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Schizotypy dimensions are associated with altered resting state alpha connectivity

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ABSTRACT

The *disconnection hypothesis* of schizophrenia says that symptoms are explained by dysfunctional connections across a wide range of brain networks. Despite some support for this hypothesis, there have been mixed findings. One reason for these may be the multidimensional nature of schizophrenia symptoms. In order to clarify the relationship between symptoms and brain networks, the current study included individuals at risk for schizophrenia-spectrum disorders who either report extreme levels of positive schizotypy traits (perceptual aberrations and magical ideation, or "PerMag"; $n = 23$), or an extreme negative schizotypy trait (social anhedonia, or "SocAnh"; $n = 19$), as well as a control group ($n = 18$). Resting-state alpha electroencephalography was collected, and functional networks for each subject were measured using the phase-lag index to calculate the connectivity between channel pairs based on the symmetry of instantaneous phase differences over time. Furthermore, graph theory measures were introduced to identify network features exclusive to schizotypy groups. We found that the PerMag group exhibited a smaller difference in node strength and clustering coefficient in frontal/occipital and central/occipital regional comparisons compared to controls, suggesting a more widespread network. The SocAnh group exhibited a larger difference in degree in the central/occipital regional comparison relative to controls, suggesting a localized occipital focus in the connectivity network. Regional differences in functional connectivity suggest that different schizotypy dimensions are manifested at the network level by different forms of disconnections. Taken together, these findings lend further support to the disconnection hypothesis and suggest that altered connectivity networks may serve as a potential biomarker for schizophrenia risk.

1. Introduction

Central to the theoretical formulation of schizophrenia is the *disconnection hypothesis*, where symptoms of schizophrenia are explained by dysfunctional connections across a wide range of brain networks rather than region-specific abnormalities (Friston, 2002; Friston and Frith, 1995). Despite emerging empirical evidence to support the disconnection hypothesis, there are mixed findings in the literature. One reason for this could be the multidimensional nature of symptoms associated with schizophrenia. That is, schizophrenia is a heterogenous and complex disorder characterized by distinct positive (i.e., cognitive and sensory abnormalities), negative (i.e., diminished experiences in emotion and behavior), and disorganized symptoms (i.e., disorganized thinking and behaviors) (Kwapil and Barrantes-Vidal, 2015). Thus, because schizophrenia falls on the "schizotypy" spectrum (i.e., a continuum from normalcy to frank psychosis) (Kwapil and Barrantes-Vidal, 2015, 2012), one can utilize samples of individuals at risk for developing schizophrenia-spectrum disorders who report specific symptoms in order to more clearly understand the relationship between brain networks and symptoms.

Computational analysis of functional connectivity has proven to be a valuable tool for studying human brain networks. In particular, scalp electroencephalogram (EEG) has been used for this purpose due to its non-invasive nature and temporal precision in the millisecond range, similar to the synchronous neuronal oscillations that underlie communications within and between brain regions (Fries, 2015, 2005; Varela et al., 2001). Previous studies have also shown that these neuronal communications are conveyed in a frequency dependent manner, with the alpha band oscillation playing a vital role in inhibitory top-down control processes (Fries, 2015; Klimesch et al., 2007). Specifically,

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alpha oscillations have been shown to reflect a gating mechanism whereby irrelevant processing systems are inhibited to allow for selective processing of relevant information (Klimesch et al., 2007). Given that inhibitory control has been variously demonstrated to be impaired in schizotypy (Ettinger et al., 2015; Steffens et al., 2018), functional connectivity in the alpha frequency band could be a sensitive marker for such control deficits.

Because the alpha oscillation is most pronounced at rest, a growing number of studies have examined resting state alpha connectivity across the schizotypy continuum. However, results have been mixed. Studies involving individuals with schizophrenia have reported evidence for elevated, reduced, and intact alpha connectivity (Maran et al., 2016). While EEG analysis of resting state connectivity in at-risk individuals has been scant, conflicting findings have also been shown. For example, while one study reported elevated alpha connectivity (Liu et al., 2019), other studies did not report a significant difference between the at-risk group and healthy controls (Andreou et al., 2015; Winterer et al., 2001). These inconsistent findings in individuals with schizophrenia and at-risk individuals might partly result from the diverse approaches used in measuring functional connectivity (Maran et al., 2016). For example, some amplitude-based measures of connectivity are prone to artifacts and spurious connections due to the effects of common sources (Bastos and Schoffelen, 2016; Stam et al., 2007).

Moreover, little is known about the relationship between the alpha connectivity pattern and symptom dimensions. The few studies that have examined this relied on a schizophrenia patient group characterized by heterogeneous symptom profiles, providing evidence for (Hinkley et al., 2011) and against (Kam et al., 2013) differential associations with symptoms. Considering that positive schizotypy (e.g., positive-like symptoms, such as perceptual distortions and unusual beliefs) and negative schizotypy (e.g., negative-like symptoms such as anhedonia) are associated with distinct etiology and symptom presentation, separately examining these two dimensions may help parse the heterogeneity in schizotypy (Kwapil and Barrantes-Vidal, 2015; Siever and Davis, 2004).

Here, we used EEG to examine resting state alpha connectivity in subjects who were at risk for developing schizophrenia-spectrum disorders. We employed an extreme-groups approach (Preacher et al., 2005) that separately compared (a) people characterized by positive schizotypy traits (perceptual aberrations and magical ideations, or “PerMag”) (b) people characterized by negative schizotypy traits (social anhedonia, or “SocAnh”), and (c) healthy controls. In addition to being able to examine relationships with specific symptoms, the use of at-risk samples can eliminate some of the confounds of patient research, such as medication usage and recurrent hospitalization. To calculate alpha-based functional connectivity while addressing spurious connections, we used a robust phase-based measure called the phase-lag index (PLI) (Khadem and Hossein-Zadeh, 2014; Stam et al., 2007). Due to the prior mixed findings of alpha connectivity in patients with schizophrenia and those at risk, the current study is largely exploratory in nature. As the first study to systematically investigate alpha connectivity across different schizotypy dimensions, our objective was to identify connectivity patterns associated with positive and negative schizotypy.

2. Methods

The current study was carried out in accordance with the Declaration of Helsinki and was approved by the University's Institutional Review Board.

2.1. Participants

Subjects in the study were undergraduate students attending a West Coast, public university. They were recruited from 2329 individuals who completed the short versions of the Wisconsin Schizotypy Scales (Winterstein et al., 2011). The Short Wisconsin Schizotypy Scales consisted of: (1) a 15-item Short Perceptual Aberration Scale (α in current study = 0.88) to measure psychotic-like distortions, (2) a 15-item Short Magical Ideation Scale (α in current study = 0.85) to measure unusual beliefs, and (3) a 15-item Short Revised Social Anhedonia Scale (α in current study = 0.78) to measure lack of relationships and lack of pleasure from relationships. Individuals with high scores on the Perceptual Aberration and Magical Ideation scales have been shown to be at risk for developing psychosis (Chapman et al., 1994), while those with high scores on the Revised Social Anhedonia Scale have been shown to be at risk for developing schizophrenia-spectrum disorders (Kwapil, 1998). Compared to the full versions of these scales (Chapman et al., 1978; Eckblad et al., 1982; Eckblad and Chapman, 1983), the short versions have superior psychometric properties in ethnically diverse samples (Cicero et al., 2019; Li et al., 2020) and thus were used in the current study.

