Psychiatry Research: Neuroimaging 270 (2017) 22–31

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Decreased functional connectivity in schizophrenia: The relationship between social functioning, social cognition and graph theoretical network measures

Burak Erdeniz[a,*], Emin Serin[b], Yelda İbadi[c], Cumhur Taş[c]

[a] İzmir University of Economics, Faculty of Arts and Sciences, Department of Psychology, Turkey
[b] Humboldt-Universitätzu Berlin, Berlin School of Mind and Brain, Berlin,Germany
[c] Üsküdar University, Faculty of Humanities and Social Sciences, Department of Psychology, İstanbul, Turkey

ARTICLE INFO

Keywords:
Default-mode
Graph theory
FMRI
Small - world
Schizophrenia
Social functioning
Social cognition

ABSTRACT

Schizophrenia is a complex disorder in which abnormalities in brain connectivity and social functioning play a central role. The aim of this study is to explore small-world network properties, and understand their relationship with social functioning and social cognition in the context of schizophrenia, by testing functional connectivity differences in network properties and its relation to clinical behavioral measures. Resting-state fMRI time series data were acquired from 23 patients diagnosed with schizophrenia and 23 healthy volunteers. The results revealed that patients with schizophrenia show significantly decreased connectivity between a range of brain regions, particularly involving connections among the right orbitofrontal cortex, bilateral putamen and left amygdala. Furthermore, topological properties of functional brain networks in patients with schizophrenia were characterized by reduced path length compared to healthy controls; however, no significant difference was found for clustering coefficient, local efficiency or global efficiency. Additionally, we found that nodal efficiency of the amygdala and the putamen were significantly correlated with the independence-performance subscale of social functioning scale (SFC), and Reading the Mind in the Eyes test; however, the correlations do not survive correction for multiple comparison. The current results help to clarify the relationship between social functioning deficits and topological brain measures in schizophrenia.

1. Introduction

Schizophrenia is a chronic mental health disorder which is associated with abnormalities in social functioning (Green and Leitman, 2008). Poor social functioning is one of the major factors affecting the quality of life in schizophrenia, which can lead to decrease in the ability to work independently, and thus lead to unemployment (Heinrichs et al., 1984; Couture et al., 2006; Brüne et al., 2007; Penn et al., 2008). It is believed that the neurocognitive capacity for social cognition plays a critical role in healthy social functioning (Henry et al., 2016). More specifically, social cognition, especially theory of mind and social emotion processing, has emerged as an important factor which influences social functioning in schizophrenia (Pinkham et al., 2003; Brunet-Gouet and Decety, 2006; Bae et al., 2010; Fett et al., 2011).

Over the last decade, brain imaging studies on social cognition in schizophrenia have created much interest in psychiatry and neuroscience (Sugranyes et al., 2011). These previous studies showed that the involvement of multiple brain regions is critical for social cognition, including fusiform gyrus (FG), superior temporal sulcus, amygdala, and medial prefrontal cortex (Rilling et al., 2008). Among other functions, these regions play a major role in social cognition through emotion regulation (Banks et al., 2007; Hare et al., 2005), and social judgement processes (Adolphs et al., 1998). In the literature, these regions are collectively referred to as the social cognition network (Adolphs, 1999; Van Overwalle, 2009; Schurz et al., 2014; Molenberghs et al., 2016). Patients with schizophrenia show signs of abnormal activations in the brain regions involved in the social cognition network (Li et al., 2009; Kühn and Gallinat, 2011; Green et al., 2015). Impairment in social cognition and its sub-domains, such as emotion processing, theory of mind or social perception, can prevent adaptation to various social situations and general social functioning (Bae et al., 2010). While there have been several studies carried out on social functioning and functional brain imaging (Hooker et al., 2011; Dodell-Feder et al., 2014; Mothersill et al., 2017; Wojtalik et al., 2017; Fox et al., 2017), it is important to further explore the relationship between these two topics, and our study aims to fill the gap in the literature on topological

* Corresponding author.
E-mail address: burak.erdeniz@ieu.edu.tr (B. Erdeniz).

http://dx.doi.org/10.1016/j.pscychresns.2017.09.011
Received 8 August 2016; Received in revised form 14 September 2017; Accepted 16 September 2017
Available online 28 September 2017
0925-4927/

changes in patients with schizophrenia.

Recently, resting-state functional magnetic resonance imaging, a non-invasive imaging technique which has been used to measure spontaneous brain activity (Biswal, 2012), revealed disorder-related abruptions in functional connectivity in patients with schizophrenia (Bluhm et al., 2007; Liang et al., 2006; Salvador et al., 2010). These abruptions mainly occur in frontotemporal regions (Friston and Frith, 1995; Tanet al., 2005) and occipitotemporal regions (Kim et al., 2003). Zalesky and colleagues (2010) used network-based statistic (NBS) method to identify abnormal functional connectivity in patients with schizophrenia. They showed that patients with schizophrenia have decreased connectivity between temporal and frontal lobes (Zalesky et al., 2010; Fornito et al., 2012). Parallel to the resting state functional connectivity studies, graph theoretical studies also reveal that brains of normal healthy subjects show small-world network-like functional connectivity indicated by high local clustering (e.g., clustered connectivity around individual nodes indicate high functional segregation) and short path lengths (e.g., gathering information between nodes indicating high functional integration) (Bullmore and Sporns, 2012). Graph theoretic measurements of resting state brain networks in patients with schizophrenia have revealed decreased small-world properties (changes in the balance between functional integration and segregation), that include decreased clustering and decreased efficiency (Bassett et al., 2008; Bullmore et al., 2009; Liu et al., 2008). Indeed, the graph theoretical approaches have provided a powerful tool for characterizing topological properties of complex brain networks on a whole brain scale (Bullmore and Bassett, 2011; He et al., 2009; Lynall et al., 2010; Skudlarski et al., 2010). According to these studies, compared to healthy brains, information processing in the brain of patients with schizophrenia follows a longer and less efficient path, indicating a greater energetic cost (Fornito et al., 2012), and less efficient information processing (Zalesky et al., 2010). Two previous fMRI studies using graph theory (Liu et al., 2008; Yu et al., 2011), revealed deviations in small-world network properties in patients with schizophrenia. More specifically, they showed that frontal, parietal and temporal regions show a dysfunctional integration of information. Given the anatomical and functional connectivity differences between healthy participants and patients with schizophrenia (Pettersson-Yeo et al., 2011; Fornito et al., 2012), it remains unclear how these abnormalities are related to social functioning and small-world network properties.

Although previous studies have revealed changes in the resting state functional connectivity in patients with schizophrenia, there is a lack of clarity regarding the relationship between symptoms of social functioning and brain networks (Wojtalik et al., 2017; Fox et al., 2017). In the current study, in order to identify the brain regions with hypo or hyper connectivity, we first compared functional connectivity between individuals with schizophrenia, and healthy controls using the network-based statistic (NBS) approach (Zalesky et al., 2010). Based on previous studies, we hypothesized that patients with Schizophrenia should show decreased functional connectivity between frontal, temporal and limbic regions. Furthermore, in order to identify which network measures are affected by the disease, we compared small-world network properties (i.e., clustering coefficient and characteristic path length), network efficiency (i.e., global and local efficiencies) and local network properties (nodal efficiency and nodal degree) in those connections with decreased connectivity, and assessed the correlational relationship between these network measures and clinical measures of social functioning.

Overall, the aim of this study is to explore changes in functional brain connectivity in patients with schizophrenia, and identify the types of brain connectivity changes (i.e., global or local network metrics) that are correlated with patients' social functioning and social cognition scores. To test our hypothesis, we collected resting-state fMRI with 23 patients with schizophrenia and 23 healthy controls, and compared global and local graph theoretical network metrics in relation to symptom severity and social functioning measures.

