Consortium for Parsing Intermediate Phenotypes (B-SNIP 1) (Tamminga et al., 2014) containing healthy control subjects ($N = 21$; 38.76 ± 11.45 years; 11 female), Schizophrenia patients ($N = 24$; 35.88 ± 15.05 years; 7 female) and Bipolar 1 patients ($N = 34$; 38.5 ± 13.61 years; 28 female) from all consortium acquisition sites. For detailed demographic and diagnostic information refer to Supplementary Table 1 and Supplementary Table 2. Patients were not currently in acute psychotic states, and all were on medication. The sample was age balanced before the recruitment of the participants. Healthy participants were selected only if they had no history of psychiatric disorders as assessed by the DSM-IV and had no first-degree family history of mental disorders. Subjects were further excluded from the selection if their EEG recording consisted of less than 64 electrodes.

The sample of this study was initially selected as part of a larger study for biomarkers in various psychiatric disorders represented in the BSNIP consortium dataset. The inclusion criterium for this study was that subjects had recordings with 64 channels. Of the initial 736 subjects, 155 had eyes-open resting state recordings available, 79 of which were non-relative healthy control subject, schizophrenia or bipolar patients. The study was approved by Institutional Review Boards of the respective consortium site and all study participants gave written informed consent prior to participation. Our local REB approved of the data sharing (REB # 2021002). The dataset is available upon reasonable request at https://nda.nih.gov/edit_collection.html?id= 2274.

2.2. EEG recording & experimental setup

EEG was recorded from 64 Ag/AgCl electrodes at an impedance of < 5 KΩ. A Neuroscan Quick Cap (Compumedrics, El Paso, TX, USA) with mid-forehead ground and nose reference was used to obtain the recordings. Electrodes were placed on the scalp according to the 10–10 system. Signals were sampled with 1000 Hz, digitally amplified 1000 times and filtered using a high pass DC filter and a low pass filter at 2 KHz. The procedure for data collection was identical for all consortium acquisition sites and the personnel responsible for running recording sessions were specifically trained to guarantee data quality consistency across all sites. Resting-state EEG recordings were obtained from all subjects while they had they had their eyes open, and their gaze directed at a fixation cross.

2.3. Preprocessing

EEG recordings were processed for further analysis using EEGLAB (v2019) (Delorme and Makeig, 2004). The continuous data were then low- and high-pass double-zero phase Finite Impulse Response (FIR) filtered from 0.5 to 80 Hz. Channels that showed flat activity for longer than 5 s or noisy channels where the mean correlated less than 0.85% with other channels for five seconds or where the mean value over five seconds exceeded four standard deviations from the mean of all channels were removed (Bigdely-Shamlo et al., 2015). Data was re-referenced to an average of all channels and removed channels were spherically interpolated. Electrical line noise was removed via the Cleanline method (Mullen, 2012) at 60 Hz with non-overlapping sliding window length and step size of four seconds. Default smoothing factor was set to 100, default p-value of 0.01 for detection of significant sinusoids and an FFT default padding factor of 2 were used. Eye movements and blinks were reduced using ICA and Multiple Artifact Rejection Algorithm (Winkler et al., 2011; Winkler et al., 2014).

2.4. Sample entropy of nominal frequency phase stability

Phase cycles were matched over subjects based on the subject with the smallest phase cycle count (1189 cycles). Cycles allowed into the analysis were taken from the middle of the five-minute recording. One subject was excluded due to being an outlier (96 cycles).

The cycle-to-cycle differences (Fig. 1A, STEP 4) form a time series (Fig. 2; blue line) that can be used to calculate the (dis)orderliness or complexity of the stability of phase cycles, via Sample Entropy. A high sample entropy value indicates high complexity, i.e., that the orderliness of the phase cycle durations is low and highly variable over time, whereas lower values indicate more self-similar and regular signals, in this case relative orderliness and stability in the phase.

Specifically, sample entropy (Richman et al., 2000) was calculated as

$$H(x, m, r) = -\log \frac{C(m+1, r)}{C(m, r)}$$

where m is the embedding dimension (= order), r is the radius of the neighborhood set to 0.2*std(x), $C(m+1,r)$ is the number of embedded vectors of length m+ 1 having a Chebyshev distance inferior to r and $C(m,r)$ is the number of embedded vectors of length m having a Chebyshev distance inferior to r. The algorithm from the python entropy toolbox for EEG ('antropy') (https://github.com/raphaelvallat/antropy, accessed 2023/01/08) was used to calculate the individual values.

