Abnormal Low-Gamma Small-World Response After Visual Stimulation in Schizophrenia

Lucas Galdino (✉ galdino@neuro.ufm.br)
Federal University of Paraíba

Thiago Fernandes
Federal University of Paraíba

Kerstin Erika Schmidt
Federal University of Rio Grande do Norte

Natanael Antonio dos Santos
Federal University of Paraíba

Research Article

Keywords: Schizophrenia, functional dysconnectivity syndrome, visual processing, low-gamma

DOI: https://doi.org/10.21203/rs.3.rs-690074/v1

License: ☀️ This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

Schizophrenia can be described as a functional dysconnectivity syndrome that affects the brain's circuits in a generalized way. Global disconnection in schizophrenia has been manifold described by applying graph theory and quantifying parameters of network connectivity. However, little is known about how sensory stimulation modulates networks in schizophrenia, such as small-worldness during visual processing. In order to address this question, we applied graph theory algorithms to EEG recordings and classified the functional network in the alpha (8–13 Hz) and low-gamma (36–55 Hz) bands of 13 patients with schizophrenia (SCZ) and 13 healthy controls (HC) during the presentation of a visual stimulus. We measured the amplitude of visual-evoked potentials and the number of nodes, edges, mean degree centrality, clustering coefficient, characteristic path length (L), and small-worldness (SW). As expected, patients presented smaller peak amplitudes of evoked-potentials than HC. Interestingly, in contrast to the controls, SCZ did not change their small worldness index during visual stimulation. This implies that schizophrenia-related dysconnectivity has an impact on the ability of the low-gamma network to react to new sensory input. These results provide evidence about a possible electrophysiological signature of the global deficits revealed by the application of graph theory onto the EEG in schizophrenia.

Introduction

Scientists have spent several decades trying to establish a biochemical marker that assists in the diagnosis of schizophrenia (LAI et al., 2016; DAVISON et al., 2018), while, at the same time, the global dysconnectivity syndrome hypothesis has gained attention (FRISTON; FRITH, 1995; FRISTON, 1999; COYLE et al., 2016). This theory has been changing our perspective regarding psychotic disorders since it claims that schizophrenia may be classified as a syndrome, which affects the connectivity of the brain in a generalized way (ROMME et al., 2017; ROLLS et al., 2020). In accordance with this theory, functional dysconnectivity in psychotic disorders has been observed at different source scales, from single neuron activity (ZICK et al., 2018), to electroencephalography (EEG) power/connectivity measures (CANUET et al., 2011; PELED et al., 2001; BOB et al., 2008; CANUET et al., 2011) and fMRI recordings (DU et al., 2018; LEWANDOWSKI et al., 2019).

Using the mathematical framework of graph-based network analysis (BULLMORE; SPORNS, 2009; SPORNS, 2007), the brain can be described as a complex system with functional and anatomical boundaries expressed by nodes, which are defined on the basis of physiological, or cytoarchitectonical features and whose interactions are described as directed or undirected connections (SALVADOR et al., 2005). Parameters extracted from graph analysis have been well associated with the dysconnectivity theory of psychosis, as they allow description and quantification of a large number of datasets with several sites of anatomical or functional recordings (BULLMORE; SPORNS, 2009). Furthermore, they return optimal accuracy estimates for classifying psychotic and healthy subjects (HEUVEL et al., 2010; MOTA et al., 2012; OLEJARCZYK; JERNACZYK, 2017). Supporting the idea of the dysconnectivity syndrome, there is plenty of evidence that psychotic patients, specifically those diagnosed with
schizophrenia, exhibit altered network properties, such as overall reduced modularity of the functional and anatomical networks (ALEXANDER-BLOCH et al., 2010; BASSETT et al., 2008), decreased clustering coefficients during cognitive tasks (GOMEZ-PILAR et al., 2017; ZHAO; WANG, 2019) and absent or disrupted small-worldness (MICHELOYANNIS et al., 2006; LIU et al., 2008; WANG et al., 2012; ZHAO et al., 2018).

The small-worldness (SW) stood out from the multitude of graph-extracted parameters quantifying brain network properties (e.g. centrality, betweenness, resiliency, synchronizability, and modularity), because its characteristics allows to approximate an ideal brain structure as one which would exhibit both local segregation and global integration (Figure 1) as expressed by higher clustering coefficients (C) and lower characteristics path lengths (L) (BULLMORE; SPORNS, 2009; RUBINOV et al., 2009; RUBINOV; SPORNS, 2010). Typically, a small-world network may maintain a considerable level of clustering among its nodes while some emergent edges integrate non-expected nodes, increasing the randomness of the complex network, and decreasing the average path length between nodes.

So far, graph analysis of (electro)-physiological patterns involved in schizophrenia psychopathology has pointed towards disturbance of small-worldness during resting state recordings (YU et al., 2011b; TOMASI; VOLKOW, 2014) and auditory processing (YU et al., 2011a; SHIM et al., 2014; ZHU et al., 2016).

Apart from the known auditory, patients with schizophrenia also exhibit several visual impairments that are reflected in the whole-scalp EEG network and can even predict the stage of the disorder (MATHALON; FORD; PEFFERBAUM, 2000; BUTLER et al., 2001). Visual networks are likely to resemble a small world just like other perceptual systems (SPORNS; ZWI, 2004; HILGETAG; GOULAS, 2016) since their anatomical organization promotes visual integration between local and global cortical and non-cortical sites through a cost-efficient SW-oriented response (BAEK; PARK; PAIK, 2020). Though they very likely exist, small world patterns have not yet been described for EEG activity obtained during visual processing. Therefore, in order to analyze the parameters of global functional connectivity related to visual perception in healthy subjects and patients with schizophrenia, we recorded pattern-reversal visual evoked potentials and quantified the graph-based network measures.

**Results**

**Pattern-Reversal Visual Evoked Potential (PR-VEP)**

We measured the amplitude and latency of PR-VEP for each of the stimulus onset (P1a and P1b, see methods) for the occipital electrodes (O1, Oz and O2) and compared them between the two groups: healthy controls (HC) and patients diagnosed with schizophrenia (SCZ). Our result indicates that the amplitude of the PR-VEP is affected globally in SCZ for all occipital electrodes (Figure 2). In detail, SCZ patients showed lower amplitudes in O1 for P1a (median ± SD [HC = 7.69 ± 1.5; SCZ = 4.67 ± 1.43], U = 42; p = 0.29) and P1b (median ± SD [HC = 8.19 ± 1.68; SCZ = 0.85 ± 1.41], U = 26; p < 0.01), OZ for P1a (median ± SD [HC = 8.40 ± 2.38; SCZ = 1.38 ± 2.12], U = 26; p < 0.01) and P1b (median ± SD [HC = 8.40 ± 1.76; SCZ = 0.71 ± 2.89], U = 18; p < 0.01) and O2 for P1a (median ± SD [HC = 7.88 ± 2.73; SCZ = 1.78
On the other hand, the PR-VEP latencies behave similarly between SCZ and HC groups for P1a and P1b (\( p > 0.05 \)) suggesting that only time-lagged electrophysiological patterns involved in occipital activity during visual stimulation may be largely preserved in SCZ.