2. Methods

2.1. Participants

The participants were twenty-three patients (male: 14, female: 9) between the ages of 21–44 (M = 32.09; SD = 6.32) meeting the diagnostic criteria for schizophrenia *DSM–IV-TR* (American Psychiatric Association, 2000). The control group consisted of twenty-three (male: 14, female: 9) healthy participants between the ages of 20–45 (M = 31.04; SD = 6.58), recruited from the general community and score less than 0.5 in Symptom Check-List 90 R (SCL-90R) subscales that include somatization, obsession, depression, anxiety, hostility, phobic anxiety, paranoid ideas and psychoticism (Derogatis, 1994). Additionally, for the healthy control group, we excluded those with a family history of psychosis, drug or alcohol addiction problem. We also excluded participants with neurological conditions or any significant head injury that may have caused permanent damage to cognitive or sensory functions. All patients with schizophrenia in the study were recruited compliant to an atypical neuroleptic pharmacotherapy, based on self- and clinician-report. The patients recruited in this study were clinically stable, i.e. not hospitalized in the previous 12 months, and had received a stable dose of antipsychotic medication over the previous 6 months. Patients who used drugs or alcohol were also excluded from the study; however, smoking was not an exclusion criterion. Approximately 44% of patients were using biperiden, and the rest were on quetiapine medication. Additionally, 40% were taking an antidepressant or mood-stabilizing medication. Symptom severity was assessed using the Positive and Negative Syndrome Scale (Kay et al., 1989). With regard to symptom levels, mean scores of patients with schizophrenia in the present study were 16.43 (SD= 5.41) for positive symptoms, 17.13 (SD= 6.99) for negative symptoms, 29.13 (SD= 10.19) for general psychopathology, and 62.71 (SD= 21.10) for the-total scale. The present study was approved by the Ethics Committee of Üsküdar University (Table 1).

2.2. Behavioral scales

We administered the Positive and Negative Syndrome Scale (PANSS), Social Functioning Scale (SFS), and the Reading the Mind in the Eyes Test on both the healthy and the patient group. The details of the statistical differences are reported in Table 2. More specifically, the Symptom severity was measured with *Positive and Negative Syndrome Scale,* developed by Kay and colleagues (1989). The scale contains 30 items, with a 7 - point Likert scale ranging from 1 (absent) to 7 (extreme). Social functioning of the participants was measured using the *Social Functioning Scale* (SFS)(Birchwood et al., 1990), designed to measure seven areas of social functioning necessary for daily living, especially in patients with schizophrenia. The SFS has seven dimensions: social engagement/withdrawal, interpersonal behavior, pro–social activities, recreation, independence – competence (the degree to which an individual is able to perform skills required for independent living), independence – performance (performance of skills required for independent living) and employment. Higher SFS scores indicate better social functioning. *The Reading the Mind in the Eyes Test* designed by Baron – Cohen and colleagues was used to test theory of mind ability

Table 1
Demographic and Clinical Characteristics of the Study Sample.

Demographics, mean (± SD)	Groups Schizophrenia (N = 23)	Healthy Controls (N = 23)	P value
Age	32.09 (6.32)	31.04 (6.58)	> 0.05
Education Year	11.35 (2.79)	14.96 (3.72)	> 0.05
Gender, M / F	14 / 9	14 / 9	–
Duration of the Illness, years	15.5 (6.9)	–	–

Table 2
Mean scores of participants in Social Functioning Scale and Reading the Mind in the Eyes test and group differences between schizophrenia and healthy controls.

	Schizophrenia		Healthy Controls				
	M	SD	M	SD	*t*-value (*df* = 44)	Sig.	Cohen's *d*
Social Withdrawal/Engagement	9.70	2.88	12.96	1.80	− 4.60[a]	< 0.01	1.36
Interpersonal Interaction	2.70	2.18	7.57	1.56	− 8.70[a]	< 0.01	2.57
Independence - Performance	21.83	8.29	33.00	5.14	− 5.94[a]	< 0.01	1.62
Independence - Competence	33.39	6.08	37.96	2.14	− 3.40[a]	< 0.01	1.00
Recreation	13.13	5.94	19.61	5.43	− 3.86[a]	< 0.01	1.14
Pro-Social Activities	11.22	6.86	25.70	10.79	− 5.43[a]	< 0.01	1.60
Employment	3.96	3.57	10	0.00	− 8.11[a]	< 0.01	2.39
Social Functioning Scale Total	95.91	25.30	146.78	19.92	− 7.58[a]	< 0.01	2.23
Reading the Mind in the Eyes Test	16.04	5.58	24.52	3.88	− 6.16[a]	< 0.01	1.77

[a] *t*-value is significant at the 0.01 level (2-tailed).

and social emotion processing (Baron-Cohen et al., 2001). The test is common in the evaluation of individuals' ability to understand the mental states of others and affective theory of mind. The current written version of the test contains 36 items, with four choices for each item. During the test, participants choose between 1 of 4 adjectives or mental states that best define each visual stimuli.

2.3. Functional MRI data acquisition

Data acquisition was performed on 1.5 T Philips Achieva scanner at the Istanbul Neuropsychiatry Hospital. Foam pads ensured minimum head movement within the coil while imaging. We collected T1 weighted MPRAGE type anatomical images (TR/TE = 8.54/3.99 ms, flip angle = 8°, FOV = 24 * 24 cm, matrix = 256 × 256, 0.94 mm isotropic voxel size). The MPRAGE acquisition took approximately 18 min. Functional images were gathered using a gradient-echo-planar imaging sequence (TR = 2640 ms, TE = 40 ms, flip angle = 90°, FOV = 240 mm* 240 mm, matrix = 64 * 64). The whole brain was imaged in 32 slices with a width of 3.5 mm * 3.5 mm * 3.5 mm in-plane spatial resolution. The fMRI imaging session lasted a total of 11 min, during which participants had their eyes open and were instructed to focus on the fixation cross on the screen.

2.4. Image preprocessing

Image pre-processing was performed with statistical parametric mapping toolbox (SPM 8, Wellcome Department of Imaging Neuroscience, London (Friston et al., 1995), UK, using MATLAB version R2010a) and consisted of: removal of first 10 volumes, slice timing correction, realignment of functional images using 2nd degree B-Spline interpolation, coregistration, normalization of coregistered images to MNI template, resampling to 3-mm isotropic voxels respectively. Regarding motion correction, none of the subjects showed head movement that was excessive, i.e., greater than 2 mm. Additionally, to ensure that there was no difference between schizophrenia and control group for head movement, we compared averaged framewise displacement (FD, Power et al., 2012), which is a scalar quantity that represents instantaneous head motion. The analysis revealed no significant difference for head movement (t (44) = − 1.24, $p > 0.05$) (see Supplementary Table 4). After normalization and pre-processing, the functional images were spatially smoothed using a Gaussian kernel of 4 mm full width at half-maximum. The calculation of the functional connectivity maps was carried out using the Data Processing Assistant for Resting-State fMRI (DPARSF) software package (Yan, 2010) and the Resting-State fMRI Data Analysis Toolkit (REST, http://www.restfmri.net) (Song et al., 2011). Image detrending and temporally band-pass filtering (0.01–0.08) (Greicius et al., 2003) was applied to functional images. Six head motion realignment parameters (3 rotations and 3 translations) in addition to signals from the WM and CSF were regressed out during the calculation of functional connectivity maps (Jo et al., 2013). 4 mm ROI seeds were then placed to the MNI coordinates in the left and right brain hemispheres defined by the AAL atlas (Tzourio-Mazoyer et al., 2002).

2.5. Graph theoretical analysis and network metrics

2.5.1. Node and edge definition

In order to apply Network based statistics (NBS) method (Zalesky et al., 2010), it is necessary to identify the connectivity matrix between regions-of-interest for each subject. The automated anatomical labeling (AAL,Tzourio-Mazoyer et al., 2002) template was employed to divide the brain into 90 standardized regions-of-interest. All regions included in the analysis are based on the AAL atlas, and are listed in Supplementary Table 1. The total number of connections for N = 90 was calculated as $N*(N-1)/2 = 4005$ connections (Zalesky et al., 2010). The cerebellum was excluded due to inconsistent sampling across participants during data acquisition. The residuals from the above-described regression were spatially averaged over the voxels comprising each region, yielding a set of 90 regional time series, representing 11 min of resting-state. The functional connectivity between each pair of regions was quantified independently using the Pearson correlation coefficient, resulting in a symmetric 90 by 90-connectivity matrix for each participant; and then normalized using z-transformation (see Fig. 1).

2.5.2. Network based statistics (NBS)

We used the NBS method (Zalesky et al., 2010) to identify the hypo and hyper connected components in patients with schizophrenia. The purpose of the NBS is to identify any pairwise associations that are significantly different between groups. (Bullmore et al., 2009). The two main difference between NBS from other threshold techniques are its capacity to estimate family-wise error correction for pairs of associations between nodes, and its sensitivity to distributed networks with multiple connections (Zalesky et al., 2010), whereas the false discovery rate (FDR), is more sensitive to focal, isolated single connections (Zalesky et al., 2010). Therefore, we administered NBS threshold and FDR threshold separately to provide a network comparison.