Individuals with a perceptual aberration or magical ideation score of at least 1.5 standard deviations above the mean were recruited to the PerMag group, while individuals with a social anhedonia score of at least 1.5 standard deviations above the mean were recruited to the SocAnh group (with norms based on a large unselected college sample; Gross et al., 2012). Healthy controls were defined as those scoring < 0.5 standard deviations above the mean on all three scales. Additional inclusion criteria included: (1) 18 years of age or older, (2) right hand-dominant, (3) no neurological illness or movement disorder (e.g., seizures, epilepsy, stroke, brain injury, Parkinson's disease), and (4) no history of medication to change their mood, emotions or the way they thought or acted (e.g., mood stabilizers, anti-depressants, stimulants). All subjects provided informed consent for the following protocol and received compensation through course credits and monetary compensation.

A total of 65 subjects completed the study, of whom five were excluded (3 PerMag and 2 SocAnh) due to software malfunction (1 PerMag and 1 SocAnh) and insufficient data (2 PerMag and 1 SocAnh) as described in Section 2.2. Final groups consisted of 23 PerMag subjects, 19 SocAnh subjects, and 18 healthy controls. Demographic information of the participants is summarized in Table 1. Groups did not significantly differ in gender or ethnicity composition (both $ps > .10$), but there was a trend-level difference in age ($p = .07$). Post-hoc analysis using Tukey's HSD showed that the PerMag group was marginally younger than the control group, $p = .06$. All results reported below remained largely the same when age was added as a covariate.

2.2. EEG acquisition and processing

Subjects were instructed to sit comfortably in a dimly lit room and instructed to switch between eyes-open and eyes-closed for one-minute blocks for eight blocks. EEG was recorded using an EEG cap (ANT Neuro, Enschede, The Netherlands) with 33 electrodes (FP1, FPz, FP2,

Table 1
Participant demographics.

	PerMag $n = 23$	SocAnh $n = 19$	Control $n = 18$	Test statistics
Female *n* (%)	15 (65.22)	17 (89.47)	16 (88.89)	$p = .10$ (two-tailed Fisher's exact test)
Age *M* (*SD*)	19.17 (1.40)	19.68 (1.73)	21.00 (3.88)	$F(2, 57) = 2.80$, $p = .07$
Race *n* (%)				$p = .10$ (two-tailed Fisher's exact test)
Asian	14 (60.87)	5 (26.32)	8 (44.44)	
African American	0 (0)	2 (10.53)	0 (0)	
Caucasian	4 (17.39)	1 (5.26)	4 (22.22)	
Latino/a	4 (17.39)	7 (36.84)	5 (27.78)	
Other	1 (4.35)	4 (21.05)	1 (5.56)	

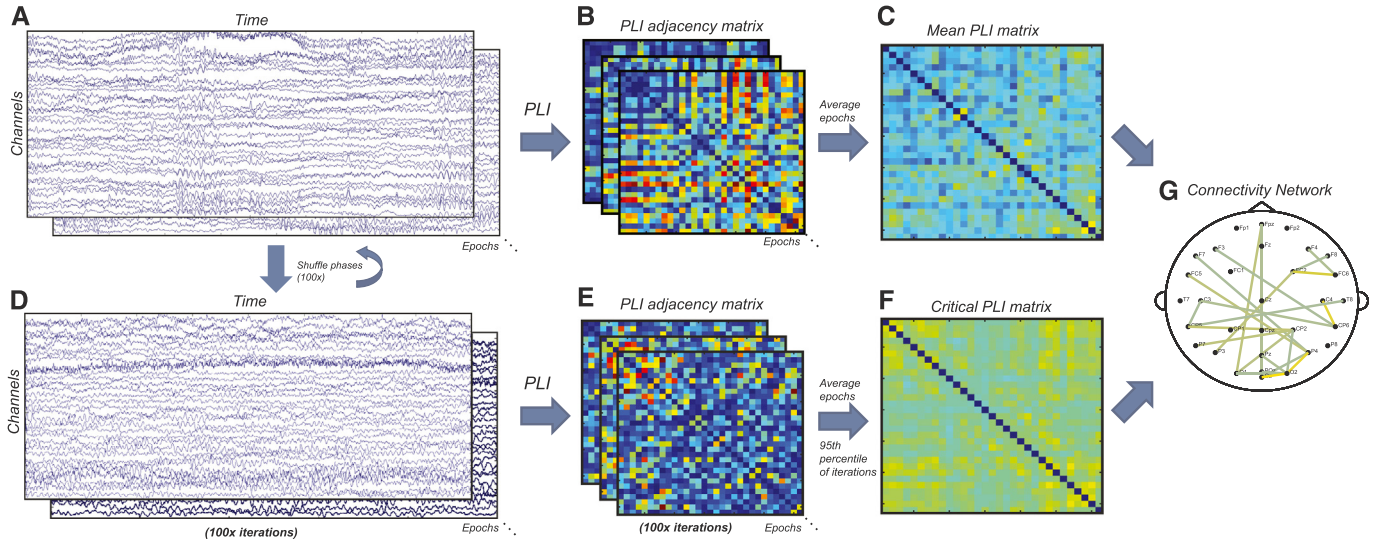

Fig. 1. Summary of the functional connectivity analysis. (A) EEG data were separated into epochs. (B) PLI was calculated for each epoch, and (C) the mean adjacency matrix was calculated across all epochs. (D) Significance testing was done by creating 100 iterations of shuffled data, (E) calculating the PLI for each epoch of shuffled data, and (F) calculating a critical PLI value using the average shuffled adjacency matrix. (G) Significant connections were identified by comparison to the critical values and are visually represented in a functional connectivity network.

Fz, F3, F4, F7, F8, FC5, FC1, FC2, FC6, Cz, C3, C4, T7, T8, CP1, CP2, CP5, CP6, Pz, P3, P4, P7, P8, POz, Oz, O1, O2, M1, M2, CPz) placed according to the expanded international 10–20 system (American Electroencephalographic Society, 1994). All channels were referenced online to CPz and amplified with an eego sports amplifier (ANT Neuro, Enschede, The Netherlands). Data were sampled at 1000 Hz with impedances kept below 5 kΩ at all electrodes.

