The Self and Its Prolonged Intrinsic Neural Timescale in Schizophrenia

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Schizophrenia (SCZ) can be characterized as a basic self-disorder that is featured by abnormal temporal integration on phenomenological (experience) and psychological (information processing) levels. Temporal integration on the neuronal level can be measured by the brain's intrinsic neural timescale using the auto-correlation window (ACW) and power-law exponent (PLE). Our goal was to relate intrinsic neural timescales (ACW, PLE), as a proxy of temporal integration on the neuronal level, to temporal integration related to self-disorder on psychological (Enfacement illusion task in electroencephalography) and phenomenological (Examination of Anomalous Self-Experience [EASE]) levels. SCZ participants exhibited prolonged ACW and higher PLE during the self-referential task (Enfacement illusion), but not during the non-self-referential task (auditory oddball). The degree of ACW/PLE change during task relative to rest was significantly reduced in self-referential task in SCZ. A moderation model showed that low and high ACW/PLE exerted differential impact on the relationship of self-disorder (EASE) and negative symptoms (PANSS). In sum, we demonstrate abnormal prolongation in intrinsic neural timescale during self-reference in SCZ including its relation to basic self-disorder and negative symptoms. Our results point to abnormal relation of self and temporal integration at the core of SCZ constituting a "common currency" of neuronal, psychological, and phenomenological levels.

Key words: self-disorder/intrinsic neural timescale/auto-correlation window/power law exponent/EEG/rest-task modulation/enfacement illusion/EASE

Introduction

Temporal Integration I—"Common Currency" of Phenomenological, Psychological, and Neuronal Levels

The disturbance of the basic self (a structural instability of the first person-perspective) has been proposed to constitute a core trait-phenomenological feature of schizophrenia (SCZ).[1–3] Basic self-disorder can be assessed with a well-established phenomenological instrument, ie, the EASE-scale (Examination of Anomalous Self-Experience).[4] One key aspect of basic self-disorder is abnormal temporal integration (see below for definition) on a phenomenological level (time experience).[5–8] Abnormal temporal integration is also described on the psychological (time perception) level[6,9–15] as related to a discontinuous sense of self.[2,5,8,16–18] The neuronal correlates of abnormal temporal integration as a key aspect of basic self-disorder remain unknown.

We understand temporal integration in a wide way, as connecting different time points by pooling and summing them (see also refs. [19,20]). Connection between different time points can occur on different levels, phenomenological, psychological, and neuronal levels, thus providing their "common currency."[21]

On the phenomenological level, different time points are integrated into experience of time as it is manifest in the "stream of consciousness"[22–24] and "inner time consciousness."[5–8] Psychologically, different stimuli at different time points are integrated into perception when we perceive a coherent scene or a melody composed of stimuli occurring at different time points; the distinction of psychological and phenomenological levels is relative

and operational (rather than absolute and ontological) as both provide different methods to access related or even the same temporal integration. Finally, neural activities at different time points are also pooled, summed, and integrated, which can be measured by the brain's intrinsic neural timescale.[20]

Temporal Integration II—The Brain's Intrinsic Neural Timescale

Information processing in the brain is shaped by the spontaneous activity's spatiotemporal dynamics constituting an intricate temporal structure. Such temporal structure is manifest in what has been described as "intrinsic neural timescale."[25–28] The intrinsic neural timescale provides temporal windows within which different stimuli can be integrated and processed together (temporal integration on the psychological level).[20,29] The intrinsic neural timescale can be investigated by calculating the autocorrelation window (ACW). The ACW measures repeating and correlating patterns in a signal, enabling us to test the relationship, eg, correlation in neural activity patterns across different points in time.[25] It has been applied at cellular[25,30,31] and system levels[32–34] measuring temporal integration on the neuronal level.[20,25–27,29]

Longer ACW is related to slow frequencies while shorter ACW is modulated by stronger power in faster frequencies.[29] The balance in power between slow and fast frequencies can be measured in frequency characteristics of periodic oscillations in electroencephalography (EEG) calculating power-law exponent (PLE) as an index if arrhythmic scale-free ("1/f noise") brain activity.[35–40] Like ACW in the time domain, the PLE can be conceived an index of temporal integration albeit in the frequency domain, ie, it measures the degree of integration in the power of different frequencies.[26,27,29,38]

Healthy subject studies in functional magnetic resonance imaging (fMRI)[37] and EEG[32] show that inter-individual variation in intrinsic neural timescales (ACW, PLE) explains a high degree of inter-individual variation in self-consciousness (see refs. [41–43]). These data suggest that temporal integration on the neuronal level, ie, ACW and PLE, is related to temporal integration on psychological and phenomenological levels of self—this provides the background of our study.