2.5.3. Small-world network metrics

For brain networks, we calculated both global network measures, which involve metrics computed using all nodal connections, and also regional network measures, which are calculated using only certain nodes or group of nodes. For the network metric analysis, we used GRETNA software (Wang et al., 2015). The global measures for small-world network parameters include the calculation of clustering coefficient Cp (depicts functional segregation based on the number of triangles in the network), normalized clustering coefficient, γ (clustering coefficient normalized by the random network), path length Lp (depicts functional segregation based on the shortest path length between all pair of nodes), normalized path length, (depicts path length normalized

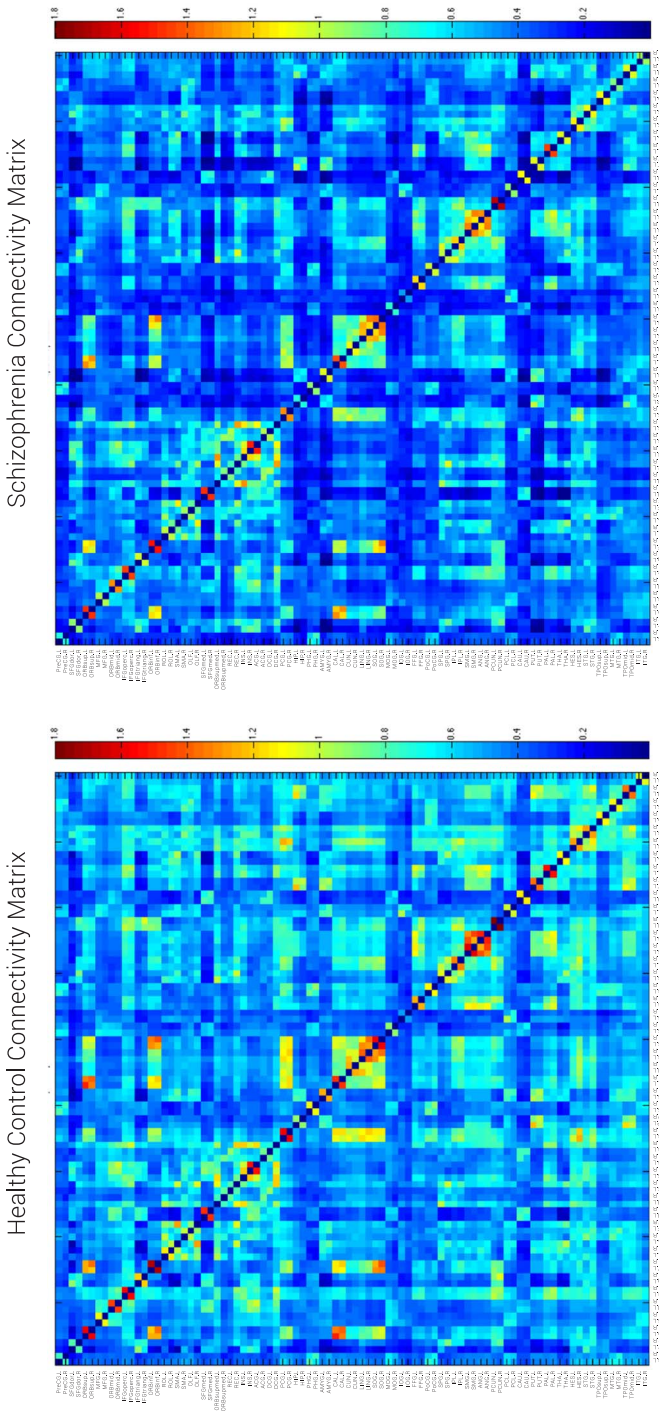

Fig. 1. Functional connectivity (correlation coefficient) matrix for healthy (on the left) and individuals with schizophrenia (on the right). The axes represent the 90 AAL brain regions used in the analysis (see, Supplementary Table 1). The color of each entry represents the level of connectivity depicted by normalized (Fisher's *r*-to-*z* transformation) correlation coefficient.

by the random network), network efficiency measures (depicts parallel information flow) and small-world-ness Σ (clustering coefficient/path length). Other calculations were local efficiency, which measures of the shortest path length between two disconnected networks, and finally, global efficiency, which is an inverse measure of shortest path length that finds the number of disconnected networks (see Supplementary Material for details). For the calculation of individual local network metrics for each significant node (based on the results from NBS analysis), we calculated two nodal centrality metrics: the degree of a node (measures the number of links connected to a specific node), and the efficiency of a node (for a recent review on uses and interpretations of these network measures)(see Rubinov and Sporns, 2010; Wang et al., 2015; Zhang et al., 2011). For each network metric of each individual subject, we first calculated the metric values before performing between subject *t*-tests in order to quantify any group-level difference between the patients with schizophrenia and the healthy group, and include only significantly different regions in the correlation analysis with social functioning measures (see Sections 3.3 and 3.4).

3. Results

3.1. Behavioral results

Between-group differences (healthy control vs. schizophrenia) for the behavioral ratings conducted before the scanning session revealed significant mean differences for all subscales of social functioning (Social Withdrawal/Engagement (t (44) = − 4.60, $p < 0.01$), Interpersonal Interaction (t (44) = − 8.70, $p < 0.01$), Independence-Performance (t (44) = − 5.94, $p < 0.01$), Independence - Competence (t (44) = − 3.40, $p < 0.01$), Recreation (t (44) = − 3.86, $p < 0.01$), and Pro-social Activities (t (44)= − 5.43, $p < 0.01$), Employment (t (44) =− 8.11, $p < 0.01$) as well as for total social functioning score (t (44) = − 7.58, $p < 0.01$) (see Table 2). Furthermore, significant differences were observed between groups for Reading the Mind in the Eyes test (t (44) = −6.16, $p < 0.01$). Based on Cohen's effect size benchmark values, comparison between the patient and healthy group showed large effect sizes for behavior; the detailed results for the behavioral differences and effect sizes are reported in Table 2.

3.2. Network based statistics

A between subject *t*-test was administered using the NBS software, in order to compare the connectivity matrices for schizophrenia > healthy control and healthy control > schizophrenia contrasts. Connection weights below the value of $t = 3.1$ were excluded from the analysis. A family-wise error (FWE) corrected p-value was calculated for the size of each resulting pair using permutation testing (20000 permutations). The NBS approach identified a single network showing significantly ($p < 0.01$, FWE-corrected) decreased connectivity in individuals with schizophrenia compared to healthy controls (Supplementary Table 2). This affected network comprised of 191 edges, involving 72 of the 90 brain regions, indicating that 80% of the regions showed reduced connections in the schizophrenia group (Supplementary Figure 1). However, there were no significant results for the schizophrenia > healthy control contrast. We also repeated the analysis with the FDR threshold, which strictly controls the false positives rate at the level of individual connections (Zalesky et al., 2010). We set the FDR correction level to$p < 0.01$ (20000 permutations) for both the schizophrenia > healthy control and schizophrenia < healthy control contrast. The affected network for schizophrenia < healthy control with FDR correction comprised of 13 nodes and 11 edges (Fig. 2). Figures were visualized with the BrainNet Viewer (Xia et al., 2013) and the NBS software (https://www.nitrc.org/projects/nbs/) revealing no significant results were found for schizophrenia > healthy control ($p > 0.01$, FDR corrected)

Within the NBS analysis framework, regardless of the thresholding technique, all connections revealed a lower value for both long and short distance connectivity in the schizophrenia group, as compared to healthy controls. More specifically, FDR correction indicated decreased connectivity in the subcortical regions, including the bilateral putamen, left amygdala, right posterior cingulate gyrus. Additionally, the right superior frontal gyrus showed decreased long distance connections with bilateral inferior occipital gyrus (see, Fig. 2).

In order to determine whether there was a significant group difference in global network metrics which applied to all of the 90 AAL regions, we first calculated the between-subject group difference for each network metric value. No significant difference was found for the clustering coefficient, normalized clustering coefficient, normalized path length, or global and local efficiency ($p > 0.05$, see Supplementary Table 5). However, compared to healthy controls, patients with schizophrenia showed a trend for higher levels of average path length, t (44) = 1.97, $p = 0.055$, suggesting a trend for increased path length in patients with schizophrenia (Fig. 3).

