Schizophrenia Research 206 (2019) 103–110

Contents lists available at ScienceDirect

Schizophrenia Research

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

Ventral and dorsal visual pathways exhibit abnormalities of static and dynamic connectivities, respectively, in patients with schizophrenia

Yanjia Deng [a,1], Kai Liu [a,1], Dongliang Cheng [a,b], Jingyu Zhang [a], Hui Chen [a], Bingguang Chen [c], Yingjia Li [d], Wensheng Wang [e], Youyong Kong [f,**], Ge Wen [a,*]

[a] Medical Imaging Department, Nanfang Hospital, Southern Medical University, Guangzhou, China
[b] Department of Radiology, the First People's Hospital of Foshan, Foshan, China
[c] Mental Behavior Department, Guangdong 999 Brain Hospital, Guangzhou, China
[d] Department of Ultrasonography, Nanfang Hospital, Southern Medical University, Guangzhou, China
[e] Department of Medical Image Center, Guangdong 999 Brain Hospital, Guangzhou, China
[f] Lab of Image Science and Technology, School of Computer Science and Engineering, Southeast University, Nanjing, China

ARTICLE INFO

Article history:
Received 15 May 2018
Received in revised form 26 August 2018
Accepted 4 December 2018
Available online 10 December 2018

Keywords:
Schizophrenia
Dynamic functional connectivity
Dorsal pathway
Ventral pathway

ABSTRACT

Previous studies suggest that schizophrenia-related visual perceptual abnormalities are primarily attributed to deficits of the dorsal rather than ventral visual pathway. In this study, we comparatively explored changes in dorsal and ventral networks in schizophrenia patients in both static and dynamic functional connectivity (FC). Resting-state MR scans were acquired for forty schizophrenia patients and twenty-four healthy controls matched for age and gender. The dorsal and ventral visual networks were defined based on the resultant coordinates from activation likelihood estimation analyses. Static and dynamic network properties were calculated based on the full-range and segmented blood oxygen level dependent time series, respectively. The results indicated that the ventral and dorsal visual networks exhibited abnormalities in static FC and dynamic FC, respectively, in the schizophrenia group. Static FC assessments in the ventral visual network showed a significantly decreased clustering coefficient and shortened characteristic path length in patients with schizophrenia. Dynamic FC assessments in the dorsal visual network showed significantly higher mean temporal variability ($p = 0.026$) and higher regional FC variability of the right fusiform gyrus ($p < 0.001$) in patients with schizophrenia, and the latter was correlated with the total and negative scores of the Positive and Negative Syndrome Scale. In summary, this study reveals differential patterns of connectivity abnormalities of the ventral and dorsal visual networks in patients with schizophrenia. These preliminary evidences may help us better interpret the mechanisms underlying visual perceptual impairments in patients with schizophrenia and their relationship with psychosis.

1. Introduction

Patients with schizophrenia are known to exhibit neuropsychological deficits in terms of dysfunctions in perceptual processing (Kalkstein et al., 2010). Specifically, visual perceptual dysfunctions, which show high replicability and well-known neurobiological underpinnings, has been widely demonstrated (Butler and Javitt, 2005; Plomp et al., 2013; Silverstein and Keane, 2011). Several studies have found that impaired visual perception is correlated with the severity of schizophrenic symptoms and has thus been assumed to be a potential endophenotype involved in the genesis of psychosis (Keri et al., 2005).

The ventral pathway and dorsal pathway are considered two key brain components in visual perceptual processing (Kravitz et al., 2013). The ventral pathway connects the occipital lobe with the temporal lobe and is responsible for processing recognition information, e.g., face, object and word recognition. On the other hand, the dorsal pathway connects the occipital lobe and the parietal lobe and contributes to motion and spatial information processing (Kravitz et al., 2013). A growing body of evidence has shown that schizophrenia is

* Correspondence at: Medical Imaging Department, Nanfang Hospital, Southern Medical University, No. 1023, South Shatai Road, Baiyun District, Guangzhou, China.
** Correspondence at: Lab of Image Science and Technology, School of Computer Science and Engineering, Southeast University, Nanjing, China.
E-mail addresses: kongyouyong@seu.edu.cn (Y. Kong), wenge67@aliyun.com (G. Wen).
[1] These authors contributed equally to the manuscript.

https://doi.org/10.1016/j.schres.2018.12.005
0920-9964/

associated with dysfunctions in object recognition, face processing, reading, motion information processing and spatial vision (Belge et al., 2017; Bennett et al., 2016; Butler et al., 2008; Keane et al., 2013; Mangelinckx et al., 2017; Vinckier et al., 2014). More importantly, these visual perception impairments have found to be related to poor cognitive function and prognoses in schizophrenia patients (Butler and Javitt, 2005; Sergi et al., 2006).