Temporal Integration III—"Common Currency" of Neuronal, Psychological, and Phenomenological Changes of Self in SCZ

Several studies using fMRI[44–47] or EEG[9–13,48–53] observed changes during self-referential stimuli in SCZ; ie, reduced activity in cortical midline structures (medial prefrontal cortex and posterior cingulate cortex) (fMRI)[44,46] and decreased amplitudes in event-related potentials.[49–53]

A multisensory self-recognition task (Enfacement illusion)[54,55] found behavioral deficits in SCZ[56,57] possibly related to deficits in temporal integration on the psychological level, the neuronal mechanisms of which remain unclear.

SCZ has been characterized by decreases in faster frequency power (gamma,[58–60] alpha,[61,62] and theta[63–65]). Given reduced fast frequency power in SCZ as well as the dependence of ACW and PLE on slow-fast frequency power balance, one would expect prolonged ACW and elevated PLE in SCZ on the neuronal level. Moreover, findings in healthy subjects (above) suggest that altered ACW and PLE on the neuronal level could be related to changes in temporal integration of self on psychological and phenomenological levels.

Aims, Hypotheses, and Experimental Design

The goal of our study is to investigate the brain's temporal integration on the neuronal level by probing intrinsic neural timescale for the first time in SCZ (see[33,66] for autism) including its relation to psychological and phenomenological changes of self. We hypothesized that temporal integration is abnormal in the self of SCZ providing the missing link or "common currency"[21] of phenomenological, psychological, and neuronal levels. To that end, we applied measures of temporal integration on all 3 levels: phenomenological, psychological, and neuronal.

Our first specific aim consisted in testing temporal integration on the neuronal level by measuring intrinsic neural timescales in EEG using ACW and PLE (as calculated over specifically the fractal rather than oscillatory component of the power spectrum; see Methods and Materials); ACW and PLE were measured during task states as well as in their relative difference to rest, ie, "rest-task modulation."[40,67] Based on the findings on self-referential processing,[9–13,48–53] we hypothesized that SCZ participants would show (1) prolonged ACW and abnormally high PLE and (2) reduced rest-task ACW/PLE difference during specifically the self-referential task (but not non-self-referential task).

Testing temporal integration on the psychological level during EEG, we applied a self-referential task (Enfacement illusion)[54,55,57] and a non-self-referential task (auditory oddball paradigm)[68–70]: presenting morphed pictures of one's own and another person's face in a temporal sequence requires subjects to temporally integrate (on the psychological level) the different pictures' time points under the self or, alternatively, segregate them when attributing them to the other person's face, ie, non-self.

Our second specific aim was to investigate the relation of neuronal and psychological abnormalities of self to psychopathological and phenomenological changes, ie, the basic self-disorder.[9–13,48–53] Applying a moderation model,

we hypothesized that temporal integration on the neuronal level (rest-task modulation of ACW and PLE) during a task requiring temporal integration on the psychological level (Enfacement task) would moderate the impact of the phenomenological level (basic self-disorder) on psychopathological symptoms (like negative symptoms).

Methods and Materials

Subjects

Thirty-seven patients diagnosed with SCZ (mean age 22.11 years, 14 males) and 36 matched healthy controls (HC) (mean age 24.06 years, 14 males) were included in the study. The patients were recruited from 3 psychiatric outpatient clinics in Region Zealand in Denmark between May 2017 and February 2019. The majority of patients were under treatment with atypical antipsychotics in a stable post-acute symptomatic phase of their illness (see supplementary table S1; see supplementary material for inclusion and exclusion criteria).

Written consent was obtained from all participants after having received an oral and written description of the paradigms in the study. The study was approved by the regional data agency and ethics committee in Region Zealand, Denmark and in line with the ethical standards of the Declaration of Helsinki 2013.