**Graph-based Network Measures**

In order to characterize the connectivity at different coherence scales, we calculated the graph-based Magnitude-Squared Coherence (see methods, MSC) matrices for alpha (8-12 Hz) and low-gamma (36-55 Hz) bands for two different thresholds, either the centroid average (Centroid-based Network, CBN) or a MSC score higher than 0.65 (Threshold-based network, TBN, see methods) considering only pairwise values which cross the respective threshold for the calculation of graph measures. Whereas CBN emphasizes those phase-connections close to the average value of the entire network, and TBN networks keep only those elevated (and less frequent) connections. In Figure 3, example connectivity matrices for the low-gamma coherence are illustrated for both a healthy control (A) and a patient (B). From each connectivity matrix, we measure the number of nodes, number of edges, mean degree centrality (MK), mean clustering coefficient (MC), characteristic path length (L) and small-worldness (SW). The statistical significance for each threshold and frequency intervals are presented in the subsections below.

**Low-gamma networks**

In the low-gamma band, differences between pre-stimulus and VEP epoch are significant for all analyzed network properties for the TBN threshold \( p < 0.01 \), Figure 4A-F), but only for characteristic path length (L) and small worldness (SW) in the LBC network (Figure 4E, F). Surprisingly, we observe that both these measures differ between healthy controls and patients with schizophrenia (Figure 4E, F). Accordingly, SCZ showed a slight but significant increase in L scores \( \text{mean} \pm \text{SD} \) [HC-PSI = 0.77 ± 0.08; HC-VEP = 0.51 ± 0.09; SCZ-PSI = 0.87 ± 0.11; SCZ-VEP = 0.64 ± 0.1]; \( F (1,322) = 227.61; p < 0.01; \eta^2 = 0.41; \) Figure 4E) and a significant decrease in SW values in the VEP epoch of the CBN networks \( \text{mean} \pm \text{sd} \) [HC-PSI = 0.47 ± 0.11; HC-VEP = 0.66 ± 0.19; SCZ-PSI = 0.38 ± 0.11; SCZ-VEP = 0.45 ± 0.14]; \( F (1,322) = 369.06; p < 0.01; \eta^2 = 0.53; \) Figure 4F).

**Alpha networks**

For alpha (8-13 Hz) MSC, most of the graph measures – especially in TBN networks – are sensitive to the stimulus onset (pre-stimulus versus VEP epoch) but none of them differs between the two groups, HC and SCZ subjects (Figure 5), in contrast to the low gamma band.

The stimulus onset modulates the CBN networks by decreasing their characteristic path length L \( \text{mean} \pm \text{SD} \) [HC-PSI = 0.85 ± 0.1; HC-VEP = 0.53 ± 0.09; SCZ-PSI = 0.86 ± 0.08; SCZ-VEP = 0.57 ± 0.07]; \( F(1,322) = 7963.44; p < 0.01; \eta^2 = 0.96; \) Figure 5E) and increasing small-world properties \( \text{mean} \pm \text{sd} \) [HC-PSI = 0.32 ± 0.09; HC-VEP = 0.54 ± 0.16; SCZ-PSI = 0.31 ± 0.08; SCZ-VEP = 0.46 ± 0.13]; \( F(1,322) = 692.56; p < 0.01; \eta^2 = 0.68; \) Figure 5F), but none of the remaining graph measures (Fig. 4A - D).
In contrast, all graph measures were significantly modulated by stimulus-onset (Figure 5A-F) in TBN alpha networks, for both HZ and SCZ groups. Whereas number of nodes (mean ± SD [HC-PSI = 30.26 ± 0.86; HC-VEP = 26.50 ± 2.91; SCZ-PSI = 30.46 ± 0.75; SCZ-VEP = 28.20 ± 1.84]; F(1,322) = 1016.79; p < 0.01; η² = 0.75; Figure 5A), number of edges (mean ± SD [HC-PSI = 169.89 ± 66.31; HC-VEP = 73.96 ± 35.08; SCZ-PSI = 172.03 ± 61.41; SCZ-VEP = 82.28 ± 34.57]; F(1,322) = 1314.05; p < 0.01; η² = 0.8; Figure 5B), mean degree centrality (mean ± SD [HC-PSI = 11.23 ± 4.35; HC-VEP = 5.52 ± 2.36; SCZ-PSI = 11.29 ± 4.03; SCZ-VEP = 5.81 ± 2.36]; F(1,322) = 1083.58; p < 0.01; η² = 0.77; Figure 5C), mean clustering coefficient (mean ± SD [HC-PSI = 0.68 ± 0.1; HC-VEP = 0.54 ± 0.11; SCZ-PSI = 0.69 ± 0.09; SCZ-VEP = 0.54 ± 0.1]; F(1,322) = 788.3; p < 0.01; η² = 0.71; Figure 5D), and small-worldness (mean ± SD [HC-PSI = 0.49 ± 0.17; HC-VEP = 0.32 ± 0.12; SCZ-PSI = 0.47 ± 0.14; SCZ-VEP = 0.28 ± 0.11]; F(1,322) = 125.27; p < 0.01; η² = 0.63; Figure 5F), decreased significantly with stimulus onset, the characteristic path length increased (mean ± SD [HC-PSI = 1.48 ± 0.31; HC-VEP = 1.9 ± 0.46; SCZ-PSI = 1.48 ± 0.29; SCZ-VEP = 1.92 ± 0.48]; F(1,322) = 451.54; p < 0.01; η² = 0.58; Figure 5E).

**Evoked connections**

We computed the evoked CBN graph and compared the same network measures between groups and frequency bands to describe the role of specific evoked edges after the visual stimulus. In the evoked network in the alpha band (Figure 6A), the number of edges of SCZ patients was lower (median = 103; SD = 14.26) than that of HC subjects (median = 118; SD = 11.84). A Mann-Whitney test indicated that this difference was statistically different (U = 43; p = 0.03). The mean degree centrality of SCZ patients was also lower (median = 6.96; SD = 0.92) than that of HC subjects (median = 7.86; SD = 0.75). This difference was confirmed by the Mann-Whitney test (U = 42; p = 0.02). However, no difference was observed between groups for mean clustering coefficients (U = 81; p = 0.87), characteristic path length (U = 67.5; p = 0.39), and small-worldness (U = 70; p = 0.47).