The EEG was downsampled offline to 500 Hz and filtered with a 2nd-order Butterworth filter with zero-phase shift digital filtering from 0.1 to 55 Hz. Artifactual channels were identified as those containing extreme voltage fluctuations based on Tukey's fences (i.e., the standard deviation was > 2 times the interquartile range plus the third quartile) and replaced with whole head spline interpolation. The mastoid electrodes were removed, and the data were re-referenced to the common average. All eyes-closed segments were then extracted with baseline correction applied to the entire 60s duration. Sections of data containing artifact were identified visually and with a semi-automated procedure that discarded data in a 500 ms window if the amplitude within the window exceeded 200 μV. Independent component analysis (ICA) was then implemented to remove any components with ICA activations containing extreme values and/or extreme fluctuations around its mean based on Tukey's fences. Subjects with < 1 min of data were excluded from the study due to insufficient data. After data preprocessing, 20 eight-second epochs of clean EEG data were selected for each subject, and phase-based connectivity was calculated after applying a bandpass filter in the alpha band (8–12.5 Hz). Eight-second epochs were chosen due to the high variance in PLI at lower epoch lengths (Fraschini et al., 2016). All signal processing and analysis procedures were performed in MATLAB using custom scripts, the EEGLAB toolbox (Delorme and Makeig, 2004), and the ERPLAB toolbox (Lopez-Calderon and Luck, 2014).

2.3. Network construction

For each subject, the functional connectivity network was calculated based on the phase synchronization between channel pairs in the alpha band. The PLI was used to estimate the phase synchronization between all 31 electrodes (Stam et al., 2007):

$$\mathrm{PLI} = \left| \frac{1}{N} \sum_{n=1}^{N} sign(\Delta\varphi(t_n)) \right|.$$

The instantaneous phase in the alpha band was obtained by taking the Hilbert transform of the filtered EEG signal for each channel and epoch. For each channel pair within an epoch, the PLI calculates the mean signum of the instantaneous phase difference between the two channels at time n, which is denoted $\Delta\varphi(t_n)$. The PLI ranges between zero and one, where zero indicates that there is a symmetrical phase difference between the two signals. A PLI of one represents an asymmetrical phase difference between the two signals, indicating that the phase of one signal is consistently leading or lagging the other signal. PLI was chosen as it is robust to spurious connections due to volume conduction (Stam et al., 2007). Calculating the PLI for each channel pair yielded a 31-by-31 adjacency matrix for each epoch, where each element denotes the phase synchronization between the respective channel pair. The functional connectivity of a subject was calculated by averaging the adjacency matrices over all epochs.

Significant connection pairs in the mean adjacency matrix were determined using surrogate data analysis. To generate the surrogate data, the Fourier transform was taken for each electrode in each epoch, and the data was permuted in the frequency domain to shuffle the phases while retaining the original amplitude profile of the signal (Olejarczyk and Jernajczyk, 2017). We used the inverse Fourier transform to convert the signal back to the time domain, and the PLI was calculated using this new signal. This process was repeated 100 times to create a null distribution of PLI values for each electrode pair, in which the pairs have no phase-based relationship. The mean adjacency matrix was then compared to the 95th percentile of the surrogate data, where any insignificant connection was discarded. Fig. 1 summarizes the data analysis procedure for the calculation of functional connectivity.

2.4. Differences between schizotypy groups using graph theory

Graph theory measures were used to quantify the differences in network properties between groups. For each subject, nodes were represented by EEG electrodes, while edges were represented by the PLI measure between the two nodes (Rubinov and Sporns, 2010). Three different graph theory measures were used to quantify the differences between the three groups: (1) node strength, (2) degree, and (3) clustering coefficient. The connectivity strength of a node was calculated as

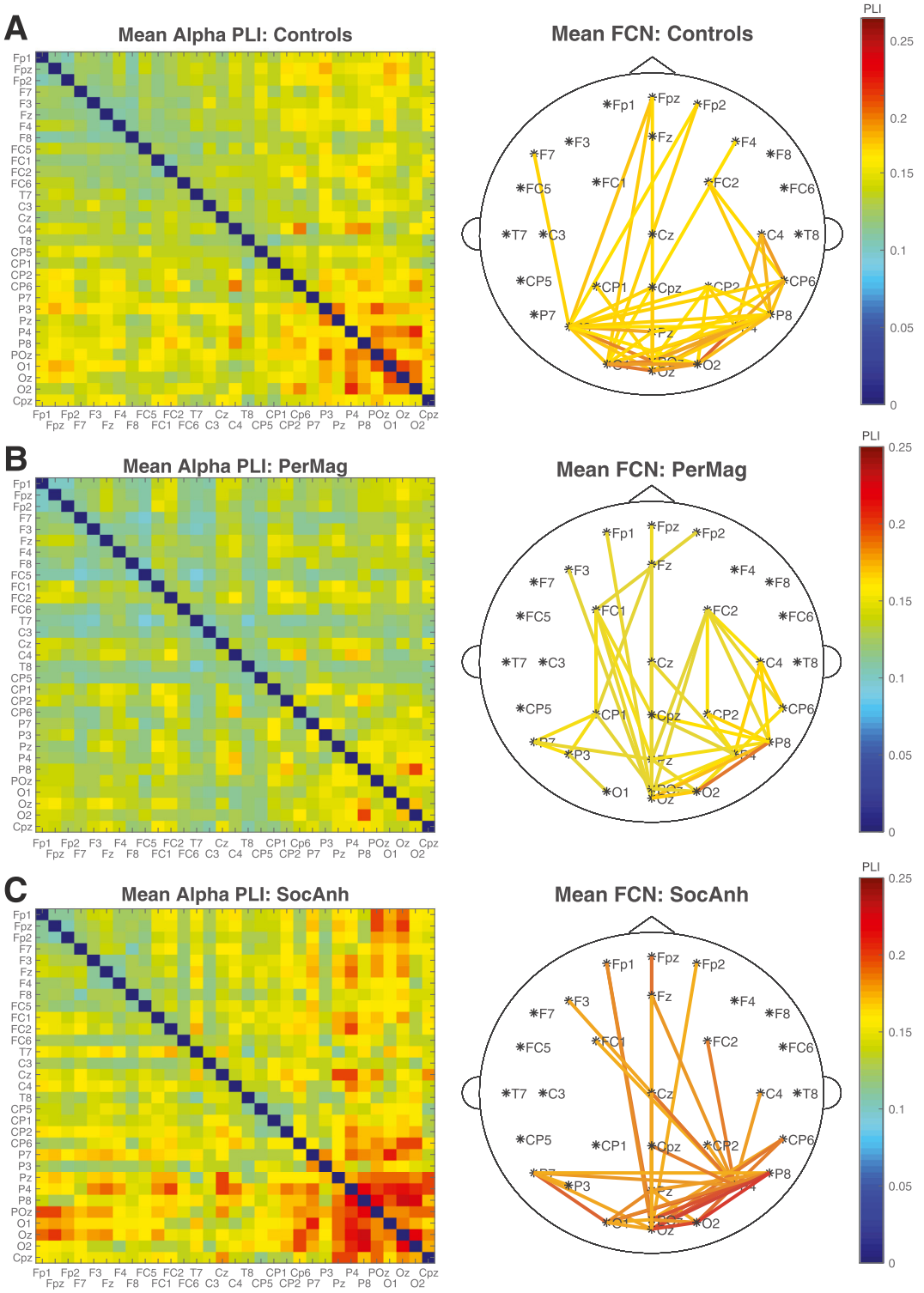

Fig. 2. Average adjacency matrix (left) and functional connectivity networks (right) for (A) healthy controls, (B) PerMag subjects, and (C) SocAnh subjects. The strongest 10% of connections are shown.

the sum of all weighted PLI values connected to the node prior to surrogate analysis. The degree of each node was calculated as the number of significant connections after surrogate thresholding. The clustering coefficient of each node was calculated based on the tendency of the node's neighbors to be connected to each other using the weighted adjacency matrix prior to surrogate analysis.