3.3. Relationship between global network metrics and clinical variables: an exploratory analysis

Furthermore, in order to investigate the relationship between global network metrics of each patient with schizophrenia and clinical scale measures, we performed a multiple correlation analysis between network metrics, Reading the Mind in the Eyes test and Social Functioning Scale. An additional area for investigation is the relationship between altered topological connections and symptom severity in patients with schizophrenia (Liu et al., 2008). In order to explore this relationship, we performed correlation analysis between PANSS scores and global network metrics. The results revealed that the scores of social withdrawal subscale were significantly negatively correlated with γ ($r = − 0.56$, $p < 0.05$, uncorrected) and small-world-ness ($r = − 0.61$, $p < 0.05$, uncorrected); interpersonal interaction subscale scores were also significantly negatively correlated with γ, ($r = − 0.49$, $p < 0.05$, uncorrected) and small-world-ness ($r = − 0.46$, $p < 0.05$, uncorrected). Additionally, we found significant positive correlation between the employment subscale and λ, ($r = 0.42$, $p < 0.05$, uncorrected). We also performed the same multiple correlation analysis applying Bonferroni and Benjamini-Hochberg (FDR) corrections, but none of the network measures significantly correlated with the social scale measures. The complete list of results can be found in Supplementary Table 6.

3.4. Relationship between local network metrics and clinical variables: an exploratory analysis

Firstly, in order to determine whether there was a significant difference between patients with schizophrenia and healthy controls, we calculated local network metric values (nodal degree and nodal efficiency) for the 13 regions identified from the FDR (false discovery rate) corrected NBS analysis. A between subjects *t*-test was performed to compare these values. Of the 13 regions that were identified a priori, we found a significant difference in three regions for nodal degree, and six for the nodal efficiency (See, Supplementary Table 7). These significant regions were then included in the correlation analysis with social functioning questionnaire and with Reading the Mind in the Eyes test. The correlation analysis revealed that the scores of independence performance subscale significantly positively correlated with the nodal efficiency of the left amygdala ($r = 0.34$, $p < 0.05$, uncorrected), and the nodal efficiency of the right putamen ($r = 0.30$, $p < 0.05$, uncorrected) as well as with the nodal degree of the right putamen ($r = 0.32$, $p < 0.05$, uncorrected). Also, the scores of Reading the Mind in the Eyes test significantly positively correlated with: the nodal efficiency of the left amygdala ($r = 0.33$, $p < 0.05$, uncorrected), the nodal efficiency of the right putamen ($r = 0.31$, $p < 0.05$, uncorrected), the nodal degree of the left middle temporal gyrus ($r = 0.36$, $p < 0.05$, uncorrected) (Table 3). However, we found no significant correlation

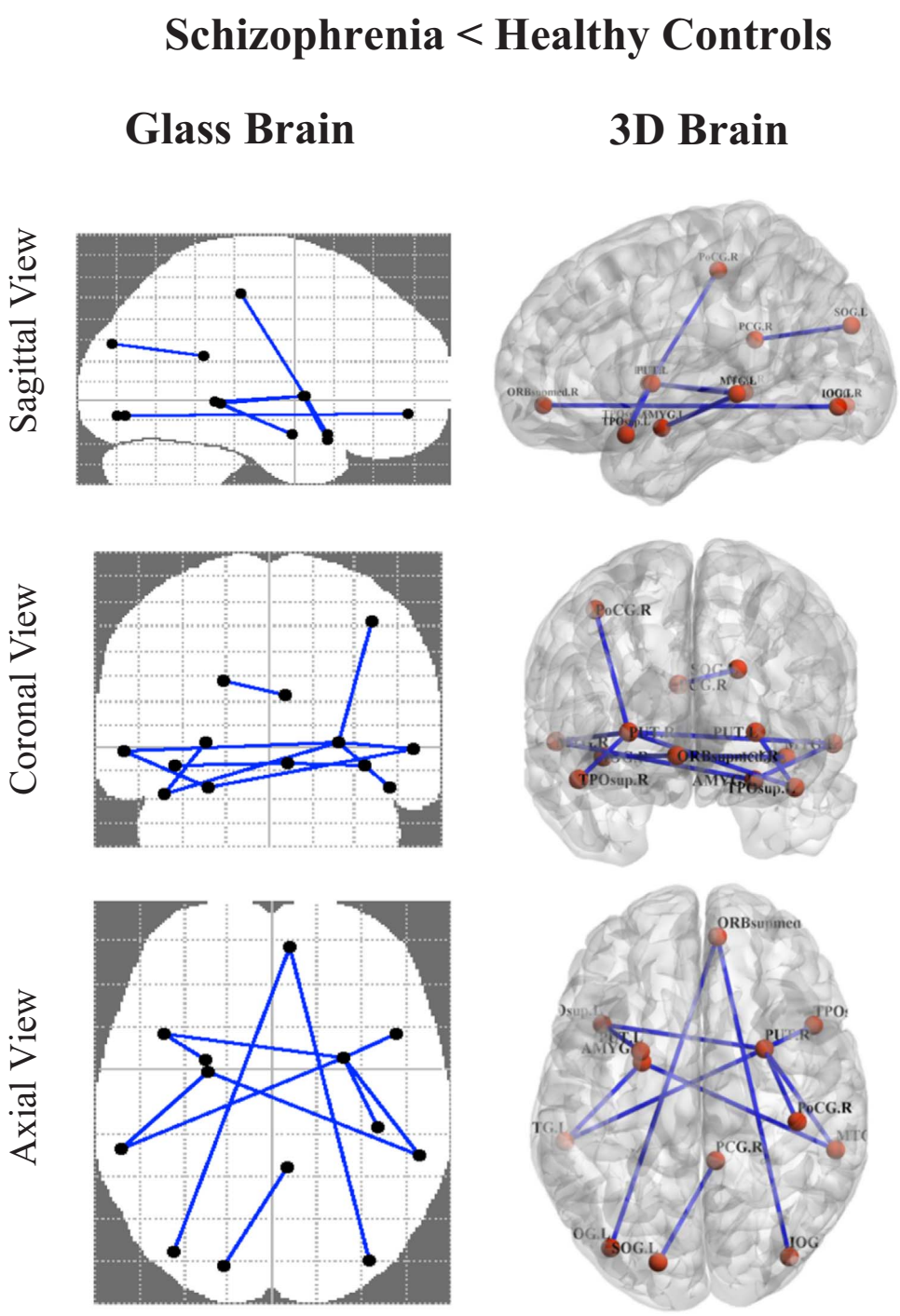

Fig. 2. The figure on the left side shows brain regions (nodes) and suprathreshold links (edges) with significantly decreased functional connectivity in schizophrenia compared to healthy control overlaid on a glass brain. The figure on the right shows significant nodes defined by Automated Anatomical Labeling (AAL) atlas, and grey lines represent suprathreshold links comprising the affected network identified with the False Discovery Rate ($p < 0.01$, 20000 permutations). The axial view illustrates the involvement of interhemispheric connections. The sagittal view illustrates the involvement of frontal, temporal, and parietal lobes in the affected network. Abbreviations: ORB.supmed. R: Right superior frontal gyrus-medial orbital part, PCG.R: Right posterior cingulate gyrus, AMYG.L: Leftamygdala, SOG.L: Left superior occipital, IOG.L: Left inferior occipital, IOG.R Right inferior occipital, PoCG.R: Right postcentral gyrus, PUT.L: Left putamen,PUT.R: Right putamen, TPOsup. L: Left superior temporal pole, TPOsup. R: Right superior temporal pole, MTG.L: Left middle temporal gyrus, MTG.R: Right middle temporal gyrus.

after performing Bonferroni and FDR corrections.