In the low-gamma band (Figure 6B), the evoked network of SCZ patients exhibited a decreased number of edges (median ± SD [SCZ = 120 ± 16.89; HC = 151 ± 16.64]; U = 27.5; p < 0.01), a lower mean degree centrality (median ± SD [SCZ = 7.79 ± 0.93; HC = 9.8 ± 1.02]; U = 23; p < 0.01), and a lower clustering coefficient (median ± SD [SCZ = 0.24 ± 0.07; HC = 0.33 ± 0.05]; U = 37; p = 0.01) in comparison to healthy controls. Notably, their evoked low-gamma network revealed intrinsic SW characteristics supporting the idea of a disrupted evoked-response in schizophrenia. In detail, their characteristic path length was higher (median = 0.7; SD = 0.12) than that of HC subjects (median = 0.58; SD = 0.15), a difference confirmed by the Mann-Whitney test (U = 45.5; p = 0.04). Along this line, the small-worldness of SCZ patients showed a more regular pattern with a lower score (median = 0.34; SD = 0.12) than HC subjects (median = 0.5; SD = 0.16), which express optimal small-world properties (index close to 0.5, see Figure 1).

This could indicate that MSC networks of SCZ patients are impaired to reach large distances, specifically for frequencies in the low gamma band. In order to represent the behavior of those networks in a topographically manner, we illustrate the evoked CBN graph networks of one subject of each group according to the 10/20-electrode placement for alpha and low-gamma in Figure 6CD, respectively.
Discussion

We recorded topographic EEG signals driven by a full contrast visual stimulation using pattern reversal checkerboards and analyzed graph-based properties of Magnitude-Squared Coherences of the visual-evoked potentials in patients with SCZ and HC. We found characteristic network differences between resting state activity and visual evoked potentials in both healthy control and patients as quantified from medium phase coherence networks during both phases, suggesting that visual input modulates the cortical network during visual stimulation regardless of the group. However, our results also indicate that, during visual stimulation, topographic cortical integration in the low-gamma band (36-55 Hz), as measured by L and SW values is specifically impaired in SCZ patients.

The visual deficits observed in patients with schizophrenia as measured by the amplitude of evoked potentials are a hallmark of schizophrenia psychopathology (JUTAI et al., 1984; FOXE et al., 2001). Our PR-VEP amplitude results from occipital cortex electrodes are in accordance with these findings. Such deficits in visual processing of elemental features (such as contrast, luminance and orientation of the stimulus) are well described at various stages of the disorder, from the first episode (KIM et al., 2005; MURPHY & ÖNGÜR, 2019) to later stages (Çavuş et al., 2012). Although different visual circuits may contribute to these deficits, the magnocellular pathway seems to exert a greater global contribution to the visual impairments observed in SCZ patients (BUTLER et al., 2001; KÉRI et al., 2002; SCHECHTER et al., 2005; MARTÍNEZ et al., 2008; SKOTTUN & SKOYLES, 2007; MARTÍNEZ et al., 2012; JAHSHAN et al., 2017; FERNANDES et al., 2019).

However, due to their local nature, the well-described deficits in the visual pathways of patients with SCZ are not directly in line with the disconnection theory about the schizophrenic brain. Moreover, our study is the first to describe not only the known amplitude differences in EEG recordings, but also the dynamic interactions between different recording sites using phase connectivity measures during visualization of the stimulus. Our results indicate that a PR-VEP stimulus modifies network properties (number of nodes and edges, mean degree centrality, clustering, characteristic path length and small-worldness) in patients with schizophrenia and healthy volunteers in both frequency bands when compared with pre-stimulus activity (PSI).

In contrast to healthy HC volunteers, the pattern reversal visual stimulus does neither increase small-worldness nor the characteristic path length for EEG responses in the low-gamma band of patients with SCZ. In detail, our visual stimulus paradigm drives an increase of small-worldness in HC subjects. This suggests that under healthy conditions visual input changes the phase network organization (VEP epoch) when compared to the pre-stimulus activity (PSI epoch), in a characteristic manner. Visual inputs seem to increase the randomicity of the complex network and the organization of the edges involved in stimulus processing creating a more random network (characterized by a highly clustered network with reduced characteristic path length, See Figure 1). The same stimulus does not evoke as many new edges in patients as in healthy subjects, as illustrated in Figure 6CD, and the stimulus-induced increase in randomicity is lacking. Therefore, the hypothesis stands to reason that this inability to alter the low-
gamma network according to new sensory inputs – especially in response to a high-contrast visual stimulus – could be one of the manifestations of the disconnection syndrome in psychosis.

The reduced small-world phenomenon supporting dysconnectivity in schizophrenia is mostly described as a feature of structural networks estimated from MRI or fMRI recordings at rest or during a cognitive task. Lynall et al. (2010), for instance, showed substantial reductions in clustering, small-worldness and the probability of high degree hubs in SCZ patients. But these structural influences in the characteristic path length and clustering coefficient in psychosis are not only derived from the neuronal fibers themselves, but also from the local cortical thickness, as shown by Zhang et al., (2012), for example. The reduction of the small-world network towards greater global regularity in schizophrenia (see Fig. 1) is also described in a few EEG studies using resting state recordings (Sakkalis et al., 2006; Rubinov et al., 2009) or during working memory tasks (Micheloyannis et al., 2006), but these studies did not describe deficits in specific oscillatory frequency bands. While Olejarczyk & Jernajczyk (2017) showed differences in connectivity using phase-locking value in the alpha band, to date, Gomez-Pilar et al., (2018) is the only study that investigates the EEG network responding to a certain sensory stimulus - in this case, an auditory P300 oddball task. Corroborating with our main finding, they found a decrease in characteristic path length in the theta band exposed by the auditory task. Interestingly, in their pioneer study Uhlhaas and colleagues (2006) analyzed long-range synchrony through phase-locking during Gestalt perception and described that specific Gestalt deficits in schizophrenia were associated with a loss of beta, rather than gamma, phase synchrony, but, in general, reduced gamma band synchronization indicating impaired medium- and long-range interactions in patients was also reported (Hirvonen et al. 2017).

Our observation opens up many questions about frequency-specific functional connectivity in schizophrenia expressed in graph complex networks in visual perception, which is widely affected in schizophrenia even before the first episode (Mathalon; Ford; Pfefferbaum, 2000; Butler et al., 2001; Yeap et al., 2006; Schultze-Lutter et al., 2007; Friedman et al., 2012). All results show that patients with schizophrenia have lower amplitudes in both visual evoked potentials (P1a and P1b), which might support the conclusion that this deficit could change the connectivity in all band frequencies in a systemic manner. However, the amplitude reduction in patients seems to be associated with a lack of edge rearrangements and consequently, altered small world properties, after the visual stimulus onset in CBN networks of only the low-gamma and not the alpha band, suggesting a perceptual impairment in a specific frequency band.