In neuroscience in general and schizophrenia research in particular, several entropy are being used, the discussion of which would certainly exceed this article (Akar et al., 2016; Bai et al., 2022). We chose sample entropy, because it is a well validated simple algorithm that has a reduced bias towards self-matching in comparison to older ways of calculating entropy in timeseries, i.e., Approximate Entropy (Richman et al., 2000; Delgado-Bonal and Marshak, 2019). At the same time, sample entropy does not run into interpretation difficulties as is the case for more complicated algorithms. It is therefore ideally suited for a first application in a new methodological tool such as NFPS. If applying multiscale variations of sample entropy on theta phase cycles, longer EEG recordings will be required for a reliable calculation, as the 1189 phase cycles might not be sufficient for complexity estimation over especially longer timescales (Costa et al., 2005).

2.5. Shuffling

The assumption of this study was that phase processes in narrow frequency bands show increased temporal disorder in the resting state of schizophrenia patients compared to healthy controls. To further investigate this hypothesis, we shuffled the order of the time series of phase angle differences, i.e. randomized there temporal order (Fig. 2, *dashed gray line*). We hypothesized that after randomization, previously existing differences between groups in terms of sample entropy calculated from the time-series would disappear.

2.6. Statistical analysis

Statistics were computed using python 3.7 and R 4.2. One-way ANOVAs were used to investigate group differences of Sample Entropy

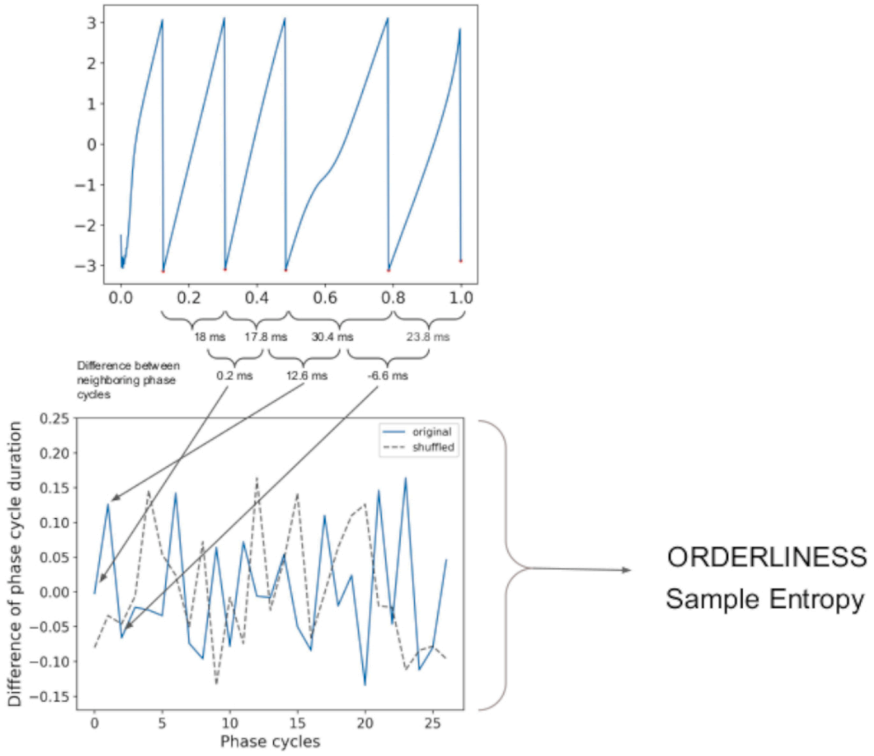

Fig. 2. Extraction of the time series of phase angle differences and its shuffling. Each point in the time-series represents the difference of one phase cycle duration and the duration of the consecutive cycle. Sample entropy is calculated over this time series and a shuffled version of it.

in the time-series of phase angle differences. Complimentarily, multiple linear regression was used to test for the same differences while accounting for age and gender differences. For testing differences of before and after shuffling we also computed a one-way ANOVA. Given previous findings (Chidharom et al., 2021) all tests were performed on frontocentral electrode FCz. Finally, sample entropy was correlated with the Positive and Negative Symptom Scale (PANSS) and Young Mania Rating Scale (YMRS). Effects of medication was controlled based on guidelines for using dose equivalencies for various type of medications (Phillips et al., 2008; Baldessarini and Baldessarinl, 1977; Ashton, 2011) (see supplementary material).

3. Results

3.1. Theta NFPS sample entropy

A one-way analysis of variance (ANOVA) of theta NFPS sample entropy showed significant differences (F=4.95, p = 0.009) between the three groups. Pairwise comparison (Fig. 3) between the groups with a Tukey post-hoc test revealed that schizophrenia patients had significantly higher sample entropy than healthy controls (mean difference=0.06, p = 0.026) as well as Bipolar Patients (0.06, p = 0.009). However, no such significant difference between healthy control subjects and bipolar patients was found (mean difference=−0.003, p = 0.99).(Fig. 4).