In recent years, the dysconnectivity hypothesis has been proposed, which states that disrupted connectivities among different brain regions jointly contribute to the main symptoms of schizophrenia, rather than separate abnormalities in localized brain regions (Stephan et al., 2009). Many neuroimaging studies have demonstrated both abnormal functional connectivity (FC) and abnormal structural connectivity in patients with schizophrenia (Harvey et al., 2011; Kang et al., 2011; Kaufmann et al., 2015; Pettersson-Yeo et al., 2011). These findings suggest that there are possible impairments in the visual perceptual cortices of the ventral and dorsal pathways, which are highly connected with "hot-spot regions" involved in schizophrenia (Chen et al., 2017; Harvey et al., 2011; Kaufmann et al., 2015) and that the patterns of these impairments are perhaps related to different disease phenotypes. Combined with the reported visual perceptual dysfunctions at a behavioral level, this evidence may lead to a focused investigation on the connectivity of the ventral and dorsal pathways in patients with schizophrenia.

However, to date, the whole-network level connectivity changes in the dorsal/ventral streams have not been comprehensively characterized in schizophrenia patients. One major limitation to this process is the lack of a comprehensive localization of the dorsal and ventral visual pathways in the brain. This limited localizability is because the function of the dorsal and ventral pathways involves a variety of categories and cannot be comprehensively tested by several paradigms in a single functional magnetic resonance imaging (fMRI) study. To address this issue, we constructed ventral and dorsal pathway maps by performing activation likelihood estimation (ALE) analysis on the coordinates from 74 fMRI assessments of eight major categories of visual perceptual functions (Deng et al., 2016). Using these dorsal and ventral pathway maps, we achieved a comprehensive localization of the visual cortices, thus helping us explore the overall network architecture of the visual perceptual cortices in schizophrenia patients.

On the other hand, traditional FC studies are usually performed by averaging brain activity from resting-state scans over several minutes and may thus overlook the time-varying properties of FC (Calhoun et al., 2014; Du et al., 2016; Yaesoubi et al., 2015; Zalesky et al., 2014). Recently, it was noted that both whole and subnetworks of the brain exhibit dynamic FC (Hutchison et al., 2013; Kucyi and Davis, 2014). Therefore, to better understand schizophrenia-related abnormalities in visual network connectivity, it is important to capture these nonstationary connectivity patterns, which may be overlooked in traditional static FC analyses (Damaraju et al., 2014; Du et al., 2016).

Therefore, in this study, we comparatively explored both static and dynamic changes in the dorsal and ventral pathways in schizophrenia patients to better determine the pattern of FC abnormalities. To date, this is the first comprehensive characterization of the visual perceptual network in schizophrenia patients. We hope our study can provide additional evidence for interpretations of the underlying mechanisms involved in visual perceptual impairments in patients with schizophrenia and their relationship to psychosis.

2. Methods

2.1. Subjects

All procedures involving human participants were performed in accordance with the Declaration of Helsinki. Ethical approval was obtained from the institutional ethics committee. Written informed consent was collected from each subject. In total, forty patients with schizophrenia (15 females and 25 males; mean age, 26 years) and 24 healthy controls (10 females and 14 males; mean age, 27 years) were included in this study. Among the 40 patients, 19 and 21 were respectively recruited from outpatient and inpatient department settings. A diagnosis of schizophrenia was based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) performed by two experienced clinical psychiatrists. The healthy controls were interviewed to exclude those with potential psychosis according to the SCID and were further screened for present or past neurological or substance abuse disorders during a prescan interview. For all subjects, the inclusion criteria included age ranging from 15 to 45 years, right handedness, and no family history of psychosis. All patients were stable at the time of the experiment, and treatment had been unchanged for at least 3 weeks. The exclusion criteria for all subjects included active substance abuse or dependency, current mood disorder, history of a neurological disorder or head injury with a loss of consciousness lasting >10 min, any organic lesion in brain, documented intellectual impairment, suicidal ideation or behavior (assessed using the Scale for Suicide Ideation, SSI), and any contraindication for MR examinations. Moreover, all schizophrenia patients were interviewed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