4. Discussion

The initial aim of the current study was to assess how the abnormalities in functional connectivity in patients with schizophrenia relate to social functioning and social cognition. In order to identify differences, we performed functional connectivity analysis to compare significant differences between patients with schizophrenia and healthy controls. Previous studies showed evidence of decreased functional connectivity in patients with schizophrenia (Fornito et al., 2012; Friston, 1998; Zalesky et al., 2011, 2012). Based on two thresholding techniques, we found that for patients with schizophrenia, 80% (FWE corrected) and 14% (FDR corrected) of the brain regions in the NBS analysis showed decreased connectivity, particularly in the links between frontal, temporal and striatal regions. Frith and Frith (2007) suggested that frontal and temporal cortex play a role in social cognition, especially in theory of mind, it is possible that disconnectivity in these regions contributes to impaired social cognition in schizophrenia (Bora et al., 2009). Our findings are also consistent with a wide range of studies implicating frontal dysfunction as a core feature of schizophrenia pathophysiology (Carlsson and Carlsson, 1990; Robbins, 1990; Tekin and Cummings, 2002). In addition to frontotemporal regions, we found a significant reduction in connectivity in posterior cingulate gyrus. It has been suggested that posterior cingulate gyrus is involved in affective processing of social information, and also in disorders such as Capgras delusion (Ellis and Young, 1990; Rilling et al., 2004; Saxe and Powell, 2006). Interestingly, apart from other striatal regions, we only

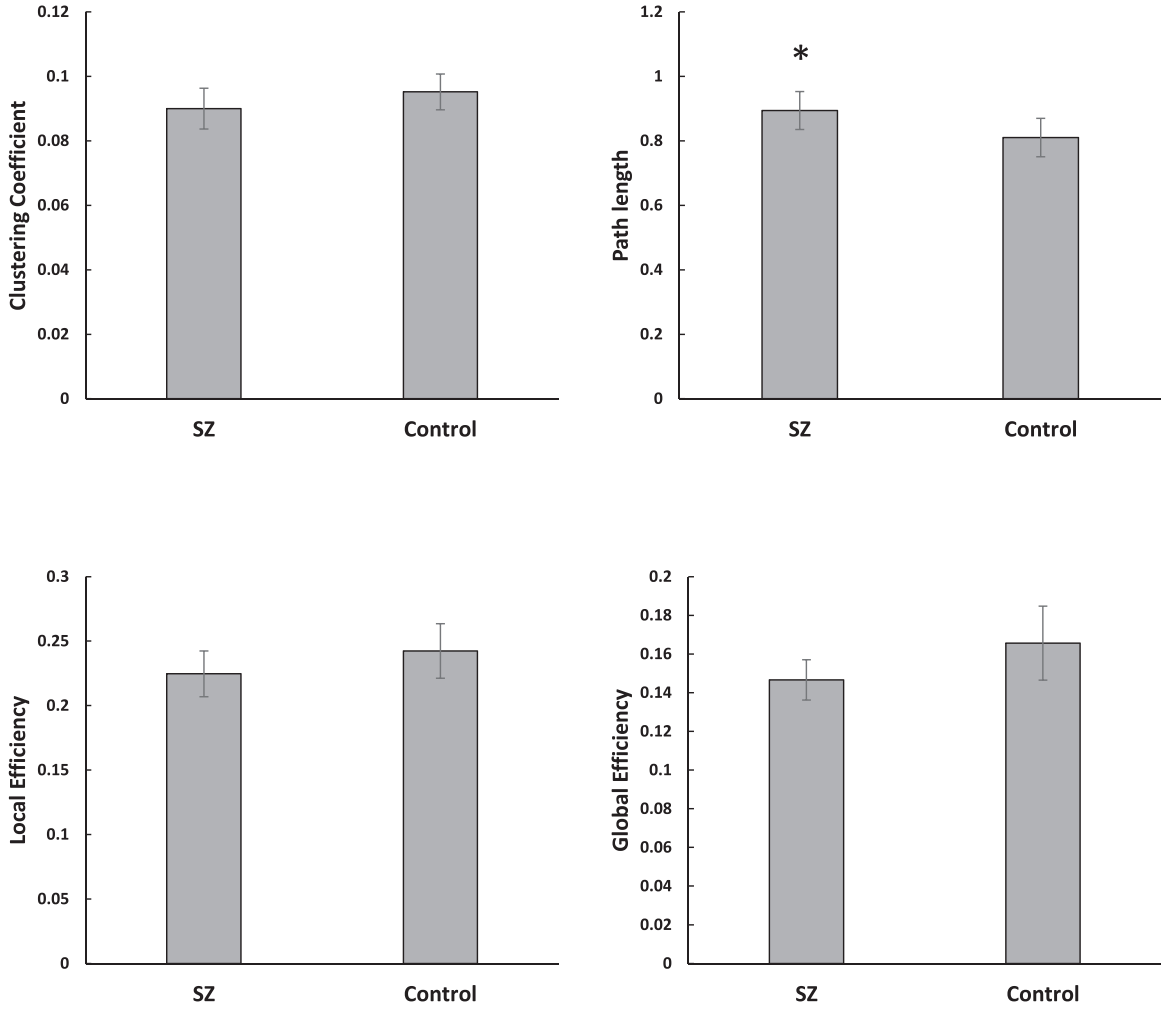

Fig. 3. Differences in topological properties of functional brain networks (including all 90 regions) between individuals with schizophrenia (SZ) and healthy controls (Control). * Depicts a trend for a difference for path length (p = 0.055, uncorrected). No significant differences were found for clustering coefficient, local efficiency or global efficiency ($p > 0.05$, uncorrected).

Table 3
Shows significant correlations between nodal efficiency and nodal degree with social symptom scales.

Nodal Efficiency	Behavioral Tests	Correlation Coefficient (r)	Sig.	95% Confidence Interval of the Correlation	
				Lower	Upper
Left Amygdala	Independence Performance	0.342[a]	0.020	0.067	0.568
	Reading the Mind in the Eyes Test	0.327[a]	0.026	0.05	0.557
Right Putamen	Independence Performance	0.301[a]	0.042	0.022	0.537
	Reading the Mind in the Eyes Test	0.308[a]	0.038	0.029	0.542
Nodal Degree					
Right Putamen	Independence Performance	0.324[a]	0.028	0.047	0.555
Left Middle Temporal Gyrus	Reading the Mind in the Eyes Test	0.359[a]	0.014	0.087	0.582

Results showed that only positive correlation exists, showing that increases in social scale measure values are significantly correlated with increases in Nodal Efficiency and Nodal Degree.

[a] Correlation is significant at the 0.05 level (2-tailed).

found reduced bilateral putamen connectivity. Supporting this finding, a recent study by Tu and colleagues (2012) found that, compared with healthy controls, patients with Schizophrenia showed significantly reduced functional connectivity in the bilateral putamen. Other studies have suggested that as well as the functional connectivity of the frontostriatal and frontotemporal regions, the structural connectivity is also affected in schizophrenia (Zhu et al., 2016). Thus, underlying neuroanatomical disturbances in these regions might be responsible for the overall decreased functional connectivity in schizophrenia.

Previous studies comparing network metrics in patients with schizophrenia found decreased small-world-ness (Yu et al., 2011), efficiency (Su et al., 2015), and shortest path length (Rubinov et al., 2009). However, of these three factors, we found only a trend toward significance for increased shortest path length in the schizophrenia group (see Micheloyannis et al., 2006). Hadley et al., (2016) showed that patients who responded to antipsychotic medications regain their resting state connectivity. It is plausible that, due to our patients' long-term treatment (M =15 years) and their clinically stability, their functional connectivity had recovered to a certain degree, possibly accounting for the difference in findings compared to the mentioned previous studies.

In the current study, when investigating the relationship between individual network measures and their correlation with social scale measures, we observed a significant negative correlation between small-world parameter and Social Withdrawal/Engagement score.

Additionally, we found a negative correlation between normalized path length and Social Withdrawal/Engagement score. These results suggest a possible relationship between underlying differences in small-world network properties and social functioning. Furthermore, unlike Wang and colleagues (2012), who showed a negative correlation with positive symptom scores and local efficiency of the anatomical networks, we observed no relationship between PANSS score and network measures. Differences on this finding might be related to the anatomical variations caused by the duration of the disease; in the study by Wang and colleagues, the average disease duration was only 10 years, an average of 5 years less than in our study.

We found differences in nodal efficiency and nodal degree between schizophrenia patients and the healthy control group, the former group showing decreased nodal degree and efficiency. More specifically, we noted decreased nodal degree, particularly in the right putamen, and bilateral middle temporal gyrus, whereas nodal efficiency was significantly decreased, particularly in the amygdala, posterior cingulate gyrus, and right putamen. The putamen has long been known to play a significant role in mediating motor function, and is a major site for antipsychotic medication (Tamminga, 2000). It is plausible that the nodal degree of this region might be related to the rewarding properties of social situations and interpersonal relations (Báez-Mendoza and Schultz, 2013; Krach et al., 2010). The relationship between nodal metrics and social scale measures, and the finding related to amygdala are consistent with previous studies that suggest a role for amygdala in theory of mind performance in healthy subjects (Siegal and Varley, 2002; Stone et al., 2003). As showed by Fine and colleagues (Fine et al., 2001), performance on theory of mind task can be impaired by left amygdala damage. The results of the current study also revealed that node efficiency of left amygdala positively correlated with the scores of Independence - Performance, and Reading the Mind in the Eyes test scores. There are three possible reasons. Firstly, when we consider the amygdala and its relation to independence performance scores, it is plausible that intact processing of social cues might enhance social relations as suggested by other studies (Brunet-Gouet and Decety, 2006). Secondly, as considering the Reading the Mind in the Eyes test, previous articles have showed that amygdala is involved in both theories of mind and social intelligence (Baron-Cohen et al., 1999; Churchman, 2001; Fine et al., 2001; Levine et al., 2008). Given the importance of its role in social cognition, it is possible that decreased amygdala connectivity contributes to decreased perception of intentions of others in schizophrenia (Siegal and Varley, 2002). Finally, there was a significant positive correlation between nodal degree of middle temporal gyrus and Reading the Mind in the Eyes test scores, in line with studies highlighting the role of the middle temporal gyrus in theory of mind, an area which is considered to be key component of social cognition (Blakemore, 2008; Wang et al., 2015). Finally, it is important to note that, although we observed large effect sizes for the correlations reported for the relationship between local network metrics and clinical variables, and for the relationship between global network metrics and clinical variables, these were uncorrected for multiple comparison. After correction for multiple comparisons, none showed sufficient significance. Therefore, caution should be exercised in interpreting these results.