To check for gender and age effects, a multiple regression model of the relationship of theta NFPS Sample Entropy with the two factors as covariates was computed. Results support the results of the ANOVA and post hoc tests. Group was a significant predictor for sample entropy for the healthy versus schizophrenia (0.0598 increase from HC to SZ, p = 0.0198), as well as for the Schizophrenia versus Bipolar (0.0506 decrease from SZ to BP, p = 0.0331), but not for Healthy versus Bipolar groups (0.00163 increase from HC to BP, p = 0.895). No significant explanatory value was found for either of the group pairings for neither age (HC vs. SZ: −0.001, p = 0.282 HC vs. BP: −0.0009, p = 0.344; SZ vs. BP: −0.0009, p = 0.225), sex (HC vs. SZ: −0.0025, p = 0.92; HC vs. BP: −0.0023, p = 0.93; SZ vs. BP: −0.0119, p = 0.62) nor antipsychotic medication (see supplementary material).

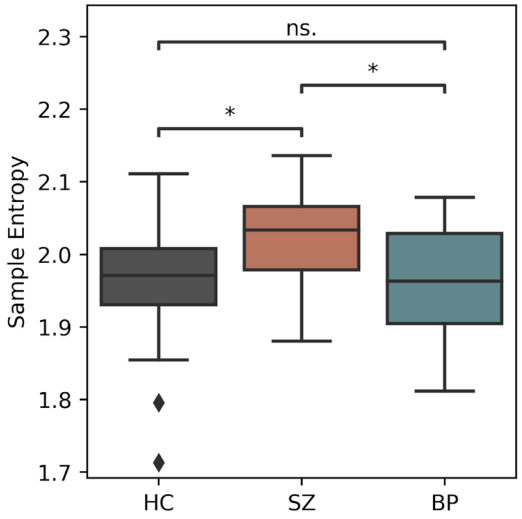

Fig. 3. Group differences in sample entropy calculated over the time-series of phase angel differences. Schizophrenia patients show increased entropy compared to both healthy controls and bipolar patients.

3.2. Differences in sample entropy in shuffled time series of phase angle differences

As expected, the differences observed in the sample entropy of the initial time-series disappeared with the shuffling (F=2.67, p = 0.076). There were no group differences in Tukey Post Tests between healthy controls and schizophrenia patients (0.041 decrease from HC to SZ,