2.2. Image acquisition

All participants underwent MRI scanning on a 3-T GE Signa HDXT scanner. For the resting-state fMRI (rs-fMRI) protocol, a single-shot echo-planar imaging (EPI) sequence was adopted with 180 time points, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°, field of view (FOV) = 240 × 240 mm, matrix = 64 × 64, voxel size = 3.75 × 3.75 mm, and slice thickness/gap = 4.0 mm/0.6 mm. For a segmentation-based normalization (Kong et al., 2015), high resolution 3D T1-weighted images (WI) were acquired using a 3D-BRAVO sequence with TR = 8.9 ms, TE = 3.5 ms, 176 slices, flip angle = 13°, FOV = 240 × 240 mm, matrix = 256 × 256, voxel size = 0.94 × 0.94 mm, and slice thickness = 1.0 mm.

2.3. Rs-fMRI data preprocessing

Preprocessing of the rs-fMRI data was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). The first 10 image volumes were discarded, and a slice timing correction was performed for the remaining rs-fMRI volumes. Then, the images were corrected for head motion, and the subjects with excessive head motion were excluded (six-parameter spatial transformation excluding >1.5 mm displacement in any direction or >1.5° of any angular motion). Next, the resultant images for each subject were coregistered to individual 3D-T1 WI and then normalized to the MNI (Montreal Neurological Institute) space (resampled into $3 \times 3 \times 3$ mm^3 voxels) using the DARTEL (Diffeomorphic Anatomical Registration using Exponentiated Lie algebra) tool of SPM. Additional processing included spatial smoothing with a Gaussian kernel of 8 mm full width at half maximum (FWHW), detrending, filtering with a bandpass filter of 0.01–0.08 Hz, and regression of the white matter signal, cerebrospinal fluid signal and six motion parameters.

2.4. Construction of a high-level visual network

The dorsal and ventral visual networks were constructed based on the ALE coordinates of dorsal and ventral visual pathways, respectively, in our previous study (Deng et al., 2016). Briefly, ventral and dorsal pathway maps were generated by performing ALE analysis on the coordinates from 74 fMRI assessments of eight major categories of visual perceptual functions. The coordinate with the maximum ALE value in each resultant cluster was recognized as the center of a visual cortical region (Tables S1 and S2), and a spherical region of interest (ROI) with a 5-mm radius was created at this location (Fig. 1A and B). For the ALE clusters with large voxel sizes that crossed more than one