Functional connectivity network differences between PerMag, SocAnh, and healthy controls were examined both globally and regionally. Multilevel models (MLMs) were used to model channel-specific and subject-specific variability through random effects. This increases the model's power to detect an effect as a result of partitioning sources of variance from the error term. To examine global differences across the 31 channels, graph theory measures (i.e., node strength, degree, and clustering coefficient) were predicted by Subject Group (PerMag vs. SocAnh vs. control) in an MLM with random intercepts of subjects and channels. Regional differences in graph theory measures

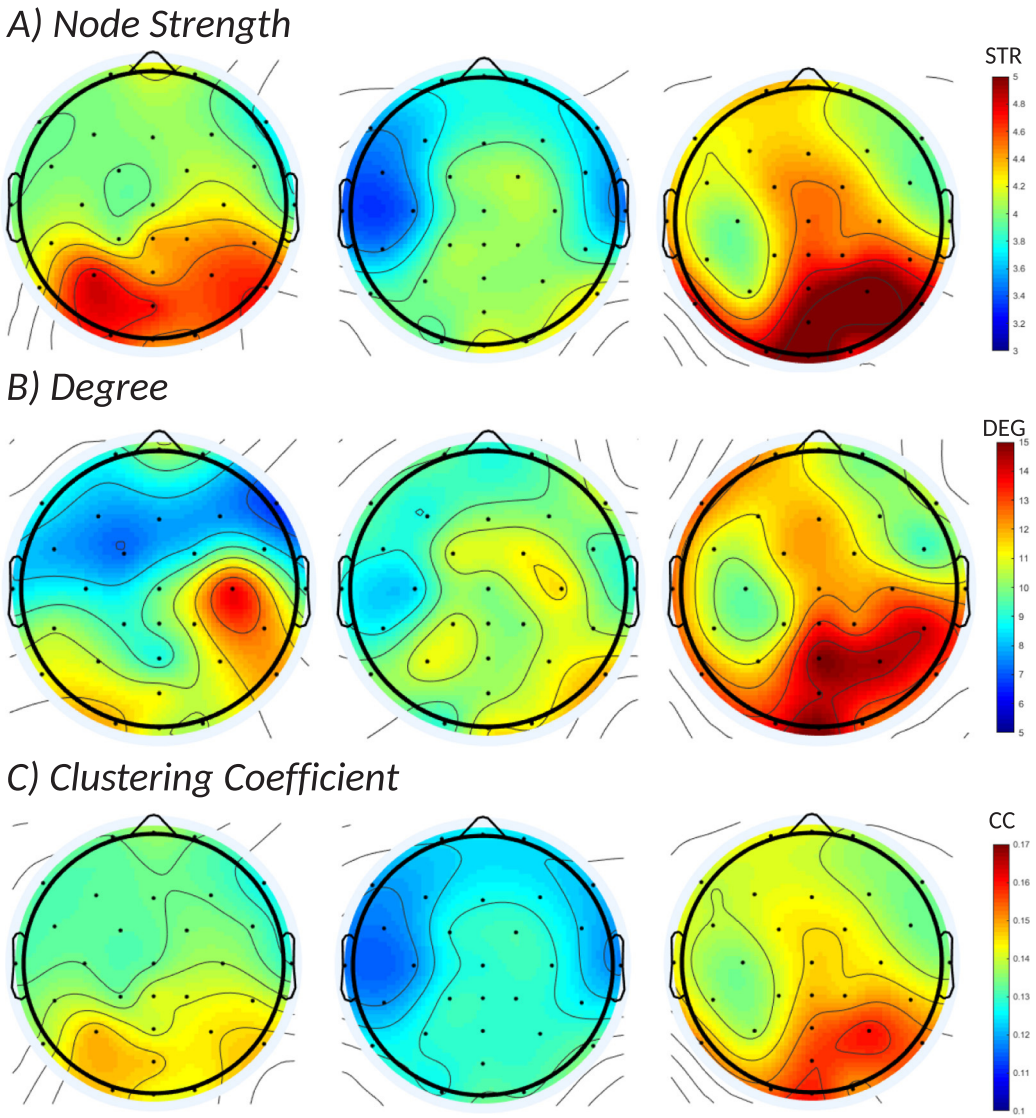

Fig. 3. Topoplots for (A) node strength, (B) node degree, and (C) clustering coefficient measures in healthy controls (left), PerMag (middle), and SocAnh (right) subjects.

Table 2
Parameter estimates of global graph theory measures as a function of group.

Fixed effects	*B* (SE)	*t*	*df*	*p*	95% CI	
					Lower	Upper
Strength						
Intercept	4.22 (0.32)	13.16	59.18	< .001	3.60	4.84
PerMag (vs. control)	−0.36 (0.42)	−0.85	57.00	.40	−1.18	0.46
SocAnh (vs. control)	0.24 (0.44)	0.54	57.00	.59	−0.62	1.10
Degree						
Intercept	9.69 (1.41)	6.86	58.44	< .001	6.95	12.44
PerMag (vs. control)	0.36 (1.88)	0.19	57.00	.85	−3.28	4.01
SocAnh (vs. control)	2.42 (1.96)	1.23	57.00	.22	−1.39	6.22
Clustering coefficient						
Intercept	0.137 (0.010)	13.89	57.95	< .001	0.118	0.156
PerMag (vs. control)	−0.012 (0.013)	−0.88	57.00	.38	−0.037	0.014
SocAnh (vs. control)	−0.007 (0.014)	0.53	57.00	.60	−0.019	0.034

were examined by an MLM of Region (Frontal vs. Central vs. Occipital) × Subject Group (PerMag vs. SocAnh vs. control), with random intercepts of subjects and channels. The electrodes FP1, FPz, FP2, F3, Fz, and F4 were chosen for the frontal region, electrodes C3, Cz, C4, CP1, CPz, and CP2 were chosen for the central region, and electrodes P3, Pz, P4, POz, O1, Oz, and O2 were chosen for the occipital region.

3. Results

3.1. Global functional connectivity network measures did not differ between groups

Fig. 2 shows the average adjacency matrices and functional connectivity networks in the alpha band for healthy controls, PerMag, and SocAnh subjects. The mean PLI values were 0.141 (*SD* = 0.051) for healthy controls, 0.125 (*SD* = 0.036) for PerMag subjects, and 0.141 (*SD* = 0.034) for SocAnh subjects.