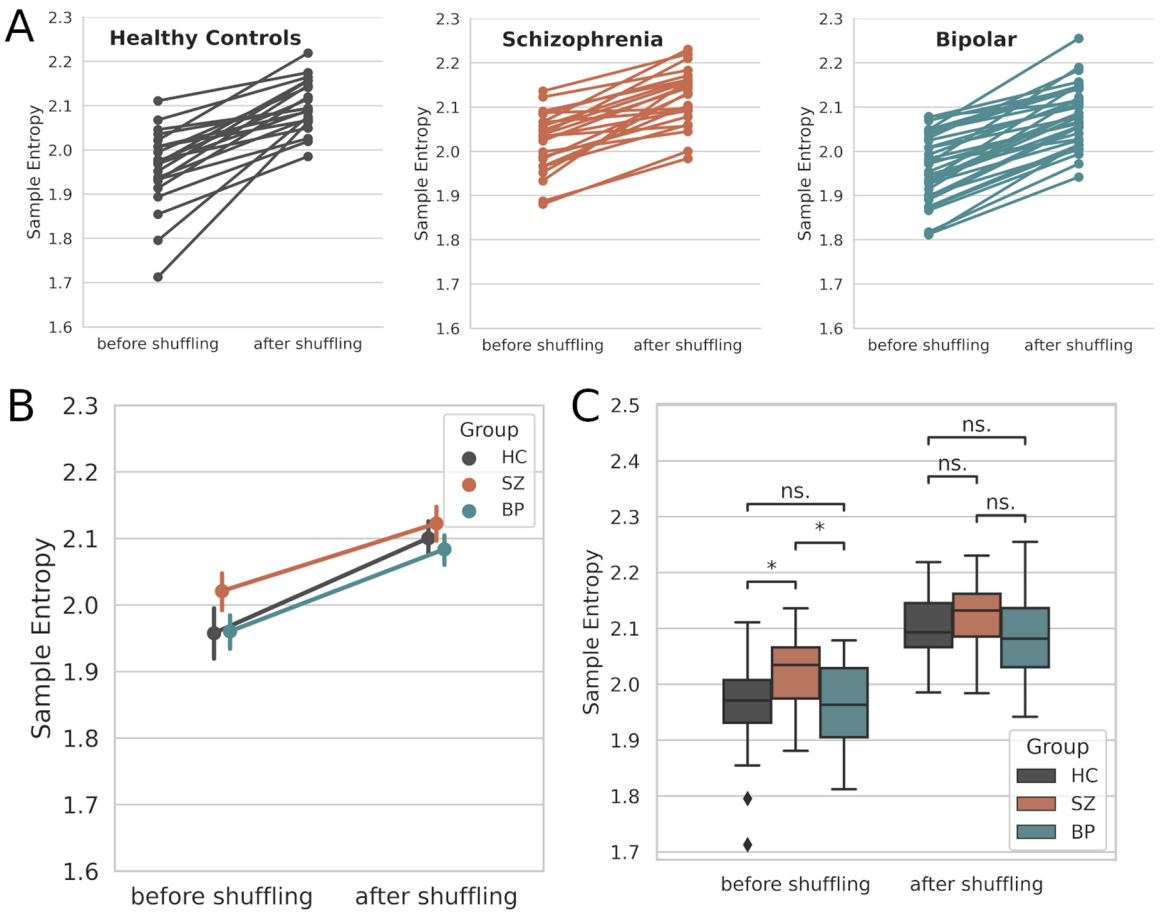

Fig. 4. Group differences in sample entropy calculated over the time-series of phase angel differences (*before shuffling*) vs the randomly shuffled time series (*after shuffling*). **A** Differences between unshuffled and shuffled sample entropy results for the separate groups. **B** Mean differences between before and after shuffling of time series for the three groups. **C** Comparison to group differences before shuffling shows that schizophrenia patients are comparable to healthy controls and bipolar patients after shuffling.

$p = 0.061$), and schizophrenia and bipolar disorder patients (0.022 decrease from BP to SZ, $p = 0.36$). Also, the relationship between healthy controls and bipolar patients remained insignificant (0.019 increase from BP to HC, $p = 0.47$). Within group differences of sample entropy before and after shuffling were present for all three groups. As expected, healthy controls and bipolar patients had a larger difference from before to after shuffling, compared to schizophrenia patients. Together, these observations indicate that phase processes in schizophrenia are already more random before shuffling; hence shuffling had a smaller effect on the before-after difference in schizophrenia compared to bipolar and healthy groups.

3.3. Correlation of sample entropy with symptom scales

We did not find a correlation with items of the "Positive and Negative Symptom Scale" nor the Young Mania Rating Scale (Supplementary Table S3) with Sample Entropy. While this may come as surprise it is in line with the basic self-disturbance in schizophrenia which also does not corelate in a direct one-to-one way with psychopathological symptoms (Sandsten et al., 2022). Analogously, we suppose that temporal imprecision with higher entropy of phase variance constitutes the basic or generative disturbance of schizophrenia.

4. Discussion

Here we first introduce a novel method, nominal frequency phase stability, that allows for measurement of resting-state phase stability in the millisecond range in narrow frequency bands. We applied this method to investigate temporal precision deficits in schizophrenia and bipolar disorder and could show that schizophrenia, but not bipolar patients had an abnormally high entropy over their individual phase cycles in the theta band. By shuffling the time series of phase cycle differences and in consequence making them more random we could show that schizophrenia subjects were already closer to the randomized time series before shuffling; shuffling had therefore less of an effect than in healthy participants and bipolar patients.

The findings obtained with this method are in line with prior reports that resting-state phase processes on longer timescales (over 5 s) are impaired in schizophrenia (Koshiyama et al., 2021; Sanders, 2019), but offer additional evidence that phase abnormalities are present already on the millisecond timescale, i.e. individual phase cycles. They also fit well with research on decreased ITPC that shows imprecision in phase resetting to incoming stimuli as well as increase in SNR and millisecond temporal fluctuations in the amplitudes of ERPs (Wolff et al., 2022; Karanikolaou et al., 2022). Specifically, one would assume that the here observed entropic phase instabilities in the resting state become accentuated during task states by preventing a coherent phase synchronization during stimulus onset, as measured by intertrial phase coherence (ITPC) which, turn, introduces temporal imprecision in the amplitude. However, future studies linking resting state phase instability to ITPC and amplitude in task states are necessary to support our assumption. In a similar way, we have recently reported that changes in temporal dynamics in the resting state translate to deficits in basic stimulus processing, by showing that intrinsic neural timescales (INT)

during rest are shifted from shorter (segregation) to longer (integration) INT in schizophrenia and that this prolongation is related to deficits in ITPC in schizophrenia (Lechner and Northoff, 2023).