Clinical Evaluation

The psychiatric evaluation was performed by K.E.S., a senior resident in psychiatry, who was reliability tested and trained by the founder of the EASE scale (J.P.) and a senior EASE expert (J.N.). All participants were evaluated with a comprehensive psychopathological examination, including Assessment of Positive and Negative Syndrome Scale (PANSS),[71] the Operational Criteria Checklist for Psychotic Illness and Affective Illness (OPCRIT),[72] the perceptual domain of the Bonn-scale (BSABS),[73] and Examination of Anomalous Self Experience (EASE), that targets different domains of self-disorder (see supplementary material).[4] A focused neurological examination was performed for vision, hearing, and sensation.

EEG—Rest and Task

Resting State. EEG was recorded with participants lying down with eyes open for 5 minutes. Participants were asked to fix their gaze at a particular point on the wall while relaxing. EEG was recorded continuously during the following paradigms:

Enfacement Illusion. The task consisted of 3 blocks of 4 facial recognition tasks. The tasks comprised pictures of the participants face and/or other faces, being dynamically morphed into each other on a screen. Each block had 4 morphing conditions: self-other, other-self, other1-other2, and other2-other1 (in randomized order). For further details, see ref. [56].

Oddball Paradigm. The paradigm consisted of 1000 tones at 1000 Hz, 60dB, presented with an inter-stimulus interval of 500 ms; 900 tones (90%) were standard tones of 50 ms duration and 100 (10%) were deviants of 100 ms duration. All tones were presented in a randomized order binaurally through headphones, while the participants watched a mute video on a screen.

EEG Acquisition and Analysis

Recording. The EEG recording system used was a Nicolet Nervus, version 5.94.1.534 with a V44 amplifying system and a sampling rate at 250 Hz. The Ag/AgCl electrodes were distributed with a WaveGuard cap-system comprising 20 electrodes applied according to the 10/20 system. Six additional low-row electrodes were used with eye-flick transducer, 2 ECG-electrodes, and a built-in NONN pulse oximetry.

Preprocessing. EEG preprocessing of the data was performed with Harvard Automated Preprocessing Pipeline for EEG (HAPPE).[74] Data were filtered with a 1-Hz FIR highpass filter in EEGLAB.[75] Because the Cleanline procedure traditionally used in the HAPPE pipeline failed to adequately suppress line noise in our data, we replaced this step with notch filtering at 50 and 100 Hz. Bad channels were rejected using HAPPE's normalized log-power heuristic, and wavelet-thresholded ICA was performed to prepare data for regular ICA decomposition. Artifactual ICA components were rejected using MARA.[76] Data were then segmented into 2-second non-overlapping epochs, and bad channels and segments were repaired using FASTER.[77] To preserve the continuity of time series for subsequent analyses, no segments were rejected at this step. Finally, data were re-referenced to a common average reference.

Calculation of ACW. The ACW was calculated according to the methods of Honey et al.[29] Autocorrelation was calculated using windows of 20-second length with an overlap of 50%. The maximum lag was set to 0.5 seconds, given that we have previously established that the ACW values agree for different maximum lag values (ranged from 0.1 to 1 seconds) (Wolff et al).[32] The full-width-half-maximum of the main lobe of each of the autocorrelation functions was then computed for each epoch. ACW was estimated as the average of these values over all the epochs for each electrode and condition. ACW values represent the extent of the periodicity of the EEG signal, whereby longer ACWs can be interpreted as greater stability of the signal over time. The length of the ACW can be seen, therefore, as an index that summarizes the degree of regularity of a signal, with longer ACW associated with more a regular EEG signal.

Calculation of PLE.   The PLE was calculated on the fractal (rather than oscillatory) component of the power spectrum (see supplementary material for details).

Calculation of Rest-Task Differences (ACW, PLE).   See supplementary material for details.

Statistical Analysis

Differences in ACW and PLE between SCZ and HC were assessed using cluster-based permutation testing (FDR-correction)[78] implemented in the Fieldtrip toolbox.[79] The Wilcoxon rank-sum statistic was used for channel-level statistics, and neighboring electrodes were determined using triangulation. For the moderation model[80] testing for correlation of ACW/PLE with the interaction between psychopathological components (from principal component analysis [PCA]), the mean values of task-related ACW and PLE (for Enfacement illusion) all electrodes were used. For each PCA component and for each neural variable, we fit a linear model with the neural variable of interest plus its interactions with the other components as independent variables. For example, for component 1 and ACW, the model included terms for ACW plus its interactions with component 2, component 3, and the 3-way interaction.