4.1. Limitations

There are several limitations that need to be further addressed. Firstly, in the current study, regions of interests involved in the network analysis are derived from the AAL atlas, based on previous studies with high test-retest reliability results, which is an important consideration when the goal is to compare clinical populations (Faria et al., 2012). However, several studies have found differences in small-world-ness various across different atlases, highlighting the importance of parcellation strategy (Wang et al., 2009; Zalesky et al., 2010). This is a potential issue for exploration in the future studies. It should also be noted that some participants were on anti-depressant medication. It is plausible that decreased social functioning might be related to depression (Rieckmann et al., 2005). Another limitation of the current study was that the data collection was performed on a 1.5 T scanner, whereas using an MRI scanner with increased magnetic field strength could potentially result in more accurate detection of the differences in the map of connections. Moreover, due to feasibility reasons, it was necessary to use SCL-90 rather than a clinical interview to rule out psychiatric diagnosis in the control group. Nonetheless, no psychiatric medication or history of a psychiatric disorder was identified in the control group. Finally, it is important to mention that some recent studies argue that failing to correct for autocorrelation in fMRI time-series results in "spurious" correlation coefficients especially in resting state fMRI studies (Christova et al., 2011; Georgopoulos and Mahan, 2013). A recent study by Arbabshirani et al. (2014) compared functional connectivity in patients with schizophrenia and healthy controls, and showed that correlations remain similar before and after correcting for autocorrelations. We believe that this is an important issue in respect to accuracy of the results, but we assume that the effect of autocorrelation would be similar in our study, due to insignificant differences in head motion between groups, and as a result autocorrelation might be washed out by the independent sample *t*-test, as Arbabshirani et al. (2014) proposed. In order to avoid such limitations, we believe that future studies should consider performing autocorrelations and comparing motion parameters between groups.

5. Conclusion

The current study has identified a number of differences in network connectivity between the nodes showing both contralateral and ipsilateral long-range connections, as identified by decreased connectivity in fronto-occipital edges. An important role in this altered network might be played by subcortical brain regions, particularly the amygdala and putamen, which also showed differences in local network metric values, probably affecting information processing in the small-world structure of the whole brain network. These regions also showed decreased connections with several frontal and temporal regions, supporting the interpretation of disconnectivity hypothesis of neural networks in this illness. These findings are supported by contemporary neuropsychological theories regarding impaired social cognition and social functioning in schizophrenia, and provide new insight into the neural correlates of schizophrenia.

Contributors

The Authors B. E. and E. S. analysed the data and wrote the article, Y. I. and C. T. collected the data and reviewed the manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2017.09.011.

References

Arbabshirani, M.R., Damaraju, E., Phlypo, R., Plis, S., Allen, E., Ma, S., Calhoun, V.D., 2014. Impact of autocorrelation on functional connectivity. Neuroimage 102, 294–308.

Adolphs, R., 1999. Social cognition and the human brain. Trends Cogn. Sci. http://dx.doi.org/10.1016/S1364-6613(99)01399-6.

Adolphs, R., Tranel, D., Damasio, A.R., 1998. The human amygdala in social judgment. Nature 393, 470–474. http://dx.doi.org/10.1038/30982.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, Text. Washington. ⟨http://dx.doi.org/10.1002/jps.3080051129⟩.

Bae, S.-M., Lee, S.-H., Park, Y.-M., Hyun, M.-H., Yoon, H., 2010. Predictive factors of social functioning in patients with schizophrenia: exploration for the best