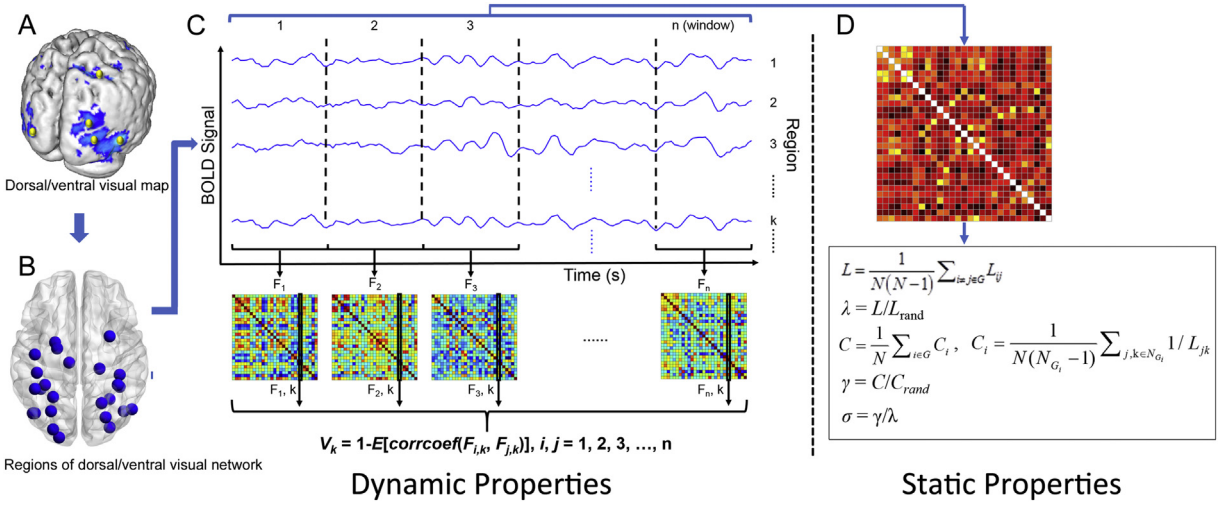

Fig. 1. Calculation of dynamic and static functional connectivity (FC) network properties of the dorsal/ventral visual networks. A) Activation likelihood estimation (ALE) analysis was performed to locate the ventral/dorsal visual cortices. B) Spherical regions of interest (ROIs) in the dorsal/ventral visual networks were created and centered at the peak coordinates of the ALE analysis. C) The blood oxygen level dependent (BOLD) time series of each ROI was segmented into n successive, nonoverlapping time windows, and the connectivity matrices were created at each time window. Then, the temporal variability of the FC was calculated for each ROI. D) The static network properties were calculated based on the connectivity matrix across the whole BOLD time series.

Brodmann area (BA), the coordinate with the highest ALE value in each BA region was counted as an individual ROI center. In further steps, the created visual ROIs were used as seeds to calculate pair-wise functional connectivities and served as nodes in the construction of the dorsal and ventral visual networks.

2.5. Calculation of static network properties

A previously established network quantification method based on graph theory was used in this study to calculate network parameters (Watts and Strogatz, 1998). First, association matrices based on pair-wise interregional resting-state functional connectivity (RSFC) were created independently for the ventral (29×29) and dorsal (25×25) visual networks for each subject. Then, the matrices were thresholded into binary matrices with a range of network densities (0.1–0.5, with intervals of 0.01) to ensure that the resultant networks of different subjects were comparable. Based on our data, the averaged group-level small-worldness of ventral and dorsal visual networks dropped below 1.2 respectively at the densities of 0.37 ($\sigma = 1.198$) and 0.49 ($\sigma = 1.196$). Thus, we set 0.5 as the maximum threshold of density range to ensure the network properties be efficiently estimated and comprehensively observed, while the number of spurious edges minimized. Here, the binary matrix was recognized as a graph, each ROI as a node, and the RSFC between two nodes as an edge.

We used the three network parameters of normalized characteristic path length (λ), normalized clustering coefficient (γ) and small-worldness (σ) to quantify the integrated and segregated information processing capabilities of the visual networks (Fig. 1D). The specific calculation was summarized in Supplementary Appendix 1. Calculation of static network properties.

2.6. Calculation of dynamic network properties

We independently calculated the temporal variability of the dorsal and ventral visual networks based on the previously described method used by Zhang et al. (2016). Briefly, the blood oxygen level dependent (BOLD) time series were segmented into n successive, nonoverlapping time windows with a time length of l for each window (Fig. 1C). The specific calculation was described in Supplementary Appendix 2. Calculation of dynamic network properties.

2.7. Statistical analysis

The demographic and clinical data of the subjects were evaluated using SPSS 16.0. Two sample t-tests (or Mann-Whitney U tests for nonnormally distributed data) were performed to compare age, disease duration, antipsychotic drug dosage (counted as chlorpromazine equivalents calculated based on the standard of Danivas and Venkatasubramanian (2013), and PANSS scores between schizophrenia and control groups. The between-group difference in gender was evaluated using a χ^2 test. A statistical significance level of $p < 0.05$ was used. For the between-group comparisons of static network properties across the density range, we used a nonparametric permutation test with the randomization procedure repeated 1000 times. For the density range with significant between-group differences, we additionally extracted the area under the curve (AUC) value as the static network parameters for subsequent correlation and validation analyses. For the between-group comparisons of dynamic network properties, two sample t-tests (or Mann-Whitney U tests) were used. A statistical significance level of $p < 0.05$ was used, and a Bonferroni correction was additionally used for the ROI-level comparisons (for the dorsal visual network, $p < 0.05/25 = 0.002$; for the ventral visual network, $p < 0.05/29 = 0.0017$). Finally, to assess the relationship between the severity of clinical symptoms and the network changes in dorsal and ventral pathways, a partial correlation analysis was performed to correlate the PANSS scores to the network measurements that showed significant between-group differences, with age, gender, and antipsychotic drug dosage added as covariates. A statistical significance level of $p < 0.05$ was used.