Results

Phenomenological, Psychopathological, and Psychological Levels—Relation of EASE, PANSS, and Enfacement Illusion

The 5 domains of EASE as well as PANSS general, positive, and negative were as expected significantly higher in the SCZ group compared with HC (see supplementary table S2). In order to test for the relationship of self-disorder to positive and negative symptoms, we conducted PCA. The analysis of psychopathological symptoms yielded 3 components

(table 1). The first component explained 48% of the variance and represented mainly the EASE variables, with contribution from the Bonn scale (self-component). The second component loaded strongly on the PANSS negative score, with contribution from PANSS general and negative correlation with EASE domain 5 (negative symptom component). The third component loaded strongly on PANSS positive symptoms, with some contribution from the EASE domain 5 and negative contribution from EASE domain 4 (positive symptom component).

We found a weak but significant correlation between the total EASE score and self-recognition in the self-other direction ($r = .25$; $P = .03$) among all participants, supporting the relationship of the self-disorder on the phenomenological level to changes in self on the psychological level. Within the SCZ group separately, there was a nonsignificant weak negative correlation ($r = −.25$; $P = .16$).

Neuronal and Psychological Levels—Intrinsic Neural Timescale in Task and Task-Rest EEG

We observed significantly longer ACW in the Enfacement illusion task in SCZ compared with HC ($P = .03$) as obtained by cluster-based permutation that corresponds to FDR[78,79] (which holds for all the following statistical values of ACW and PLE) (figure 1a). The PLE showed significant group difference during the Enfacement illusion: Schizophrenia (SCH) exhibited higher PLE than HC ($P = .03$) meaning that the slope was steeper as shifted toward slower frequencies in SCH (reflecting higher regularity with more long-range correlation in arrythmic fluctuations) (figure 1b). In contrast, no differences in ACW and PLE were obtained in the non-self-referential auditory oddball task (see supplementary figure S1 and table S3.1).

Next, given the known involvement of the resting state in self-referential task activity,[32,37,41–43] we calculated the relative

Table 1. Component Weights From the Principal Component Analysis of Psychopathological Scales[a]

	Component 1	Component 2	Component 3
EASE domain 1	0.406283319	−0.09740349	−0.16122152
EASE domain 2	0.435772802	0.058453723	−0.05144734
EASE domain 3	0.391909064	0.068597697	−0.17367412
EASE domain 4	0.317294974	0.026237335	−0.46153488
EASE domain 5	0.289602831	0.419820488	0.404926189
Perceptual domain (Bonn)	0.414047859	0.063385769	0.105968483
PANSS Positive	0.208911823	0.211443414	0.740784151
PANSS Negative	0.067811038	0.734997141	0.036286068
PANSS General	0.295328966	0.465301588	−0.05395621
Explained variance	48.4%	16.8%	13.0%