Band-specific cortical oscillations directly reflect the dynamics of a group of neurons engaged in a task or at rest (Cohen, M. X., 2017; Martinez-Cañada et al., 2021; Næss et al., 2021). These oscillations reverberate in amplitude and frequency so that the amplitude decreases with the increase in the oscillatory frequency. As a consequence, lower frequency oscillations have greater energy and reach more distant cortical regions. Thus, alpha oscillations seems to be coupled in phase among different cortical areas (Linkenkaer-Hansen et al., 2001; Nikulin & Brismar, 2004; Nikulin et al., 2012; Becker et al., 2018), while gamma oscillations occur more locally, and for a short period of time due to excitation
and inhibition dynamics within a circumscribed cortical region (DONNER & SIEGEL, 2011; UHLHAAS et al., 2011; BUZSÁKI & WANG, 2012; GRÜTZNER et al., 2013; SUN et al., 2013).

Our study is limited by the sample size, the number of trials during the PR-VEP, and the polymedicated SCZ sample. It is known that, in addition to the deficits caused by the disorder itself, different antipsychotics might not only alter the visual perception (FERNANDES et al., 2019A; FERNANDES et al., 2019B), but lead to substantial changes in the overall functional network organization of SCZ patients (HADLEY et al., 2016). Thus, in future studies, we intend to assess the network expressed in graphs in a larger and homogeneously medicated sample of patients, and with a higher number of EEG electrodes. Our work is the first to show that visual stimuli alter the small-world network response in patients with schizophrenia, and various visual stimuli designed to isolate the different pathways in the visual system, such as the parvo- and koniocellular pathways, have yet to be explored.

We may conclude that phase-dependent functional connections, specifically in the low-gamma band, react less to visual input in patients with schizophrenia than in healthy conditions, indicating that functional networks in schizophrenia may be denser and thus do not allow greater cortical integration, resulting in the absence of a stimulus-induced small-world response.

**Methods**

**Participants**

All procedures were performed in compliance with the ethical principles of the Declaration of Helsinki, and were approved by the Research Ethics Committee of the Federal University of Paraíba (Registration number: 45774715.9.0000.5188). The Informed consent was obtained from all the volunteers. Twenty-three volunteers participated in the study, 13 diagnosed with schizophrenia according to 10th International Classification of Diseases (SCZ group; mean age = 38.3 years; SD = 9.61 years) and 13 healthy controls (HC group; mean age = 28.92 years; SD = 12.92 years) with no psychiatry in first and second-degree relatives. SCZ patients were recruited at the local Psychosocial Care Center. All participants had normal or corrected-to-normal (20/20) visual acuity (Raskin E Optotypes) and no color blindness (Ishihara's Test) (CLARK, 1924). Further, they had no history of drug abuse, brain trauma, diabetes, heart disease and neurological or psychiatric disorders (except for the SCZ group). Table 1 presents the sociodemographic characteristics of the samples divided according to the type of antipsychotic used in the latest 6 months before data recordings.

**Pattern-reversal Visual Evoked Potential - PR-VEP**

Visual stimuli were presented in pairs of phase-reversing checkerboards and consisted of 11 x 11 arrays of checks at maximum contrast, on a gray background with approximately 30 cd/m² of luminance. A block of 49 pattern-reversals was presented on a 20’ monitor at a 150 cm distance from the subjects. Each pattern was presented for 120 ms, with intervals of 800 ms (Figure 7). Participants were instructed
to keep their eyes fixed at the center point of the screen until the task was completed (approximately one minute) and avoid excessive body movement, blinks, lateral eye movements, and biting.

**EEG recording and preprocessing**

During presentation of pattern reversals, the EEG was recorded using a 32 active channel system (actiCHamp, Brain Products, Herrsching, Germany) with DC recording sampled at 500 Hz and impedances below 10 kΩ (kilo ohms) per electrode during all experiment sessions. The electrodes were connected to an air-permeable cap with adjustable size to the participant’s head (Easy-cap, Herrsching, Germany) using a spatial distribution following the international 10/10 system (JURCAK; TSUZUKI; DAN, 2007).

We applied saline gel (SuperVisc, EasyCap GmbH, Herrsching, Germany) to facilitate signal transduction and promote the correct electrode contact. After the recording section, data were re-referenced by common-average, band-passed using a Butterworth filter of order 2 between 0.6 and 100 Hz. The artifacts were removed through a semiautomatic Independent Component Analysis using ICLabel (PIONTONACHIN; KREUTZ-DELGADO; MAKEIG, 2019). After the preprocessing step, the data was visually inspected and imported to MATLAB to perform the analysis of the visual evoked potential and graph-based connectivity.

**PR-VEP analysis**

After identifying the stimulus onset per trial using the photo sensor data, EEG time-series data were windowed into valid segments of 700 ms (100 ms of PSI activity and 200 ms of VEP) only on the occipital electrodes (O1, Oz and O2) and identified the amplitude and latencies of P1a and P1b components per trial, referring to the first and second checkerboard visual responses, respectively. For each subject, all amplitude and latencies were then concatenated and averaged.

**Connectivity measures and graph analysis**

We measured the Magnitude-Squared Coherence (MSC) (Equation 1) for the alpha (8 - 13 Hz) and low-gamma (36-55 Hz) band to estimate the bidirectional coupling across functional phase connectivity among all pairs of electrodes and measured during PSI and VEP using the function `mscohere`. The MSC estimates the phase coupling between x and y signals at a frequency (f) by measuring the squared magnitude of the complex cross power spectral density (Pxy) divided by the auto-spectral densities (Pxx) and (Pyy). For PSI, we calculated the MSC 200 ms before the stimulus onset with a 100 ms Hamming window with 50% overlap, while for the VEP coherence we used a 200 ms Hamming window with 50% overlap. It resulted in adjacency matrices per each trial/condition (PSI and VEP) and groups (HC and SCZ). We then set two thresholds to measure the network at different points of view: 1) the centroid-based Network (CBN) which considers only MSC +/- 0.5 standard deviation of the average MSC to provide the graph-based analysis of the mean subject-to-subject phase synchrony. 2) the threshold-based network (TBN) which considers only MSC higher than 0.65 and below 1 to estimate the phase synchrony at elevated coherences. The TBN network represents a rare network present throughout the connectivity
matrix, since it is derived from a limit that removes more substantial nodes and edges below the defined value, leaving only the highest MSC values that may not fully represent the network during visual activity. Thus, TBN networks tend to exhibit fewer nodes and edges, but highly connected functional networks (BORDIER ET AL., 2017).

\[
MSC(f) = \frac{|P_{xy}(f)|^2}{P_{xx}(f)P_{yy}(f)} \tag{1}
\]

Each dataset containing its significant connections (pairwise MSC that fit the threshold criteria) was used in graph estimations. To this end, we identified each pair of the resultant electrodes and transformed the resultant vectors in a graph (G) composed by a set of Vertices V(G) and Edges E(G) (SPORNS, 2010). In our model, each electrode represents a node (or vertex), while the links between them represent the undirected MSC scores (or edges) (Figure 2). To evaluate the complex dynamics during PSI and PR-VEP, we estimated the resultant number of nodes, number of edges, mean degree centrality, characteristic path length (Equation 2), clustering coefficient of the network (Equation 3), and the small-worldness (Equation 4).