2.8. Validation analysis

First, to ensure that the observed network changes in patients with schizophrenia were not dependent on the effect of antipsychotic medications, we assessed the correlation between antipsychotic drug dosages and the network parameters that showed significant between-group differences. Second, based on the fact that the psychotic symptom in our cohort is generally severe and spans over a wide severity range (indicated by a relatively high mean PANSS score with a wide standard deviation), there was possibly a disease severity-related variation among the patients in the head motion during MR scanning. Since head motion effects on FC have been emphasized in recent studies

(Power et al., 2014), we assessed the between-group difference in mean frame-wise displacement (FD), and assessed the correlations of FD to PANSS scores and to the network parameters that showed significant between-group differences. Third, considering the possible influence of age and gender, we repeated the statistical comparisons of all the network measurements after adjusting for the effects of age and gender to ensure that the observed results were independent of these confounding factors. Moreover, the interaction effects of age * gender on the network parameters of interest were evaluated using factorial analysis.

3. Results

3.1. Demographics

Gender ($p = 0.105$) and age ($p = 0.400$) were matched between the schizophrenia and control groups. The duration of illness in the included patients ranged from 0.5 to 20 years, and the mean dosage of chlorpromazine equivalents for patients with schizophrenia was 528.35 ± 352.14 mg/day. Detailed information on the demographic and clinical statistics is summarized in Table 1.

3.2. Altered static network properties of the dorsal and ventral pathways

For the ventral visual network, significantly decreased γ and λ values were found in the schizophrenia group compared with controls, respectively over the consecutive density ranges of 0.33–0.44 and 0.33–0.50 (Fig. 2B), with the corresponding AUC values over the respective significant density ranges being $\gamma = 0.165 \pm 0.018$ and $\lambda = 0.191 \pm 0.004$ in the schizophrenia group and $\gamma = 0.178 \pm 0.029$ and $\lambda = 0.195 \pm 0.007$ in the control group (Table 2). The σ value of the ventral network in the schizophrenia group was decreased only at several scattered densities, while no continual range was observed with significant decrease. For the dorsal visual network, no significant differences in γ, λ, or σ values were found in the schizophrenia group compared with the normal controls (NC) group (Fig. 2A).

3.3. Altered dynamic high-level visual networks

We found a significantly elevated mean FC variability of the whole dorsal visual network in the schizophrenia group compared with that of the NC group ($p = 0.026$). No significant between-group difference in the mean FC variability of the whole ventral visual network was found. In the ROI-level comparisons of visual networks, the right fusiform gyrus in the dorsal network showed significantly elevated temporal variability in the schizophrenia group compared with the control group ($p < 0.001$) (Table 2, Fig. 3).

Table 1
Demographic and clinical data of schizophrenia patients (SZ) and normal controls (NC).

	NC ($n = 24$)	SZ ($n = 40$)	Test statistic	p-Value
Age (years)	26.54 ± 6.88	26.00 ± 8.19	$Z = 0.841$	0.400
Gender (male/female)	10/14	25/15	$\chi^2 = 2.627$	0.105
Frame-wise displacement	0.077 ± 0.025	0.099 ± 0.065	$Z = -0.957$	0.339
Duration of disease (years)	–	3.29 ± 3.59	–	–
Antipsychotic dosage (mg/day)	–	528.35 ± 352.14	–	–
PANSS-total	–	75.43 ± 13.43	–	–
PANSS-positive	–	19.40 ± 7.06	–	–
PANSS-negative	–	21.50 ± 8.77	–	–
PANSS-general	–	34.53 ± 8.42	–	–

PANSS = The Positive and Negative Syndrome Scale; data are presented as the mean ± standard deviation.

3.4. Correlations between PANSS scores and network parameters

The total and subscale PANSS scores were separately correlated with the network measurements that showed significant between-group differences, including the AUC values of γ and λ in the ventral visual network, the mean temporal FC variability of the dorsal visual network, and the FC variability of the right fusiform gyrus in the dorsal visual network. Significant positive correlations were found between the FC variability of the right fusiform gyrus and the total PANSS score ($r = 0.330$, $p = 0.046$) and the negative PANSS subscale score ($r = 0.512$, $p = 0.001$) (Fig. 4).