Note: EASE, Examination of Anomalous Self-Experience.
[a]Since all variables were *z*-scored before being entered into the analysis, the weights are directly comparable between scales. Variance explained by each component is included at the bottom of the table.
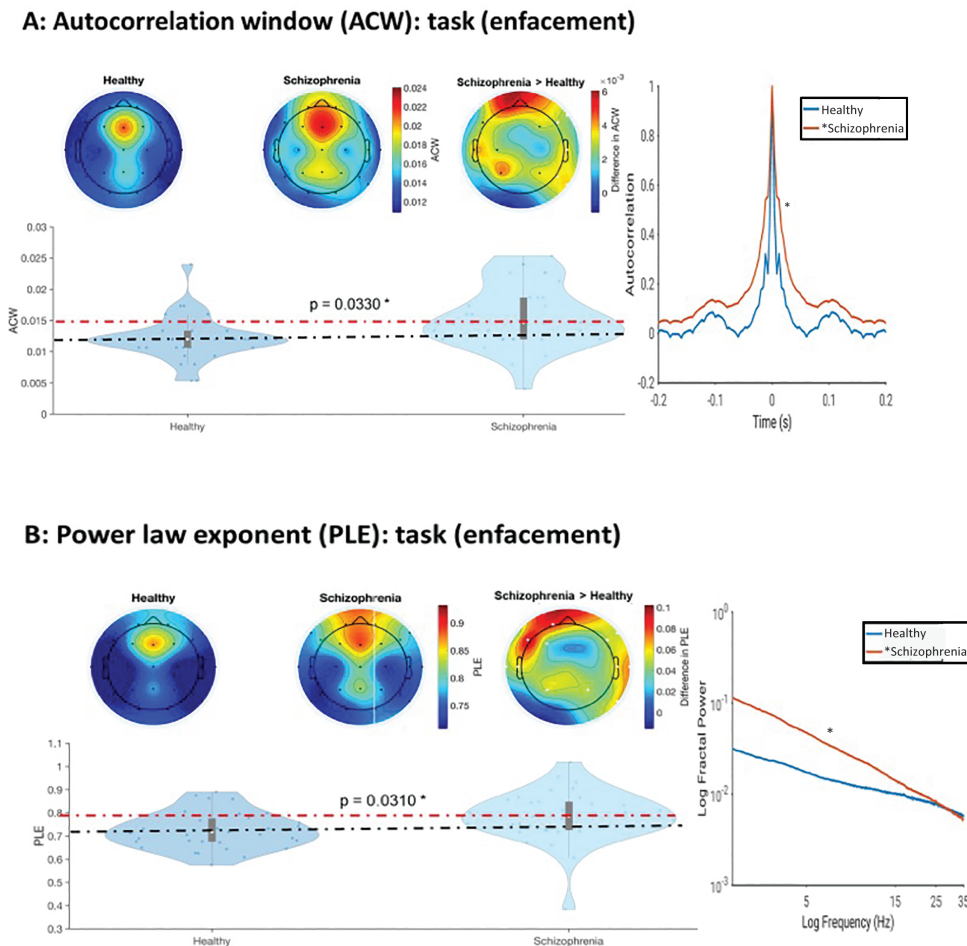
Fig. 1. (A) Altered autocorrelation window (ACW) and (B) power-law exponent (PLE) in enfacement task. Scalp topographies of the ACW and PLE values are shown on top, and violin plots of the average values are shown at the bottom. For each figure, white dots in the rightmost topoplot represent electrodes, which form part of the significant cluster (following the cluster-based permutation test described in the text). Black dots in this plot represent electrodes with significant results at the channel level, but which did not form part of the cluster. Violin plots show the average value of ACW or PLE over only the white electrodes. In each figure, insets on the very right show the extremes of individual subjects' data—the schizophrenic participant shown has the highest mean ACW or PLE over the white electrodes, and the healthy participant shown has the lowest mean ACW or PLE.

difference between task (enfacement illusion and auditory oddball task) and rest in both ACW and PLE, ie, rest-task difference. We observed significantly lower task-rest differences in both ACW and PLE in specifically the Enfacement illusion (but not the auditory oddball task) among the SCZ (figures 2a and 2b; *P* = .0370 and .0020, respectively). Power spectra and best-fit line (figure 2c) did not show any change from rest to task in both ACW and PLE in SCZ, whereas there was a clear difference in HC (see circles on the right in figure 2c; see supplementary material for further results): during the task, HC tilted their slow-fast frequency fractal power balance toward faster frequencies, whereas SCH exhibited no such shift (figure 2c).

Relation of Neuronal to Phenomenological and Psychopathological Levels—Moderation Analysis

ACW and PLE during Enfacement illusion were found to directly correlate with none of the 3 components in

a direct way. To investigate indirect relationships, we applied a moderation model[80] to test for the differential impact of high and low ACW/PLE values on the relationship of the self-disorder (first component) with negative symptoms (second component) and positive symptoms (third component). Hence, rather than targeting the direct relationship of ACW/PLE to each of our 3 psychopathological PCA components (EASE and PANSS), the moderation analysis tests whether different levels of ACW/PLE, ie, low and high, mediate the relationship between the 3 PCA components in different ways.