The Characteristic Path Length (L) measures the average shortest path length between all pair of nodes:

\[
L = \frac{1}{n(n-1)} \sum_{i \neq j} d(v_i, v_j) \tag{2}
\]

where n is the number of vertices of a Graph.

The cluster is the average of the local clustering coefficients of all the vertices:

\[
C = \frac{1}{n} \sum_{i \in N} \frac{2t_i}{k_i(k_i-1)} \tag{3}
\]

Where \(k_i\) are all connected neighbors to node i and \(t_i\) is the number of links between them.

The small-worldness is a measure of randomness, which is calculated by normalizing the ratio of the clustering coefficient (C) and the characteristic path length (L) by the same measurements for a size-matched random network (WATTS; STROGATZ, 1998):

\[
SW = \frac{C / C_{rand}}{L / L_{rand}} \tag{4}
\]

**Statistical analysis**
All statistical analysis was performed using IBM SPSS 26.0. Descriptive analysis is reported as means and standard deviations for the sociodemographic and amplitude and latency VEP measures, while means and standard error of the mean were used to describe the graph-based estimations, due to their sample size. Group differences (HC and SCZ) were measured using a non-parametric test for PR-VEP analysis (Mann-Whitney Test), and parametric Two-way repeated-measures ANOVA were applied to estimate the stimulus, group or Group x Stimulus main effect on the network measures. Statistical differences were considered if p-value was ≤ 0.05. Yet, due to the sample size of the graph estimates, we also consider the effect size (partial eta squared $\eta^2_p \geq 0.4$ as a criterion for significance.

**Declarations**

**Acknowledgements**

We thank all the subjects who participated in the study. We thank the local Psychosocial Care Center and its staff members for facilitating patient recruiting. This work was supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

**Competing Interests**

The authors declare that they have no conflict of interest.

**Author contributions statement**

L.G. designed and conceived the experiment, analyzed the data and wrote the manuscript, T.M.P.F analyzed the results and interpreted results, K.E.S analyzed data, interpreted results and revised the manuscript, N.A.S designed and conducted the research, revised the manuscript and funded the research. All authors contributed to the manuscript.

**References**

1. Alexander-Bloch, A. F. et al. Disrupted modularity and local connectivity of brain functional networks in childhood-onset schizophrenia. *Front. Systems Neuroscience* 4, 147 (2010).
2. Babiloni, C., Vecchio, F., Bultrini, A., Luca Romani, G., & Rossini, P. M. (2006). Pre-and poststimulus alpha rhythms are related to conscious visual perception: a high-resolution EEG study. Cerebral cortex, 16(12), 1690-1700.
3. Baek, S., Park, Y. & Paik, S.-B. Sparse long-range connections in visual cortex for cost-efficient small-world networks. *bioRxiv* (2020).
4. Bassett, D. S. et al. Hierarchical organization of human cortical networks in health and schizophrenia. *J. Neurosci.* 28, 9239–9248 (2008).
5. Becker, R., Van De Ville, D., & Kleinschmidt, A. (2018). Alpha oscillations reduce temporal long-range dependence in spontaneous human brain activity. *Journal of Neuroscience*, 38(3), 755-764.

6. Bob, P., Palus, M., Susta, M. & Glaslova, K. Eeg phase synchronization in patients with paranoid schizophrenia. *Neurosci. letters* 447, 73–77 (2008).

7. Bordier, C., Nicolini, C., & Bifone, A. (2017). Graph analysis and modularity of brain functional connectivity networks: searching for the optimal threshold. *Frontiers in Neuroscience*, 11, 441.

8. Brandt, M. E. (1997). Visual and auditory evoked phase resetting of the alpha EEG. *International journal of psychophysiology*, 26(1-3), 285-298.

9. Bullmore, E. & Sporns, O. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat. reviews neuroscience* 10, 186–198 (2009).

10. Butler, P. D., Schechter, I., Zemon, V., Schwartz, S. G., Greenstein, V. C., Gordon, J., ... & Javitt, D. C. (2001). Dysfunction of early-stage visual processing in schizophrenia. *American Journal of Psychiatry*, 158(7), 1126-1133.

11. Butler, P. D. et al. Dysfunction of early-stage visual processing in schizophrenia. Am. J. Psychiatry 158, 1126–1133 (2001).

12. Buzsáki, G., & Wang, X. J. (2012). Mechanisms of gamma oscillations. *Annual review of neuroscience*, 35, 203-225.

13. Canuet, L. et al. Resting-state eeg source localization and functional connectivity in schizophrenia-like psychosis of epilepsy. *PloS one* 6, e27863 (2011).

14. Çavuş, I., Reinhart, R. M., Roach, B. J., Gueorguieva, R., Teylor, T. J., Clapp, W. C., ... & Mathalon, D. H. (2012). Impaired visual cortical plasticity in schizophrenia. *Biological psychiatry*, 71(6), 512-520.

15. Clark, J. The ishihara test for color blindness. *Am. J. Physiol*. Opt. (1924).

16. Cohen, M. X. (2017). Where does EEG come from and what does it mean?. *Trends in neurosciences*, 40(4), 208-218.

17. Coyle, J. T., Balu, D., Puhl, M. & Konopaske, G. A perspective on the history of the concept of “dysconnectivity” in schizophrenia. *Harv. Review psychiatry* 24, 80 (2016).

18. Davison, J., O’Gorman, A., Brennan, L. & Cotter, D. R. A systematic review of metabolite biomarkers of schizophrenia. *Schizophr. research* 195, 32–50 (2018).

19. Donner, T. H., & Siegel, M. (2011). A framework for local cortical oscillation patterns. *Trends in cognitive sciences*, 15(5), 191-199.

20. Du, Y. et al. Dynamic functional connectivity impairments in early schizophrenia and clinical high-risk for psychosis. *Neuroimage* 180, 632–645 (2018).