The mean node strength, degree, and clustering coefficient in schizotypy groups are presented topographically in Fig. 3. Results for global group comparisons are reported in Table 2, with each comparison using the healthy controls as the reference (i.e. the intercept). There were no

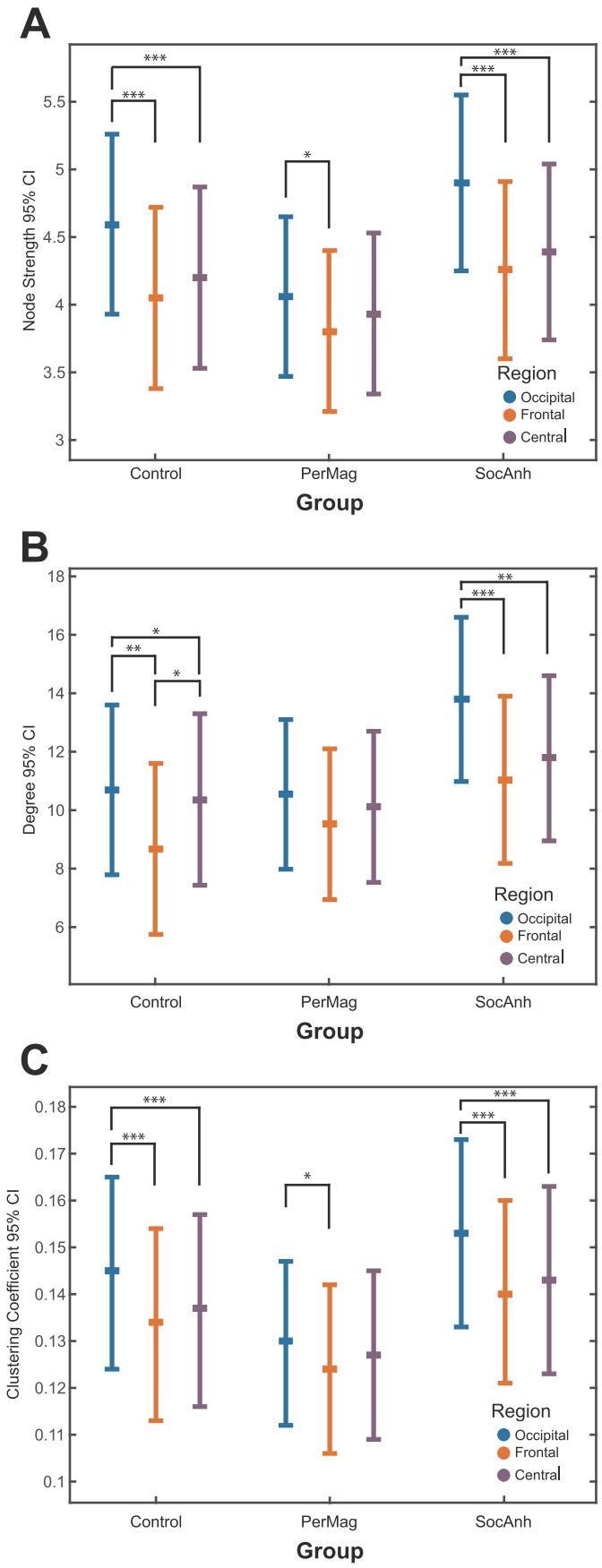

Fig. 4. (A) Node strength, (B) degree, and (C) clustering coefficient are higher in the occipital region than frontal and central regions. Significance tests shown are based on *p*-values modified with Tukey's adjustments. * $p < .05$, ** $p < .01$, *** $p < .001$.

significant group differences in global node strength, degree, and clustering coefficient in comparisons between PerMag/control and SocAnh/control (Table 2). Next, we examined whether there were any regional differences in connectivity between subject groups.

3.2. Occipital connections were strongest across all subject groups

Fig. 4 shows the MLMs for the regional differences within each group, with *p*-values corrected with Tukey's adjustment. Within healthy controls, the occipital region had a significantly greater node strength and clustering coefficient than both frontal and central regions (Fig. 4). PerMag subjects had no statistically significant differences between regions, but there was a trend of greater node strength, degree, and clustering coefficient in the occipital region compared to frontal and central regions. SocAnh subjects had a significantly greater node strength, degree, and clustering coefficient in the occipital region compared to the frontal and central regions (Fig. 4). Overall, the regional differences were consistent across the three groups, with stronger functional connections in the occipital region. Next, we examined the relative strengths in different brain regions across subject groups.

3.3. Strong functional connections were more concentrated in the occipital region for the SocAnh group, but more diffuse for the PerMag group

Results for the MLMs for both regional and regional/group comparisons are reported in Table 3, with all models using the control occipital nodes as the reference (i.e. the intercept). Regional comparisons of schizotypy groups to the control occipital region yielded no significant results (all $ps > .13$),[1] while the PerMag group showed marginally lower node strength ($B = -0.84$, $t(59.61) = 1.93$, $p = .06$), degree ($B = -3.25$, $t(62.80) = 1.72$, $p = .09$), and clustering coefficient ($B = -0.023$, $t(58.10) = 1.77$, $p = .08$) compared to the SocAnh group.

In contrast to the nonsignificant findings in global and regional measures between groups, PerMag and SocAnh groups significantly differed from the control group in relative strength between regions. The PerMag group exhibited a smaller difference in node strength and clustering coefficient for frontal/occipital and central/occipital connectivity compared to healthy controls (all $ps < .02$). At the same time, the SocAnh group exhibited a larger difference in degree for central/occipital connections relative to healthy controls ($p = .04$). Therefore, relative to healthy controls, functional connectivity appeared to be more diffuse for the PerMag group, but relatively more localized in the occipital region for the SocAnh group. These regional differences in alpha connectivity structure during resting-state suggest that abnormalities in inhibitory processes might be manifested differently across positive and negative schizotypy dimensions.

4. Discussion

The current study is the first to systematically investigate positive and negative schizotypy utilizing EEG-based functional connectivity analysis. We found that PerMag subjects exhibited more diffuse patterns of strong connections in the alpha band. In contrast, we found that for SocAnh subjects, strong functional connections in the alpha band were more concentrated in the occipital region than they were for controls. Taken together, the heterogeneity of schizotypy dimensions, represented by both positive and negative symptoms, appears to be associated with differences in functional connectivity. The current study lends further support to the disconnection hypothesis, which is

[1] Note that the when age was added as a covariate, the SocAnh group showed marginally greater degree in the occipital region than that of the Control group, $B = 3.80$, $t(61.62) = 1.88$, $p = .06$.

Table 3
Parameter estimates of graph theory measures as a function of group and region.