3.5. Validation analysis

None of the network parameters with significant between-group differences were correlated with the dosage of antipsychotic medication or FD in schizophrenia patients (all p values > 0.1). FD was found with no significant correlation to the total ($r = -0.107$, $p = 0.513$), positive ($r = -0.069$, $p = 0.674$), or negative PANSS score ($r = 0.101$, $p = 0.535$). No significant between-group difference was found in FD ($p = 0.339$). The between-group differences in all the network parameters remained after adjusting for age and gender (Table 2). Factorial analyses showed that the effects of age, gender, and the interaction effect of age * gender were insignificant for all of the network parameters with significant between-group differences (all p values > 0.1, Table S3).

4. Discussion

By combining static and dynamic connectivity assessments, this study characterized changes in the ventral and dorsal pathways in schizophrenia patients. The major findings include the following: 1) ventral and dorsal pathways exhibited static and dynamic connectivity abnormalities, respectively, in schizophrenia patients; 2) the ventral pathway network is characterized by a more integrated but less segregated organization pattern in patients with schizophrenia; and 3) the FC variabilities of the whole dorsal visual network and of the right fusiform gyrus in the dorsal network were increased in schizophrenia patients, and the variability in the latter region was found to be correlated with the overall and negative symptoms of schizophrenia.

Previous studies have suggested that visual deficits in patients with schizophrenia are attributed to impairments in the dorsal pathway, while the ventral pathway has not often been considered to be involved in the pathology of schizophrenia (Doniger et al., 2002; Plomp et al., 2013). In terms of this latter point, studies on ventral pathway-related deficiencies have largely focused on and been limited to face-processing assessments. However, in this study, we provide evidence that both the ventral and dorsal pathways show whole-network level alterations but different connectivity patterns in schizophrenia patients. Specifically, the ventral network showed abnormalities only in static connectivity, while the dorsal network showed only disrupted dynamic connectivity. This difference in abnormal patterns may be particularly in line with recent findings that the dorsal and ventral pathways exhibit deficits under different functional modalities, i.e., ventral pathway abnormalities become evident under challenging perceptual tasks (Silverstein et al., 2009) or high-demanding ventral functions (Plomp et al., 2013). However, more evidence is needed to further elucidate how the differential patterns of network disruptions between the dorsal and ventral streams could influence the behavioral outcomes in patients with schizophrenia.

In terms of the static connectivity changes in the ventral visual network, we found a significantly decreased clustering coefficient in schizophrenia patients. The clustering coefficient is considered to be the extent to which neighboring brain regions interact with each other, i.e., the network segregation (Bullmore and Bassett, 2011). Thus, our results implied a decrease in network segregation in the ventral pathway in schizophrenia patients. This finding is consistent