21. Ergenoglu, T., Demiralp, T., Bayraktaroglu, Z., Ergen, M., Beydagi, H., & Uresin, Y. (2004). Alpha rhythm of the EEG modulates visual detection performance in humans. *Cognitive brain research*, 20(3), 376-383.

22. Fernandes, T. M. P., Silverstein, S. M., Butler, P. D., Kéri, S., Santos, L. G., Nogueira, R. L., & Santos, N. A. (2019). Color vision impairments in schizophrenia and the role of antipsychotic medication type.
23. Fernandes, T. P., Shaqiri, A., Brand, A., Nogueira, R. L., Herzog, M. H., Roinishvili, M., ... & Chkonia, E. (2019). Schizophrenia patients using atypical medication perform better in visual tasks than patients using typical medication. *Psychiatry Research*, 275, 31-38.

24. Foxe, J. J., Doniger, G. M., & Javitt, D. C. (2001). Early visual processing deficits in schizophrenia: impaired P1 generation revealed by high-density electrical mapping. *Neuroreport*, 12(17), 3815-3820.

25. Friedman, T., Sehatpour, P., Dias, E., Perrin, M., & Javitt, D. C. (2012). Differential relationships of mismatch negativity and visual p1 deficits to premorbid characteristics and functional outcome in schizophrenia. *Biological Psychiatry*, 71(6), 521-529.

26. Friston, K. J. & Frith, C. D. Schizophrenia: a disconnection syndrome. *Clin Neurosci* 3, 89–97 (1995).

27. Friston, K. J. Schizophrenia and the disconnection hypothesis. *Acta Psychiatr. Scand.* 99, 68–79 (1999).

28. Gomez-Pilar, J. et al. Functional eeg network analysis in schizophrenia: evidence of larger segregation and deficit of modulation. Prog. Neuro-Psychopharmacology *Biol. Psychiatry* 76, 116–123 (2017).

29. Grützner, C., Wibral, M., Sun, L., Rivolta, D., Singer, W., Maurer, K., & Uhlhaas, P. (2013). Deficits in high-(> 60 Hz) gamma-band oscillations during visual processing in schizophrenia. *Frontiers in human neuroscience*, 7, 88.

30. Hadley, J. A., Kraguljac, N. V., White, D. M., Ver Hoef, L., Tabora, J., & Lahti, A. C. (2016). Change in brain network topology as a function of treatment response in schizophrenia: a longitudinal resting-state fMRI study using graph theory. *npj Schizophrenia*, 2(1), 1-7.

31. Hilgetag, C. C. & Goulas, A. Is the brain really a small-world network? *Brain Struct. Funct.* 221, 2361–2366 (2016).

32. Hirvonen, J., Wibral, M., Palva, J. M., Singer, W., Uhlhaas, P., & Palva, S. (2017). Whole-brain source-reconstructed MEG-data reveal reduced long-range synchronization in chronic schizophrenia. *ENeuro*, 4(5).

33. Jahshan, C., Wolf, M., Karbi, Y., Shamir, E., & Rassovsky, Y. (2017). Probing the magnocellular and parvocellular visual pathways in facial emotion perception in schizophrenia. *Psychiatry research*, 253, 38-42.

34. Jurcak, V., Tsuzuki, D. & Dan, I. 10/20, 10/10, and 10/5 systems revisited: their validity as relative head-surface-based positioning systems. *Neuroimage* 34, 1600–1611 (2007).

35. Jutai, J. W., Gruzelier, J. H., Connolly, J. F., Manchanda, R., & Hirsch, S. R. (1984). Schizophrenia and spectral analysis of the visual evoked potential. *Br. J. Psychiatry*, 145, 496-501.

36. Kéri, S., Antal, A., Szekeres, G., Benedek, G., & Janka, Z. (2002). Spatiotemporal visual processing in schizophrenia. *The Journal of neuropsychiatry and clinical neurosciences*, 14(2), 190-196.

37. Kim, D., Zemon, V., Saperstein, A., Butler, P. D., & Javitt, D. C. (2005). Dysfunction of early-stage visual processing in schizophrenia: harmonic analysis. *Schizophrenia Research*, 76(1), 55-65.
38. Lai, C.-Y. et al. Biomarkers in schizophrenia: a focus on blood based diagnostics and theranostics. World journal psychiatry, 6, 102 (2016).
39. Lewandowski, K. E. et al. Functional connectivity in distinct cognitive subtypes in psychosis. Schizophr. research 204, 120–126 (2019).
40. Linkenkaer-Hansen, K., Nikouline, V. V., Palva, J. M., & Ilmoniemi, R. J. (2001). Long-range temporal correlations and scaling behavior in human brain oscillations. Journal of Neuroscience, 21(4), 1370-1377.
41. Liu, Y. et al. Disrupted small-world networks in schizophrenia. Brain 131, 945–961 (2008).
42. Lynall, M. E., Bassett, D. S., Kerwin, R., McKenna, P. J., Kitzbichler, M., Muller, U., & Bullmore, E. (2010). Functional connectivity and brain networks in schizophrenia. Journal of Neuroscience, 30(28), 9477-9487.
43. Martínez, A., Hillyard, S. A., Bickel, S., Dias, E. C., Butler, P. D., & Javitt, D. C. (2012). Consequences of magnocellular dysfunction on processing attended information in schizophrenia. Cerebral cortex, 22(6), 1282-1293.
44. Martínez, A., Hillyard, S. A., Dias, E. C., Hagler, D. J., Butler, P. D., Guilfoyle, D. N., ... & Javitt, D. C. (2008). Magnocellular pathway impairment in schizophrenia: evidence from functional magnetic resonance imaging. Journal of Neuroscience, 28(30), 7492-7500.
45. Martínez-Cañada, P., Ness, T. V., Einevoll, G. T., Fellin, T., & Panzeri, S. (2021). Computation of the electroencephalogram (EEG) from network models of point neurons. PLOS Computational Biology, 17(4), e1008893.
46. Mathalon, D. H., Ford, J. M. & Pfefferbaum, A. Trait and state aspects of p300 amplitude reduction in schizophrenia: a retrospective longitudinal study. Biol. psychiatry 47, 434–449 (2000).
47. Mayhew, S. D., Ostwald, D., Porcaro, C., & Bagshaw, A. P. (2013). Spontaneous EEG alpha oscillation interacts with positive and negative BOLD responses in the visual–auditory cortices and default-mode network. Neuroimage, 76, 362-372.
48. Merrin, E. L., & Floyd, T. C. (1996). Negative symptoms and EEG alpha in schizophrenia: a replication. Schizophrenia research, 19(2-3), 151-161.
49. Micheloyannis, S., Pachou, E., Stam, C. J., Breakspear, M., Bitsios, P., Vourkas, M., ... & Zervakis, M. (2006). Small-world networks and disturbed functional connectivity in schizophrenia. Schizophrenia research, 87(1-3), 60-66.
50. Micheloyannis, S. et al. Small-world networks and disturbed functional connectivity in schizophrenia. Schizophr. research 87, 60–66 (2006).
51. Mota, N. B. et al. Speech graphs provide a quantitative measure of thought disorder in psychosis. PloS one 7, e34928 (2012).
52. Murphy, M., & Öngür, D. (2019). Decreased peak alpha frequency and impaired visual evoked potentials in first episode psychosis. NeuroImage: Clinical, 22, 101693.
53. Næss, S., Halnes, G., Hagen, E., Hagler Jr, D. J., Dale, A. M., Einevoll, G. T., & Ness, T. V. (2021). Biophysically detailed forward modeling of the neural origin of EEG and MEG signals. *Neuroimage*, 225, 117467.