Fixed effects	*B* (SE)	*t*	*df*	*p*	95% CI	
					Lower	Upper
Strength						
Intercept	4.59 (0.33)	13.76	61.09	< .001	3.94	5.24
Frontal (vs. Occipital)	−0.54 (0.11)	−5.03	64.88	< .001	−0.75	−0.33
Central (vs. Occipital)	−0.40 (0.11)	−3.68	64.88	< .001	−0.60	−0.19
PerMag (vs. control)	−0.54 (0.44)	−1.21	59.61	.23	−1.39	0.32
SocAnh (vs. control)	0.30 (0.46)	0.66	59.61	.51	−0.59	1.20
Frontal × PerMag	0.29 (0.12)	2.35	1058.00	.02	0.048	0.53
Central × PerMag	0.27 (0.12)	2.24	1058.00	.02	0.034	0.51
Frontal × SocAnh	−0.10 (0.13)	−0.79	1058.00	.43	−0.35	0.15
Central × SocAnh	−0.11 (0.13)	−0.86	1058.00	.39	−0.36	0.14
Degree						
Intercept	10.69 (1.45)	7.36	64.47	< .001	7.88	13.50
Frontal (vs. Occipital)	−2.02 (0.64)	−3.16	86.55	.002	−3.26	−0.79
Central (vs. Occipital)	−0.34 (0.64)	−0.53	86.55	.60	−1.57	0.90
PerMag (vs. control)	−0.14 (1.92)	−0.072	62.80	.94	−3.87	3.60
SocAnh (vs. control)	3.11 (2.01)	1.55	62.80	.13	−0.79	7.02
Frontal × PerMag	1.00 (0.78)	1.29	1058.00	.20	−0.52	2.52
Central × PerMag	−0.091 (0.78)	−0.12	1058.00	.91	−1.61	1.43
Frontal × SocAnh	−0.75 (0.81)	−0.93	1058.00	.35	−2.34	0.83
Central × SocAnh	−1.67 (0.81)	−2.06	1058.00	.04	−3.25	−0.081
Clustering coefficient						
Intercept	0.14 (0.010)	14.34	58.83	< .001	0.12	0.16
Frontal (vs. Occipital)	−0.011 (0.0022)	−5.05	60.54	< .001	−0.15	−0.0068
Central (vs. Occipital)	−0.0080 (0.0022)	−3.70	60.54	< .001	−0.012	−0.0038
PerMag (vs. control)	−0.015 (0.013)	−1.12	58.10	.27	−0.041	0.011
SocAnh (vs. control)	0.0084 (0.014)	0.60	58.10	.55	−0.019	0.036
Frontal × PerMag	0.0057 (0.0024)	2.36	1058.00	.02	0.00098	0.010
Central × PerMag	0.0055 (0.0024)	2.28	1058.00	.02	0.00078	0.010
Frontal × SocAnh	−0.0018 (0.0025)	−0.70	1058.00	.48	−0.0067	0.0032
Central × SocAnh	−0.0018 (0.0025)	−0.70	1058.00	.49	−0.0067	0.0032

apparent even in preclinical at-risk individuals. Our findings imply that altered functional connectivity networks are differentially associated with schizotypy dimensions, highlighting an altered connectivity distribution as a potential biomarker for schizophrenia risk that could be used to assist in early identification.

Alpha oscillations are typically associated with the inhibition of neuronal communications, freeing up resources for selective information processing (Klimesch, 2012). The observed increase in alpha connectivity in the occipital region within all subject groups was likely due to our use of eyes-closed data, as EEG contains higher alpha power in the posterior region when the eyes are closed (Tan et al., 2013). While functional connections in the occipital region were numerically the largest across all subject groups, schizotypy groups differed from healthy controls in the relative distribution of functional connectivity across brain regions.

In PerMag subjects, the smaller difference in alpha-based connectivity for frontal/occipital and central/occipital regional comparisons relative to healthy controls suggests a diffuse connectivity pattern. This diffuse pattern in PerMag subjects is attributed to the large decrease in occipital connectivity and moderate decrease in frontal connectivity, as seen in Fig. 2. This change in connectivity might indicate a reduction in local computational processing or a lack of synchrony between brain regions, resulting in a less efficient information flow across the cortex (Hinkley et al., 2011). The diffuse connectivity pattern found in the PerMag group is consistent with some findings from individuals with schizophrenia characterized by paranoia. Specifically, Olejarczyk and Jernajczyk (2017) reported that these patients had lower resting-state alpha connectivity than healthy controls, which is in line with our findings that the resting-state alpha connectivity in PerMag subjects was generally lower than controls. In addition, Olejarczyk and Jernajczyk (2017) also that reported patients had a greater number of posterior-frontal connections compared to healthy controls. This finding is in line with the present results, as PerMag subjects tended to have connections outside of the occipital region compared to the more focal connection structure observed in both SocAnh and control subjects. There is also indirect evidence from fMRI studies showing altered functional connectivity being associated with positive symptoms of schizophrenia. For example, increased functional connectivity in the anterior cortical midline structures has been found to correlate with positive symptoms and symptoms of delusions in patients with schizophrenia (Garrity et al., 2007; Larivière et al., 2017). Similarly, abnormalities in connectivity in the anterior cingulate cortices relative to controls have been reported during auditory hallucinations (Amico et al., 2017; Diederen et al., 2010). Because these connectivity studies look at functional changes during task-based experiments, they are valuable complements to our findings using resting-state EEG. These findings collectively suggest that positive symptoms can alter functional connectivity to a more diffuse structure across both at-risk individuals and patients with schizophrenia.

On the other hand, the focal alpha connectivity in the occipital region for SocAnh subjects suggests greater inhibitory top-down control processes (Klimesch et al., 2007). This could be attributed to an impairment in the occipital lobe, restricting information flow to other cortical regions (Klimesch et al., 2007). Furthermore, the inhibition of information flow from the occipital region may lead to altered activity in other areas in the cortex. For instance, previous functional connectivity studies reported that reduced connectivity in frontal regions was related to negative symptoms in schizophrenia (Hinkley et al., 2011; Shukla et al., 2019). This decrease in frontal lobe activity has also been attributed to the amotivation and apathy seen in schizophrenia subjects with negative symptoms (Tekin and Cummings, 2002). Similarly, a study on alpha oscillations during a passive listening task found that schizophrenia patients with predominantly negative symptoms had larger alpha amplitudes at occipital sites, with a reduced anterior response (Basar-Eroglu et al., 2013). Collectively, similar findings of increased alpha activity in the occipital region have been observed in

negative symptoms across both at risk individuals and patients with schizophrenia.