combination of variables using data mining. Psychiatry Investig. 7, 93–101. http://dx.doi.org/10.4306/pi.2010.7.2.93.
Báez-Mendoza, R., Schultz, W., 2013. The role of the striatum in social behavior. Front. Neurosci. http://dx.doi.org/10.3389/fnins.2013.00233.
Banks, S.J., Eddy, K.T., Angstadt, M., Nathan, P.J., Luan Phan, K., 2007. Amygdala-frontal connectivity during emotion regulation. Soc. Cogn. Affect. Neurosci. 2, 303–312. http://dx.doi.org/10.1093/scan/nsm029.
Baron-Cohen, S., Ring, H.A., Wheelwright, S., Bullmore, E.T., Brammer, M.J., Simmons, A., Williams, S.C.R., 1999. Social intelligence in the normal and autistic brain: an fMRI study. Eur. J. Neurosci. 11, 1891–1898. http://dx.doi.org/10.1046/j.1460-9568.1999.00621.x.
Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., Plumb, I., 2001. The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. J. Child Psychol. Psychiatry 42, 241–251. http://dx.doi.org/10.1111/1469-7610.00715.
Bassett, D.S., Bullmore, E., Verchinski, B.A., Mattay, V.S., Weinberger, D.R., Meyer-Lindenberg, A., 2008. Hierarchical organization of human cortical networks in health and schizophrenia. J. Neurosci. 28, 9239–9248. http://dx.doi.org/10.1523/JNEUROSCI.1929-08.2008.
Birchwood, M., Smith, J., Cochrane, R., Wetton, S., Copestake, S., 1990. The Social Functioning Scale. The development and validation of a new scale of social adjustment for use in family intervention programmes with schizophrenic patients. Br. J. Psychiatry 157, 853–859. http://dx.doi.org/10.1192/bjp.157.6.853.
Biswal, B.B., 2012. Resting state fMRI: a personal history. Neuroimage. http://dx.doi.org/10.1016/j.neuroimage.2012.01.090.
Blakemore, S.-J., 2008. The social brain in adolescence. Nat. Rev. Neurosci. 9, 267–277. http://dx.doi.org/10.1038/nrn2353.
Bluhm, R.L., Miller, J., Lanius, R.A., Osuch, E.A., Boksman, K., Neufeld, R.W.J., Théberge, J., Schaefer, B., Williamson, P., 2007. Spontaneous low-frequency fluctuations in the BOLD signal in schizophrenic patients: anomalies in the default network. Schizophr. Bull. 1004–1012. http://dx.doi.org/10.1093/schbul/sbm052.
Bora, E., Yucel, M., Pantelis, C., 2009. Theory of mind impairment in schizophrenia: meta-analysis. Schizophr. Res. http://dx.doi.org/10.1016/j.schres.2008.12.020.
Brunet-Gouet, E., Decety, J., 2006. Social brain dysfunctions in schizophrenia: a review of neuroimaging studies. Psychiatry Res. - Neuroimaging. http://dx.doi.org/10.1016/j.pscychresns.2006.05.001.
Bullmore, E., Sporns, O., 2012. The economy of brain network organization. Nat. Rev. Neurosci. 13, 336–349. http://dx.doi.org/10.1038/nrn3214.
Bullmore, E.T., Bassett, D.S., 2011. Brain graphs: graphical models of the human brain connectome. Annu. Rev. Clin. Psychol. 7, 113–140. http://dx.doi.org/10.1146/annurev-clinpsy-040510-143934.
Bullmore, E.T., Sporns, O., Solla, S.A., 2009. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat. Rev. Neurosci. 10, 186–198. http://dx.doi.org/10.1038/nrn2575.
Brüne, M., Abdel-Hamid, M., Lehmkämper, C., Sonntag, C., 2007. Mental state attribution, neurocognitive functioning, and psychopathology: what predicts poor social competence in schizophrenia best? Schizophr. Res. 92 (1), 151–159.
Carlsson, M., Carlsson, A., 1990. Schizophrenia: a subcortical neurotransmitter imbalance syndrome? Schizophr. Bull. 16, 425–432. http://dx.doi.org/10.1093/schbul/16.3.425.
Churchman, A.K., 2001. Book Reviews. Society. http://dx.doi.org/10.1080/03003930500157457.
Couture, S.M., Penn, D.L., Roberts, D.L., 2006. The functional significance of social cognition in schizophrenia: a review. In: Schizophrenia Bulletin. http://dx.doi.org/10.1093/schbul/sbl029.
Derogatis, L.R., 1994. SCL-90-R: Symptom Checklist-90-R: administration, scoring, and procedures manual. NCS Pearson.
Dodell-Feder, D., Tully, L.M., Lincoln, S.H., Hooker, C.I., 2014. The neural basis of theory of mind and its relationship to social functioning and social anhedonia in individuals with schizophrenia. NeuroImage: Clin. 4, 154–163.
Ellis, H.D., Young, A.W., 1990. Accounting for delusional misidentifications. Br. J. Psychiatry. http://dx.doi.org/10.1192/bjp.157.2.239.
Faria, A.V., Joel, S.E., Zhang, Y., Oishi, K., van Zjil, P.C.M., Miller, M.I., Pekar, J.J., Mori, S., 2012. Atlas-based analysis of resting-state functional connectivity: evaluation for reproducibility and multi-modal anatomy-function correlation studies. Neuroimage 61, 613–621. http://dx.doi.org/10.1016/j.neuroimage.2012.03.078.
Fett, A.K.J., Viechtbauer, W., Penn, D.L., van Os, J., Krabbendam, L., 2011. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. Neurosci. Biobehav. Rev. 35 (3), 573–588.
Fine, C., Lumsden, J., Blair, R.J., 2001. Dissociation between "theory of mind" and executive functions in a patient with early left amygdala damage. Brain 124, 287–298. http://dx.doi.org/10.1093/brain/124.2.287.
Fornito, A., Zalesky, A., Pantelis, C., Bullmore, E.T., 2012. Schizophrenia, neuroimaging and connectomics. Neuroimage. http://dx.doi.org/10.1016/j.neuroimage.2011.12.090.
Fox, J.M., Abram, S.V., Reilly, J.L., Eack, S., Goldman, M.B., Csernansky, J.G., Smith, M.J., 2017. Default mode functional connectivity is associated with social functioning in schizophrenia. J. Abnorm. Psychol. 126 (4), 392.
Friston, K.J., 1998. The disconnection hypothesis. Schizophr. Res. 115–125. http://dx.doi.org/10.1016/S0920-9964(97)00140-0.
Friston, K.J., Frith, C.D., 1995. Schizophrenia: a disconnection syndrome? Clin. Neurosci. http://dx.doi.org/10.1007/s00117-004-1160-3.
Friston, K.J., Holmes, a.P., Worsley, K.J., Poline, J.-P., Frith, C.D., Frackowiak, R.S.J., 1995. Statistical parametric maps in functional imaging: a general linear approach. Hum. Brain Mapp. 2, 189–210. http://dx.doi.org/10.1002/hbm.460020402.
Frith, C.D., Frith, U., 2007. Social cognition in humans. Curr. Biol. http://dx.doi.org/10.1016/j.cub.2007.05.068.
Green, M.F., Leitman, D.I., 2008. Social cognition in schizophrenia. Schizophr. Bull. http://dx.doi.org/10.1093/schbul/sbn045.
Green, M.F., Horan, W.P., Lee, J., 2015. Social cognition in schizophrenia. Nat. Rev. Neurosci. 16 (10), 620.
Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V., 2003. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc. Natl. Acad. Sci. Usa. 100, 253–258. http://dx.doi.org/10.1073/pnas.0135058100.
Hare, T.A., Tottenham, N., Davidson, M.C., Glover, G.H., Casey, B.J., 2005. Contributions of amygdala and striatal activity in emotion regulation. Biol. Psychiatry 57, 624–632. http://dx.doi.org/10.1016/j.biopsych.2004.12.038.
He, Y., Dagher, A., Chen, Z., Charil, A., Zijdenbos, A., Worsley, K., Evans, A., 2009. Impaired small-world efficiency in structural cortical networks in multiple sclerosis associated with white matter lesion load. Brain 132, 3366–3379. http://dx.doi.org/10.1093/brain/awp089.
Heinrichs, D.W., Hanlon, T.E., Carpenter, W.T., 1984. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. Schizophr. Bull. 10, 388–398. http://dx.doi.org/10.1093/schbul/10.3.388.
Henry, J.D., Von Hippel, W., Molenberghs, P., Lee, T., Sachdev, P.S., 2016. Clinical assessment of social cognitive function in neurological disorders. Nat. Rev. Neurol. 12 (1), 28.
Hooker, C.I., Bruce, L., Lincoln, S.H., Fisher, M., Vinogradov, S., 2011. Theory of mind skills are related to gray matter volume in the ventromedial prefrontal cortex in schizophrenia. Biol. Psychiatry 70 (12), 1169–1178.
Jo, H.J., Gotts, S.J., Reynolds, R.C., Bandettini, P.A., Martin, A., Cox, R.W., Saad, Z.S., 2013. Effective preprocessing procedures virtually eliminate distance-dependent motion artifacts in resting state FMRI. J. Appl. Math. 2013. http://dx.doi.org/10.1155/2013/935154.
Kay, S.R., Opler, L.A., Lindenmayer, J.P., 1989. The positive and negative syndrome scale (PANSS): rationale and standardisation. Br. J. Psychiatry. http://dx.doi.org/10.1093/schbul/13.2.261.
Kim, J.J., Kwon, J.S., Hae, J.P., Youn, T., Do, H.K., Myung, S.K., Dong, S.L., Myung, C.L., 2003. Functional disconnection between the prefrontal and parietal cortices during working memory processing in schizophrenia: a [15O]H 2O PET study. Am. J. Psychiatry 160, 919–923. http://dx.doi.org/10.1176/appi.ajp.160.5.919.
Krach, S., Paulus, F.M., Bodden, M., Kircher, T., 2010. The rewarding nature of social interactions. Front. Behav. Neurosci. 4, 22. http://dx.doi.org/10.3389/fnbeh.2010.00022.
Kühn, S., Gallinat, J., 2011. Resting-state brain activity in schizophrenia and major depression: a quantitative meta-analysis. Schizophr. Bull. 39 (2), 358–365.
Levine, L.H., Kasahara, H., Kopka, J., Erban, A., Fehrl, I., Kaplan, F., Zhao, W., Littell, R.C., Guy, C., Wheeler, R., Sager, J., Mills, A., Levine, H.G., 2008. Physiologic and metabolic responses of wheat seedlings to elevated and super-elevated carbon dioxide. Adv. Space Res. 1917–1928. http://dx.doi.org/10.1016/j.asr.2008.07.014.
Li, H., Chan, R.C., McAlonan, G.M., Gong, Q.Y., 2009. Facial emotion processing in schizophrenia: a meta-analysis of functional neuroimaging data. Schizophr. Bull. 36 (5), 1029–1039.
Liang, M., Zhou, Y., Jiang, T., Liu, Z., Tian, L., Liu, H., Hao, Y., 2006. Widespread functional disconnectivity in schizophrenia with resting-state functional magnetic resonance imaging. Neuroreport 17, 209–213. http://dx.doi.org/10.1097/01.wnr.0000198434.06518.b8.
Liu, Y., Liang, M., Zhou, Y., He, Y., Hao, Y., Song, M., Yu, C., Liu, H., Liu, Z., Jiang, T., 2008. Disrupted small-world networks in schizophrenia. Brain 131, 945–961. http://dx.doi.org/10.1093/brain/awn018.
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. J. Neurosci. 30, 9477–9487. http://dx.doi.org/10.1523/jneurosci.0333-10.2010.
Micheloyannis, S., Pachou, E., Stam, C.J., Breakspear, M., Bitsios, P., Vourkas, M., Erimaki, S., Zervakis, M., 2006. Small-world networks and disturbed functional connectivity in schizophrenia. Schizophr. Res. 87, 60–66. http://dx.doi.org/10.1016/j.schres.2006.06.028.
Molenberghs, P., Johnson, H., Henry, J.D., Mattingley, J.B., 2016. Understanding the minds of others: a neuroimaging meta-analysis. Neurosci. Biobehav. Rev. 65, 276–291.
Mothersill, O., Tangney, N., Morris, D.W., McCarthy, H., Frodl, T., Gill, M., Donohoe, G., 2017. Further evidence of alerted default network connectivity and association with theory of mind ability in schizophrenia. Schizophr. Res. 184, 52–58.
Penn, D.L., Sanna, L.J., Roberts, D.L., 2008. Social cognition in schizophrenia: an overview. Schizophr. Bull. http://dx.doi.org/10.1093/schbul/sbn014.
Pettersson-Yeo, W., Allen, P., Benetti, S., McGuire, P., Mechelli, A., 2011. Dysconnectivity in schizophrenia: where are we now? Neurosci. Biobehav. Rev. http://dx.doi.org/10.1016/j.neubiorev.2010.11.004.
Pinkham, A.E., Penn, D.L., Perkins, D.O., Lieberman, J., 2003. Implications for the neural basis of social cognition for the study of schizophrenia. Am. J. Psychiatry. http://dx.doi.org/10.1176/appi.ajp.160.5.815.
Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 59, 2142–2154. http://dx.doi.org/10.1016/j.neuroimage.2011.10.018.
Rieckmann, N., Reichenberg, A., Bowie, C.R., Parrella, M., White, L., Friedman, J.I., Harvey, P.D., 2005. Depressed mood and its functional correlates in institutionalized schizophrenia patients. Schizophr. Res. 77, 179–187. http://dx.doi.org/10.1016/j.schres.2005.04.007.
Rilling, J.K., King-Casas, B., Sanfey, A.G., 2008. The neurobiology of social decision-making. Curr. Opin. Neurobiol. 18, 159–165. http://dx.doi.org/10.1016/j.conb.2008.06.003.