54. Nikulin, V. V., & Brismar, T. (2004). Long-range temporal correlations in alpha and beta oscillations: effect of arousal level and test–retest reliability. *Clinical neurophysiology*, 115(8), 1896-1908.

55. Nikulin, V. V., Jönsson, E. G., & Brismar, T. (2012). Attenuation of long-range temporal correlations in the amplitude dynamics of alpha and beta neuronal oscillations in patients with schizophrenia. *Neuroimage*, 61(1), 162-169.

56. Olejarczyk, E. & Jernajczyk, W. Graph-based analysis of brain connectivity in schizophrenia. *PLoS One* 12, e0188629 (2017).

57. Peled, A. et al. Functional connectivity and working memory in schizophrenia: an eeg study. *Int. J. Neurosci*. 106, 47–61 (2001).

58. Pion-Tonachini, L., Kreutz-Delgado, K. & Makeig, S. ICLabel: An automated electroencephalographic independent component classifier, dataset, and website. *NeuroImage* 198, 181–197 (2019).

59. Rolls, E. T. et al. Beyond the disconnectivity hypothesis of schizophrenia. *Cereb. Cortex* 30, 1213–1233 (2020).

60. Romme, I. A., de Reus, M. A., Ophoff, R. A., Kahn, R. S. & van den Heuvel, M. P. Connectome disconnectivity and cortical gene expression in patients with schizophrenia. *Biol. psychiatry* 81, 495–502 (2017).

61. Rubinov, M., Knock, S. A., Stam, C. J., Micheloyannis, S., Harris, A. W., Williams, L. M., & Breakspear, M. (2009). Small-world properties of nonlinear brain activity in schizophrenia. *Human brain mapping*, 30(2), 403-416.

62. Rubinov, M. & Sporns, O. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage* 52, 1059–1069 (2010).

63. Rubinov, M. et al. Small-world properties of nonlinear brain activity in schizophrenia. *Hum. Brain Mapping* 30, 403–416 (2009).

64. Sakkalis, V., Oikonomou, T., Pachou, E., Tollis, I., Micheloyannis, S., & Zervakis, M. (2006, January). Time-significant wavelet coherence for the evaluation of schizophrenic brain activity using a graph theory approach. In *2006 International Conference of the IEEE Engineering in Medicine and Biology Society* (pp. 4265-4268). IEEE.

65. Salvador, R., Suckling, J., Schwarzbauer, C. & Bullmore, E. Undirected graphs of frequency-dependent functional connectivity in whole brain networks. Philos. Transactions Royal Soc. B: *Biol. Sci*. 360, 937–946 (2005).

66. Sauseng, P. (2012). Brain oscillations: phase-locked EEG alpha controls perception. *Current Biology*, 22(9), R306-R308.

67. Schechter, I., Butler, P. D., Zemon, V. M., Revheim, N., Saperstein, A. M., Jalbrzikowski, M., ... & Javitt, D. C. (2005). Impairments in generation of early-stage transient visual evoked potentials to magno-and parvocellular-selective stimuli in schizophrenia. *Clinical Neurophysiology*, 116(9), 2204-2215.
68. Schultze-Lutter, F., Ruhrmann, S., Hoyer, C., Klosterkötter, J., & Leweke, F. M. (2007). The initial prodrome of schizophrenia: different duration, different underlying deficits?. *Comprehensive Psychiatry*, 48(5), 479-488.

69. Shim, M., Kim, D.-W., Lee, S.-H. & Im, C.-H. Disruptions in small-world cortical functional connectivity network during an auditory oddball paradigm task in patients with schizophrenia. *Schizophr. Research* 156, 197–203 (2014).

70. Skottun, B. C., & Skoyles, J. R. (2007). Contrast sensitivity and magnocellular functioning in schizophrenia. *Vision Research*, 47(23), 2923-2933.

71. Sporns, O. & Zwi, J. D. The small world of the cerebral cortex. *Neuroinformatics* 2, 145–162 (2004).

72. Sporns, O. *Brain Connectivity*. Scholarpedia 2, 4695 (2007).

73. Sporns, O. *Networks of the Brain* (MIT press, 2010).

74. Sun, L., Castellanos, N., Grützner, C., Koethe, D., Rivolta, D., Wibral, M., ... & Uhlhaas, P. J. (2013). Evidence for dysregulated high-frequency oscillations during sensory processing in medication-naïve, first episode schizophrenia. *Schizophrenia research*, 150(2-3), 519-525.

75. Tomasi, D. & Volkow, N. D. Mapping small-world properties through development in the human brain: disruption in schizophrenia. *PloS One* 9, e96176 (2014).

76. Uhlhaas, P. J., Linden, D. E., Singer, W., Haenschel, C., Lindner, M., Maurer, K., & Rodriguez, E. (2006). Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia. Journal of Neuroscience, 26(31), 8168-8175.

77. Uhlhaas, P. J., Pipa, G., Neuenschwander, S., Wibral, M., & Singer, W. (2011). A new look at gamma? High-(> 60 Hz) γ-band activity in cortical networks: function, mechanisms and impairment. Progress in biophysics and molecular biology, 105(1-2), 14-28.

78. van den Heuvel, M. P., Mandl, R. C., Stam, C. J., Kahn, R. S. & Pol, H. E. H. Aberrant frontal and temporal complex network structure in schizophrenia: a graph theoretical analysis. *J. Neurosci*. 30, 15915–15926 (2010).

79. Wang, Q. et al. Anatomical insights into disrupted small-world networks in schizophrenia. *Neuroimage* 59, 1085–1093 (2012).

80. Watts, D. J. & Strogatz, S. H. Collective dynamics of ‘small-world’ networks. *Nature* 393, 440–442 (1998).

81. Yeap, S., Kelly, S. P., Sehatpour, P., Magno, E., Javitt, D. C., Garavan, H., ... & Foxe, J. J. (2006). Early visual sensory deficits as endophenotypes for schizophrenia: high-density electrical mapping in clinically unaffected first-degree relatives. *Archives of General Psychiatry*, 63(11), 1180-1188.