While the current study represents a valuable step toward delineating functional connectivity patterns in schizophrenia risk, there are some limitations worth noting. Groups were formed based on self-reported scores on the Wisconsin Schizotypy Scales. Thus, there were no independent ratings of symptoms via clinical interviews. However, previous research has shown that participants with elevated scores on the Wisconsin Schizotypy Scales report clinically meaningful psychotic-like experiences and anhedonia, and these schizotypy scales are moderately to strongly correlated with interview-rated symptoms (Cicero et al., 2014). Furthermore, elevated scores on these scales predict future development of schizophrenia-spectrum disorders (Chapman et al., 1994; Kwapil, 1998). Moreover, as the current study focuses on the stable expressions of schizotypy traits, replicating the same findings in subjects at high-risk states will be an important topic for the future. The age of subjects is another important factor to address, as developmental changes over time can affect both neural activation patterns and functional connectivity (Wienke et al., 2018). Since all subjects in the present study are in the young adult age range (Table 1), future studies could consider the variation in schizotypy expressions and respective changes in connectivity across developmental stages. Finally, we incorporated measures of schizophrenia-spectrum disorder risk, but we did not include other measures of psychological functioning, such as current mood, depression or substance abuse, which can affect electrophysiological responses. Future research could include such measures to test whether they account for the current findings.

In conclusion, this study utilized a robust functional connectivity method to examine resting-state alpha connectivity among subjects at risk of schizophrenia prior to clinical manifestation. Findings showed differential alpha connectivity patterns associated with positive and negative schizotypy, which may relate to the unique mechanisms contributing to the development of positive and negative symptoms of schizophrenia. As such, deviations in alpha connectivity could serve as an early biomarker of risk. Ultimately, such a biomarker could provide insight into the mechanisms associated with positive and negative symptoms, aiding in prevention and intervention efforts.

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Declaration of competing interest

None of the authors had a conflict of interest.

References

American Electroencephalographic Society, 1994. Guideline thirteen: guidelines for standard electrode position nomenclature. J. Clin. Neurophysiol. 11, 111–113.

Amico, F., O'Hanlon, E., Kraft, D., Oertel-Knöchel, V., Clarke, M., Kelleher, I., Higgins, N., Coughlan, H., Creegan, D., Heneghan, M., Power, E., Power, L., Ryan, J., Frodl, T., Cannon, M., 2017. Functional connectivity anomalies in adolescents with psychotic symptoms. PLoS One 12, 1–17. https://doi.org/10.1371/journal.pone.0169364.

Andreou, C., Leicht, G., Nolte, G., Polomac, N., Moritz, S., Karow, A., Hanganu-Opatz, I.L., Engel, A.K., Mulert, C., 2015. Resting-state theta-band connectivity and verbal memory in schizophrenia and in the high-risk state. Schizophr. Res. 161, 299–307. https://doi.org/10.1016/j.schres.2014.12.018.

Basar-Eroglu, C., Schmiedt-fehr, C., Mathes, B., 2013. Auditory-evoked alpha oscillations imply reduced anterior and increased posterior amplitudes in schizophrenia. Suppl. Clin. Neurophysiol. 62. https://doi.org/10.1016/B978-0-7020-5307-8.00008-9.

Bastos, A.M., Schoffelen, J.M., 2016. A tutorial review of functional connectivity analysis methods and their interpretational pitfalls. Front. Syst. Neurosci. 9, 1–23. https://doi.org/10.3389/fnsys.2015.00175.

Chapman, L.J., Chapman, J.P., Raulin, M.L., 1978. Body-image aberration in schizophrenia. J. Abnorm. Psychol. https://doi.org/10.1037/0021-843X.87.4.399.

Chapman, L.J., Chapman, J.P., Kwapil, T.R., Eckblad, M., Zinser, M.C., 1994. Putatively psychosis-prone subjects 10 years later. J. Abnorm. Psychol. 103, 171–183. https://doi.org/10.1037/0021-843X.103.2.171.

Cicero, D.C., Martin, E.A., Becker, T.M., Docherty, A.R., Kerns, J.G., 2014. Correspondence between psychometric and clinical high risk for psychosis in an undergraduate population. Psychol. Assess. 26, 901–915. https://doi.org/10.1037/a0036432.

Cicero, D.C., Martin, E.A., Krieg, A., 2019. Differential item functioning of the full and brief Wisconsin Schizotypy Scales in Asian, White, Hispanic, and multiethnic samples and between sexes. Assessment 26, 1001–1013. https://doi.org/10.1177/1073191117719509.

Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J. Neurosci. Methods 134, 9–21.

Diederen, K.M.J., Neggers, S.F.W., Daalman, K., Blom, J.D., Goekoop, R., Kahn, R.S., Sommer, I.E.C., 2010. Deactivation of the parahippocampal gyrus preceding auditory hallucinations in schizophrenia. Am. J. Psychiatry 167, 427–435. https://doi.org/10.1176/appi.ajp.2009.09040456.

Eckblad, M., Chapman, L.J., 1983. Magical ideation as an indicator of schizotypy. J. Consult. Clin. Psychol. https://doi.org/10.1037/0022-006X.51.2.215.

Eckblad, M.L., Chapman, L.J., Chapman, J.P., Mishlove, M., 1982. The revised social anhedonia scales. Unpublished manuscript available from L. J. Chapman. Department of Psychology, 1202 West Johnson Street, University of Wisconsin, Madison, WI 53706.

Ettinger, U., Mohr, C., Gooding, D.C., Cohen, A.S., Rapp, A., Haenschel, C., Park, S., 2015. Cognition and brain function in schizotypy: a selective review. Schizophr. Bull. 41, S417–S426. https://doi.org/10.1093/schbul/sbu190.

Fraschini, M., Demuru, M., Crobe, A., Marrosu, F., Stam, C.J., Hillebrand, A., 2016. The effect of epoch length on estimated EEG functional connectivity and brain network organisation. J. Neural Eng. 13. https://doi.org/10.1088/1741-2560/13/3/036015.

Fries, P., 2005. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn. Sci. 9, 474–480. https://doi.org/10.1016/J.TICS.2005.08.011.

Fries, P., 2015. Rhythms for cognition: communication through coherence. Neuron 88, 220–235. https://doi.org/10.1016/j.neuron.2015.09.034.

Friston, K.J., 2002. Dysfunctional connectivity in schizophrenia. World Psychiatry 1, 66–71.

Friston, K.J., Frith, C.D., 1995. Schizophrenia: a disconnection syndrome? Clin. Neurosci. 3, 89–97.

Garrity, A.G., Pearlson, G.D., Mckiernan, K., Lloyd, D., Kiehl, K.A., Calhoun, V.D., 2007. Aberrant "default mode" functional connectivity in Schizophrenia. Am. J. Psychiatry 164, 1–8. https://doi.org/10.1176/appi.ajp.164.3.450.

Gross, G.M., Silvia, P.J., Barrantes-Vidal, N., Kwapil, T.R., 2012. Psychometric properties and validity of short forms of the Wisconsin Schizotypy Scales in two large samples. Schizophr. Res. 134, 267–272. https://doi.org/10.1016/j.schres.2011.11.032.

Hinkley, L.B.N., Vinogradov, S., Guggisberg, A.G., Fisher, M., Findlay, A.M., Nagarajan, S.S., 2011. Clinical symptoms and alpha band resting-state functional connectivity imaging in patients with schizophrenia: implications for novel approaches to treatment. Biol. Psychiatry 70, 1134–1142. https://doi.org/10.1016/j.biopsych.2011.06.029.