We observed a highly significantly different impact of low and high ACW/PLE values on the relationship of the first component (self-disorders) with the second component (negative symptoms). When ACW/PLE values are low, self-disorders correlate negatively with the negative symptom component (*P* = .02042 for ACW and *P* = .02752 for PLE). In contrast, the
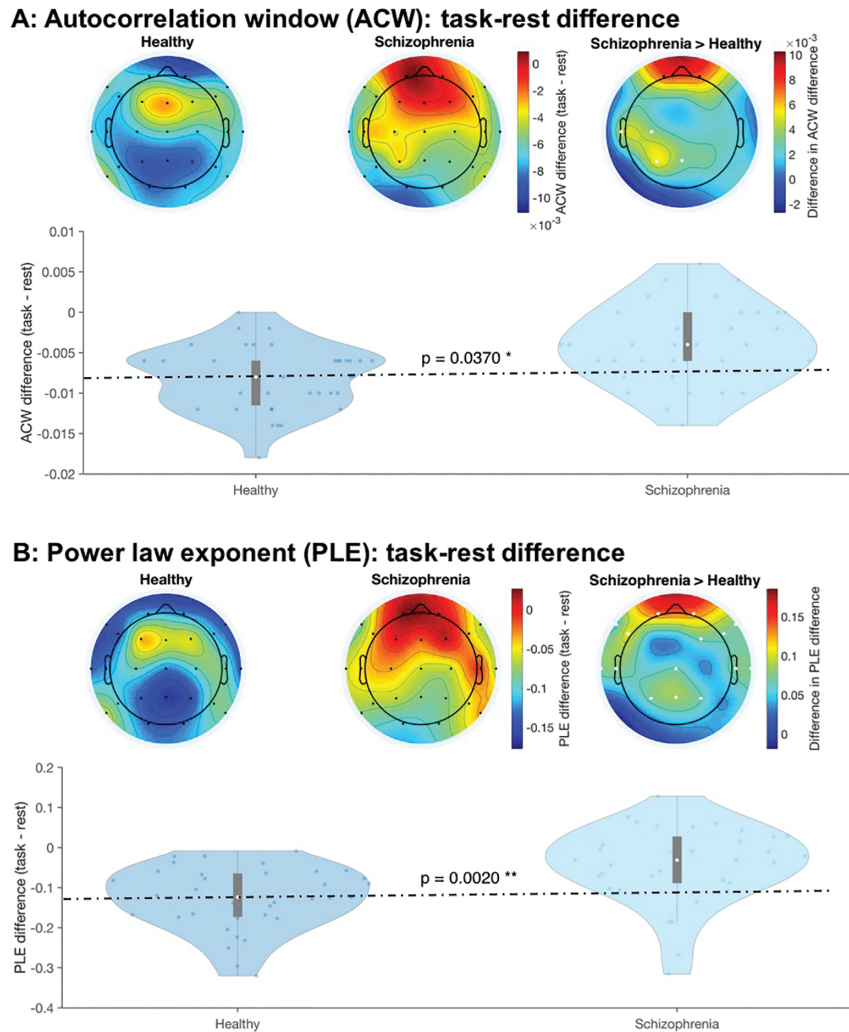
Fig. 2. Altered (A) autocorrelation window (ACW) and (B) power-law exponent (PLE) in the difference between Enfacement illusion and resting state. Scalp topographies of the ACW and PLE values are shown on top, and violin plots of the average values are shown at the bottom. The 2 left topoplots (for the 2 groups) represent the task values minus the resting-state values. The rightmost topoplot represents the group differences in this task-rest difference. White dots in the rightmost topoplot represent electrodes, which form part of the significant cluster. Black dots in this plot represent electrodes with significant results at the channel level, but which did not form part of the cluster. Violin plots show the average value of ACW or PLE over only the white electrodes. (C) Fractal power spectra of healthy and schizophrenia participants in rest and task states (x-axis: frequency range; y-axis: power). The actual data of fractal power spectra (extracted from the IRASA method) are shown left, while the best-fit lines (as plotted onto the data) used to estimate the PLE are shown right. The slope of the curve, which defines the PLE value, changes from rest to task in the healthy subjects (upper part) but not in the schizophrenia participants (lower part)— circles (on the right) indicate the shift in the slope from rest to task in the slower (upper circle) and faster (lower circle) frequency ranges. The rest and task curves are mostly parallel in both slower and faster frequency ranges in schizophrenia participants (lower right). Healthy subjects, in contrast, show deviating curves with power increase in faster frequencies (relative to slower frequencies) during the task (relative to rest) (upper right).