82. Yu, Q. et al. Altered small-world brain networks in temporal lobe in patients with schizophrenia performing an auditory oddball task. *Front. Syst. Neurosci.* 5, 7 (2011).

83. Yu, Q. et al. Altered topological properties of functional network connectivity in schizophrenia during resting state: a small-world brain network study. *PloS One* 6, e25423 (2011).
84. Zhang, Y., Lin, L., Lin, C. P., Zhou, Y., Chou, K. H., Lo, C. Y., ... & Jiang, T. (2012). Abnormal topological organization of structural brain networks in schizophrenia. *Schizophrenia Research*, 141(2-3), 109-118.

85. Zhao, Z., Cheng, Y., Li, Z. & Yu, Y. Altered small-world networks in first-episode schizophrenia patients during cool executive function task. *Behav. Neurology* 2018 (2018).

86. Zhao, Z. & Wang, C. Using partial directed coherence to study alpha-band effective brain networks during a visuospatial attention task. *Behav. Neurol*. 2019 (2019).

87. Zhu, J. et al. Alterations of functional and structural networks in schizophrenia patients with auditory verbal hallucinations. *Front. Human Neuroscience* 10, 114 (2016).

88. Zick, J. L. et al. Blocking NMDAR disrupts spike timing and decouples monkey prefrontal circuits: Implications for activity-dependent disconnection in schizophrenia. *Neuron* 98, 1243–1255 (2018).

### Tables

Table 1 - Sociodemographic characteristics divided by group and type of antipsychotics used at the time of the experiment. (SCZt) Schizophrenic patients in treatment with typical antipsychotics, (SCZat) atypical, (SCZm) mixed approaches, and non-medicated (NMed); HC = Healthy Controls; results are indicated as means (M) and standard deviation (SD).

| SCZ  | SCZt (n = 2) | SCZat (n = 5) | SCZm (n = 5) | NMed (n = 1) | HC (n = 13) |
|------|-------------|--------------|-------------|-------------|-------------|
| Male | 2 (100 %)   | 3 (60 %)     | 4 (80 %)    | 1 (100 %)   | 7 (53.8 %)  |
| Female | 0           | 2 (40 %)     | 1 (20 %)    | 6 (46.2 %)  |

|     | SCZ  | SCZat | SCZm | NMed | HC  |
|-----|------|-------|------|------|-----|
| Age | 38.5 | 40.6  | 35.8 | 28.9 | 12  |
| Scholarity | 7.5 | 10    | 16   | <1   |
Figure 1

The level of randomness of a network expressed by the Clustering coefficient (C) and the Characteristic Path Length (L). Three network types defined by their nodes and edge boundaries. A regular network shows higher C and L indexes, a small-world network has high C and low L indexes (many short distance node-to-node connections and few long connections). The graph below demonstrates how randomness increases steadily with the decay of L and subsequently C indexes. Finally, the random network exhibits the same probability of short and long node-to-node connections (both low C and L indexes).
Figure 2

Patients with Schizophrenia showed global amplitude reduction in occipital electrodes. Time-series VEP are represented in 225 ms windows containing the pre-stimulus interval (PSI) and VEP periods (200 ms) for O1 (A), Oz (B), and O2 (C) electrodes. PR-VEP grouped curves are shown at left, while violin plots (at right) show the data distribution around the median, represented by the white dotted line on each violin plot. Third and first quartiles are represented in dotted lines above and below the median, respectively.
Non-parametric Mann-Whitney significance: * $(p < 0.01)$ for paired comparisons between HC and SCZ groups.

**Figure 3**

Representative examples of connectivity matrices obtained from low-gamma coherences for pre-stimulus and VEP epochs in a HC (A) and a SCZ subject (B). Upper row: Raw pairwise MSC values, color-coded according to the bar on the right. Middle row: Matrices illustrating only those values in the same color as above, which cross either the CBN (left) or TBN (right) threshold. Blue denotes the remaining pairwise MSC values which did not cross the thresholds, respectively.
Figure 4

Changes of low-gamma small-worldness and characteristic path length after visual stimulus are selectively affected during VEP stimulus in the CBN threshold in patients with schizophrenia. (A) Number of Network Nodes. (B) Number of Edges. (C) Mean Degree Centrality (MK). (D) Mean Clustering Coefficient (MC). (E) Characteristic Path Length (L) of a network. (F) Small-worldness (SW) scores. The Black and blue bar plots represent SCZ and HC groups for both CBN and TBN networks measured during pre-stimulus (PSI) epoch and the visual evoked potential (VEP). Error bars represent standard error of the means. Two-way repeated measures ANOVA significance: * main effect of the stimulus (p < 0.01 and ηp2 > 0.4); ** main effect of the group (p < 0.01 and ηp2 > 0.4).
Figure 5

Alpha-band networks are stimulus – but not group – sensitive. (A) Number of Nodes of the networks. (B) Number of Edges. (C) Mean Degree Centrality (MK). (D) Mean Clustering Coefficient (MC). (E) Characteristic Path Length (L) of a network. (F) Small-worldness (SW) scores. The black and blue bar plots represent SCZ and HC groups for both CBN and TBN networks measured at different visual inputs (PSI and VEP). Error bars represent standard error of the means. Two-way repeated measures ANOVA significance: * main effect of the stimulus ($p < 0.01$ and $\eta^2 0.4$). Note that, in particular, graph measures of TBN networks are affected between conditions and not between groups.
CBN connections evoked by the visual stimulus reveal a less efficient network in SCZ patients in CBN networks for the low-gamma band. Network measures for alpha (8-12 Hz) (A) and low-gamma (B) compared between SCZ and HC (black and blue plots, respectively). The schematic connectivity matrices and channel-based evoked network for alpha and low-gamma bands for one HC (C) and SCZ (D). Visually SCZ subjects evoke fewer connections after the visual stimulus onset as HC subjects do, especially those
edges linked to occipital electrodes (O1, Oz, and O2), suppressing those long-range connections and decreasing the small-worldness and characteristic path length.

**Baseline**  
+  

**Pattern 1**  

**Pattern 2**  

800 ms  
120 ms  
120 ms  

**PSI** Stimulation onset  

1 trial (1040 ms)  

**Pattern-reversal VEP**  

**Figure 7**

Example of one trial of the pattern-reversal visual evoked potential paradigm. Each trial started with a pre-stimulus interval (PSI) containing a fixation point at the center of the screen for 800 ms, followed by two reversal checkerboard patterns with maximum contrast for 120 ms each pattern (VEP). Each trial lasted 1040 ms and was repeated 49 times for all volunteers.