Kam, J.W.Y., Bolbecker, A.R., O'Donnell, B.F., Hetrick, W.P., Brenner, C.A., 2013. Resting state EEG power and coherence abnormalities in bipolar disorder and schizophrenia. J. Psychiatr. Res. 47, 1893–1901. https://doi.org/10.1016/j.jpsychires.2013.09.009.

Khadem, A., Hossein-Zadeh, G.A., 2014. Quantification of the effects of volume conduction on the EEG/MEG connectivity estimates: an index of sensitivity to brain interactions. Physiol. Meas. 35, 2149–2164. https://doi.org/10.1088/0967-3334/35/10/2149.

Klimesch, W., 2012. Alpha-band oscillations, attention, and controlled access to stored information. Trends Cogn. Sci. 16, 606–617. https://doi.org/10.1016/j.tics.2012.10.007.

Klimesch, W., Sauseng, P., Hanslmayr, S., 2007. EEG alpha oscillations: the inhibition-timing hypothesis. Brain Res. Rev. 53, 63–88. https://doi.org/10.1016/j.brainresrev.2006.06.003.

Kwapil, T.R., 1998. Social anhedonia as a predictor of the development of schizophrenia-spectrum disorders. J. Abnorm. Psychol. https://doi.org/10.1037/0021-843X.107.4.558.

Kwapil, T.R., Barrantes-Vidal, N., 2012. Schizotypal personality disorder: an integrative review. In: Thomas, R. (Ed.), The Oxford Handbook of Personality Disorders., Oxford Library of Psychology. Oxford University Press, Kwapil, pp. 437–477. https://doi.org/10.1093/oxfordhb/9780199735013.013.0021. University of North Carolina at Greensboro, Greensboro, NC, US.

Kwapil, T.R., Barrantes-Vidal, N., 2015. Schizotypy: looking back and moving forward. Schizophr. Bull. 41, S366–S373. https://doi.org/10.1093/schbul/sbu186.

Larivière, S., Lavigne, K.M., Woodward, T.S., Gerretsen, P., Graff-Guerrero, A., Menon, M., 2017. Altered functional connectivity in brain networks underlying self-referential processing in delusions of reference in schizophrenia. Psychiatry Res. Neuroimaging 263, 32–43. https://doi.org/10.1016/j.pscychresns.2017.03.005.

Li, L.Y., Cicero, D.C., Dodell-Feder, D., Germane, L., Martin, E.A., 2020. Comparability of Social Anhedonia Across Epidemiological Dimensions: A Multi-national Study of Measurement Invariance of the Revised Social Anhedonia Scale. (Under Rev).

Liu, T., Zhang, J., Dong, X., Li, Z., Shi, X., Tong, Y., Yang, R., Wu, J., Wang, C., Yan, T., 2019. Occipital alpha connectivity during resting-state electroencephalography in patients with ultra-high risk for psychosis and schizophrenia. Front. Psychiatry 10. https://doi.org/10.3389/fpsyt.2019.00553.

Lopez-Calderon, J., Luck, S.J., 2014. ERPLAB: an open-source toolbox for the analysis of event-related potentials. Front. Hum. Neurosci. 8, 213. https://doi.org/10.3389/fnhum.2014.00213.

Maran, M., Grent-'t-Jong, T., Uhlhaas, P.J., 2016. Electrophysiological insights into connectivity anomalies in schizophrenia: a systematic review. Neuropsychiatr. Electrophysiol. 2, 6. https://doi.org/10.1186/s40810-016-0020-5.

Olejarczyk, E., Jernajczyk, W., 2017. Graph-based analysis of brain connectivity in schizophrenia. PLoS One 12. https://doi.org/10.1371/journal.pone.0188629.
Preacher, K.J., MacCallum, R.C., Rucker, D.D., Nicewander, W.A., 2005. Use of the extreme groups approach: a critical reexamination and new recommendations. Psychol. Methods 10, 178–192. https://doi.org/10.1037/1082-989X.10.2.178.
Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: uses and interpretations. Neuroimage 52, 1059–1069. https://doi.org/10.1016/j.neuroimage.2009.10.003.
Shukla, D.K., Wijtenburg, S.A., Chen, H., Chiappelli, J.J., Kochunov, P., Hong, L.E., Rowland, L.M., 2019. Anterior cingulate glutamate and GABA associations on functional connectivity in schizophrenia. Schizophr. Bull. 45, 647–658. https://doi.org/10.1093/schbul/sby075.
Siever, L.J., Davis, K.L., 2004. The pathophysiology of schizophrenia disorders: perspectives from the spectrum. Am. J. Psychiatry 161, 398–413. https://doi.org/10.1176/appi.ajp.161.3.398.
Stam, C.J., Nolte, G., Daffertshofer, A., 2007. Phase lag index: assessment of functional connectivity from multi channel EEG and MEG with diminished bias from common sources. Hum. Brain Mapp. 28, 1178–1193. https://doi.org/10.1002/hbm.20346.
Steffens, M., Meyhöfer, I., Fassbender, K., Ettinger, U., Kambeitz, J., 2018. Association of schizotypy with dimensions of cognitive control: a meta-analysis. Schizophr. Bull. 44, S512–S524. https://doi.org/10.1093/schbul/sby030.
Tan, B., Kong, X., Yang, P., Jin, Z., Li, L., 2013. The difference of brain functional connectivity between eyes-closed and eyes-open using graph theoretical analysis. Comput. Math. Methods Med. 2013. https://doi.org/10.1155/2013/976365.
Tekin, S., Cummings, J.L., 2002. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. J. Psychosom. Res. 53, 647–654. https://doi.org/10.1016/S0022-3999(02)00428-2.
Varela, F., Lachaux, J.P., Rodriguez, E., Martinerie, J., 2001. The brainweb: phase synchronization and large-scale integration. Nat. Rev. Neurosci. 2, 229–239. https://doi.org/10.1038/35067550.
Wienke, A.S., Basar-eroglu, C., Schmiedt-fehr, C., Mathes, B., 2018. Novelty N2-P3a complex and theta oscillations reflect improving neural coordination within frontal brain networks during adolescence. Front. Behav. Neurosci. 12, 1–14. https://doi.org/10.3389/fnbeh.2018.00218.
Winterer, G., Egan, M.F., Rädler, T., Hyde, T., Coppola, R., Weinberger, D.R., 2001. An association between reduced interhemispheric EEG coherence in the temporal lobe and genetic risk for schizophrenia. Schizophr. Res. 49, 129–143. https://doi.org/10.1016/S0920-9964(00)00128-6.
Winterstein, B.P., Silvia, P.J., Kwapil, T.R., Kaufman, J.C., Reiter-Palmon, R., Wigert, B., 2011. Brief assessment of schizotypy: developing short forms of the Wisconsin Schizotypy Scales. Pers. Individ. Dif. 51, 920–924. https://doi.org/10.1016/j.paid.2011.07.027.