Rilling, J.K., Sanfey, A.G., Aronson, J.A., Nystrom, L.E., Cohen, J.D., 2004. The neural correlates of theory of mind within interpersonal interactions. Neuroimage 22, 1694–1703. http://dx.doi.org/10.1016/j.neuroimage.2004.04.015.

Robbins, T.W., 1990. The case of frontostriatal dysfunction in schizophrenia. Schizophr. Bull. 16, 391–402. http://dx.doi.org/10.1093/schbul/16.3.391.

Rubinov, M., Knock, S.A., Stam, C.J., Micheloyannis, S., Harris, A.W.F., Williams, L.M., Breakspear, M., 2009. Small-world properties of nonlinear brain activity in schizophrenia. Hum. Brain Mapp. 30, 403–416. http://dx.doi.org/10.1002/hbm.20517.

Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: uses and interpretations. Neuroimage 52, 1059–1069. http://dx.doi.org/10.1016/j.neuroimage.2009.10.003.

Salvador, R., Sarro, S., Gomar, J.J., Ortiz-Gil, J., Vila, F., Capdevila, A., Bullmore, E., McKenna, P.J., Pomarol-Clotet, E., 2010. Overall brain connectivity maps show cortico-subcortical abnormalities in schizophrenia. Hum. Brain Mapp. 31, 2003–2014. http://dx.doi.org/10.1002/hbm.20993.

Saxe, R., Powell, L.J., 2006. It's the thought that counts: specific brain regions for one component of theory of mind. Psychol. Sci. 17, 692–699. http://dx.doi.org/10.1111/j.1467-9280.2006.01768.x.

Schurz, M., Radua, J., Aichhorn, M., Richlan, F., Perner, J., 2014. Fractionating theory of mind: a meta-analysis of functional brain imaging studies. Neurosci. Biobehav. Rev. 42, 9–34.

Siegal, M., Varley, R., 2002. Neural systems involved in “theory of mind”. Nat. Rev. Neurosci. 3, 463–471. http://dx.doi.org/10.1038/nrn844.

Skudlarski, P., Jagannathan, K., Anderson, K., Stevens, M.C., Calhoun, V.D., Skudlarska, B.A., Pearlson, G., 2010. Brain connectivity is not only lower but different in schizophrenia: a combined anatomical and functional approach. Biol. Psychiatry 68, 61–69. http://dx.doi.org/10.1016/j.biopsych.2010.03.035.

Song, X.W., Dong, Z.Y., Long, X.Y., Li, S.F., Zuo, X.N., Zhu, C.Z., He, Y., Yan, C.G., Zang, Y.F., 2011. REST: a Toolkit for resting-state functional magnetic resonance imaging data processing. PLoS One 6, e25031. http://dx.doi.org/10.1371/journal.pone.0025031.

Stone, V.E., Baron-Cohen, S., Calder, A., Keane, J., Young, A., 2003. Acquired theory of mind impairments in individuals with bilateral amygdala lesions. Neuropsychologia 41, 209–220. http://dx.doi.org/10.1016/S0028-3932(02)00151-3.

Su, T.W., Hsu, T.W., Lin, Y.C., Lin, C.P., 2015. Schizophrenia symptoms and brain network efficiency: a resting-state fMRI study. Psychiatry Res. - Neuroimaging 234, 208–218. http://dx.doi.org/10.1016/j.pscychresns.2015.09.013.

Sugranyes, G., Kyriakopoulos, M., Corrigall, R., Taylor, E., Frangou, S., 2011. Autism spectrum disorders and schizophrenia: meta-analysis of the neural correlates of social cognition. PLoS One. http://dx.doi.org/10.1371/journal.pone.0025322.

Tamminga, C.A., 2000. Treatment mechanisms: traditional and new antipsychotic drugs. Dialog-. Clin. Neurosci. 2, 281–286.

Tekin, S., Cummings, J.L., 2002. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. J. Psychosom. Res. http://dx.doi.org/10.1016/S0022-3999(02)00428-2.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15, 273–289. http://dx.doi.org/10.1006/nimg.2001.0978.

Van Overwalle, F., 2009. Social cognition and the brain: a meta-analysis. Hum. Brain Mapp. http://dx.doi.org/10.1002/hbm.20547.

Wang, J., Wang, L., Zang, Y., Yang, H., Tang, H., Gong, Q., Chen, Z., Zhu, C., He, Y., 2009. Parcellation-dependent small-world brain functional networks: a resting-state fmri study. Hum. Brain Mapp. 30, 1511–1523. http://dx.doi.org/10.1002/hbm.20623.

Wang, J., Wang, X., Xia, M., Liao, X., Evans, A., He, Y., 2015. GRETNA: a graph theoretical network analysis toolbox for imaging connectomics. Front. Hum. Neurosci. 9, 1–16. http://dx.doi.org/10.3389/fnhum.2015.00386.

Wojtalik, J.A., Smith, M.J., Keshavan, M.S., Eack, S.M., 2017. A systematic and meta-analytic review of neural correlates of functional outcome in schizophrenia. Schizophr. Bull. sbx008.

Xia, M., Wang, J., He, Y., 2013. BrainNet viewer: a network visualization tool for human brain connectomics. PLoS One 8. http://dx.doi.org/10.1371/journal.pone.0068910.

Yan, 2010. DPARSF: a MATLAB toolbox for “pipeline” data analysis of resting-state fMRI. Front. Syst. Neurosci. http://dx.doi.org/10.3389/fnsys.2010.00013.

Yu, Q., Sui, J., Rachakonda, S., He, H., Gruner, W., Pearlson, G., Kiehl, K.A., Calhoun, V.D., 2011. Altered topological properties of functional network connectivity in schizophrenia during resting state: a small-world brain Network study. PLoS One 6. http://dx.doi.org/10.1371/journal.pone.0025423.

Zalesky, A., Fornito, A., Bullmore, E.T., 2010. Network-based statistic: identifying differences in brain networks. Neuroimage 53, 1197–1207. http://dx.doi.org/10.1016/j.neuroimage.2010.06.041.

Zalesky, A., Fornito, A., Egan, G.F., Pantelis, C., Bullmore, E.T., 2012. The relationship between regional and inter-regional functional connectivity deficits in schizophrenia. Hum. Brain Mapp. 33, 2535–2549. http://dx.doi.org/10.1002/hbm.21379.

Zalesky, A., Fornito, A., Seal, M.L., Cocchi, L., Westin, C.F., Bullmore, E.T., Egan, G.F., Pantelis, C., 2011. Disrupted axonal fiber connectivity in schizophrenia. Biol. Psychiatry 69, 80–89. http://dx.doi.org/10.1016/j.biopsych.2010.08.022.

Zhang, J., Wang, J., Wu, Q., Kuang, W., Huang, X., He, Y., Gong, Q., 2011. Disrupted brain connectivity networks in drug-naive, first-episode major depressive disorder. Biol. Psychiatry 70, 334–342. http://dx.doi.org/10.1016/j.biopsych.2011.05.018.

Zhu, J., Wang, C., Liu, F., Qin, W., Li, J., Zhuo, C., 2016. Alterations of functional and structural networks in schizophrenia patients with auditory verbal hallucinations. Front. Hum. Neurosci. 10, 1–10. http://dx.doi.org/10.3389/fnhum.2016.00114.