NFPS has the potential to serve as deeper explanatory level upon which other common phase-based biomarkers of schizophrenia might be explained. Several task-based biomarkers such as event-related potentials (Karanikolaou et al., 2022; Jeon and Polich, 2003), signal-to-noise ratio and especially phase-based measures like intertrial phase coherence (Wolff et al., 2022) might ultimately be linked to brain-intrinsic phase instabilities. This might further inform currently prominent theories about schizophrenia. For example, one of the leading theories about what causes the various symptoms is the disconnection hypothesis (Schmitt et al., 2011; Friston and Frith, 1995). A possible future application of NFPS is to investigate the relationship between basic disturbances in phase processes and functional connectivity. In EEG research, connectivity is primarily measured via phase synchronized activity over distant portions of the cortex via the phase lag index or related measures (Olejarczyk and Jernajczyk, 2017). Changes in the orderliness of phase cycles within specific frequencies in single electrodes could hence serve as a good explanatory variable for elucidating how disconnection occurs in the brains of schizophrenia patients.

Finally, our results add to the mounting evidence that schizophrenia is a mental disorder that may primarily be traced to deficits in temporal precision. If timing is indeed impaired on all three levels, phenomenological (Stanghellini et al., 2016; Arantes-Gonçalves et al., 2021), psychological (Thoenes and Oberfeld, 2017; Giersch et al., 2015; Giersch et al., 2016; Martin et al., 2014; Martin et al., 2018; Martin et al., 2017) and neurological (Wolff et al., 2022; Karanikolaou et al., 2022) can one speak of a fundamental disturbance in schizophrenia? Impaired cognitive processes like working memory, attention, executive function and symptoms like delusion, hallucinations and thought disorders might then be conceived of as secondary consequences of this most fundamental basic temporal disturbance in the millisecond range observed in schizophrenia. Recent findings have demonstrated that basic self-disturbances as measured by the examination of anomalous self-experience (EASE), do not show a correlation with measures of cognitive deficits and items from the PANSS subscales, although being highly predictive for schizophrenia diagnosis (Sandsten et al., 2022). We assume the temporal disorder in schizophrenia to be a basic mechanism similar to the self-disturbance and interpret the lack of correlation with general symptoms with our measure in this light. Specifically, we assume temporal imprecision as a basic generative disturbance in schizophrenia which operating on the micro-level of milliseconds does not stand in direct relationship with psychopathological symptoms on the macro level although underlying them in general. This concept of temporal imprecision as a basic generative disturbance of schizophrenia is not only supported by the here reported findings in the millisecond range in the resting state spontaneous phase variation but also by increased variability during the task-related activity in both phase (Lechner and Northoff, 2023; Wolff et al., 2022) and amplitude (Karanikolaou et al., 2022). Finally, we want to mention that temporal imprecision as basic disturbance of schizophrenia is well in line with his original formulation by Minkowski (Minkowski, 1927) who regarded a "lack of vital contact with reality" as the basic generative disturbance in schizophrenia. More generally, this is well in line with the assumption of abnormal spatiotemporal organization on both neural and mental levels o schizophrenia as reflected in the concept of Spatiotemporal Psychopathology (Northoff and Hirjak, 2022; Northoff and Scalabrini, 2021; Northoff et al., 2020a; Northoff and Duncan, 2016; Northoff et al., 2020b).

4.1. Methodological limitations

We here focused only on resting state while leaving out task states. While NFPS allows for investigation of phase processes in the resting state, its application to task states is not as clear. The fact that it is computed over the entirety of the time series makes a distinction between different stimuli impossible and especially for the entropy could theoretically introduce sequence effects. Yet another issue that remains unclear is how the method fares with phase cycles that are not clearly defined, such as in low frequencies like delta and the slow cortical range. Further testing is needed to validate the accuracy with which NFPS can be used in those slower frequency ranges.

4.2. Conclusion

We show that temporal imprecision and irregularity of phase variance in schizophrenia already occur in the spontaneous activity, i.e., its resting state as assessed by a novel method, "nominal frequency phase stability". The findings pertain specifically to schizophrenia, as there was no significant difference between bipolar disorder patients and healthy controls. These results lend further support to the mounting evidence of temporal imprecision and irregularity in schizophrenia with our findings showing them to be present already in the resting state.

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Declaration of Competing Interest

none.

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None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ajp.2023.103654.

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