2 psychopathological components correlate positively when the values of ACW/PLE are high ($P = .0054$ for ACW and $P = .00068$ for PLE) (see supplementary figure S2 and supplementary tables S3.1–S3.3 for the detailed results). These results were obtained only for the enfacement illusion task, whereas no significant moderation effects were observed when testing for the effects of ACW/PLE during the auditory oddball task on the 3 PCA components.

Discussion

We conducted an EEG rest and task study investigating the brain's intrinsic neural timescale in order to relate temporal integration on the neuronal level to temporal integration of self on psychological and phenomenological levels. Main results are: (1) PCA revealed self-disorder as psychopathological component distinct from negative and positive symptoms; (2) longer ACW and higher PLE only in self-referential (Enfacement illusion) but not non-self-referential
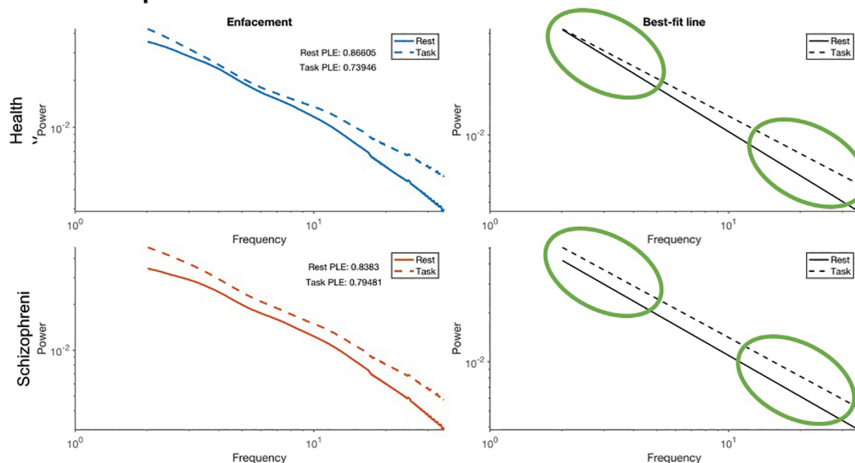
Fig. 2. Conitnued

task (oddball); (3) reduced rest-task differences in ACW and PLE during the self-referential task; and (4) ACW and PLE values, ie, low or high, moderate the relation of basic self-disorder and negative symptoms.

We observed that ACW and PLE change only during the self-referential task but not during a non-self-referential task. Hence, temporal integration on the neuronal level in SCZ is primarily altered with respect to self-referential information on the psychological level. Given that self-referential information is closely associated with resting-state activity in healthy subjects,[32,37,41,42] we tested for rest-task modulation of ACW and PLE. SCZ participants showed reduced rest-task difference: unlike healthy subjects, they could not modulate their resting-state activity during self-referential task by shifting their neural activity toward shorter time scales (shorter ACW) and faster frequency power (lower PLE).[81,82]

Our results highlight a key role for abnormal temporal integration in basic self-disorder of SCZ. Longer intrinsic neural timescales (longer ACW and higher PLE) may facilitate abnormally strong integration of stimuli across different time points which otherwise, in the healthy state, would be segregated. Abnormally long ACW (and high PLE) may mediate temporal integration of face pictures over longer duration during enfacement—more face picture are consecutively integrated with self rather than being temporally segregated from self and related to non-self. Our moderation analysis suggests that such abnormal temporal integration on neuronal and psychological levels is intimately related to the phenomenological level of basic self-disorder and its impact on negative symptoms.

Limitations

Our sample size is small but provides outstanding phenomenological, psychological, and neuronal evaluation that need to be complemented by more large-scale

studies. EEG measurements were based on the recordings of the entire Enfacement illusion task rather than single trials, including facial recognition of both self and other (see[56] and supplementary material for more details).

Conclusions

We show prolonged intrinsic neural timescale in EEG of SCZ during specifically self-referential processing including its relation to basic self-disorder and its modulation of negative symptoms. These findings support our background assumption that abnormal temporal integration could provide the link or "common currency"[21] of neuronal, psychological, and phenomenological alterations of self in SCZ. Our results suggest that psychopathological symptoms may fundamentally be based on dynamic, ie, temporal (and spatial) abnormalities (rather than being primarily cognitive deficits)—this reflects the recently introduced "Spatiotemporal Psychopathology."[83–86]

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin.*

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