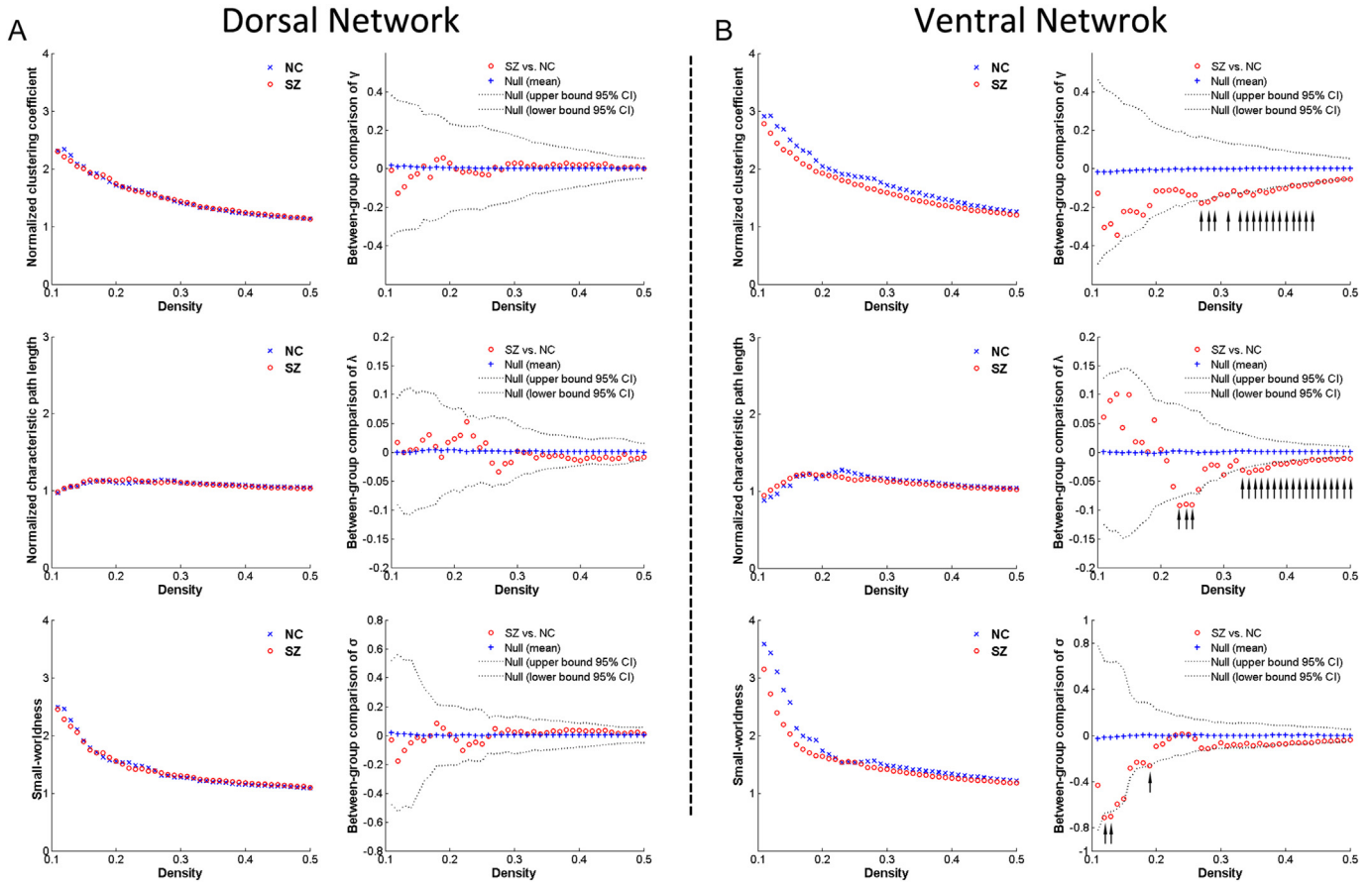

Fig. 2. Comparisons of the static network properties of the dorsal and ventral visual networks. For the dorsal visual network, no significant differences in γ, λ, and σ values were found between the schizophrenia group and the control group (A). For the ventral visual network, significantly decreased γ and λ values were found in the schizophrenia group, respectively over the consecutive density ranges of 0.33–0.44 and 0.33–0.50. Significant decreases in the σ value of the ventral network in the schizophrenia group were observed only at several scattered densities (B).

with a series of previous studies that show regional dysconnectivity within the submodules of the ventral network. Calderone's study showed schizophrenia-related impaired intranetwork connectivity in object recognition circuity (Calderone et al., 2013), which is a regional component included in the ventral network. Furthermore, electroencephalography studies have provided evidence of reduced regional connectivity within the visual cortex (Spencer, 2008).

On the other hand, we observed a shortened characteristic path length in the ventral network in patients with schizophrenia. As a shortened λ value indicates increased network integration (Bullmore and Bassett, 2011), we speculate that the lower λ value, to some extent, may compensate for decreased network segregation in information processing. This hypothesis is in line with our result that decreases in γ values showed no significant correlation with the clinical symptoms of schizophrenia. However, an efficient brain network requires an optimized balance between segregated and integrated information processing abilities (Bullmore and Bassett, 2011). Therefore, the currently observed reorganization pattern in the ventral network in patients with schizophrenia may be considered less efficient, since a tendency for decreased small-worldness compared with controls was noted. This speculation may also be supported by the fact that ventral stream functions, which are mostly intact in patients with schizophrenia,

Table 2
Network parameters that showed significant differences between schizophrenia patients (SZ) and normal controls (NC).

	NC ($n = 24$)	SZ ($n = 40$)	Group comparison results				Correlation to antipsychotic dosage		Correlation to FD	
			Statistic	p-Value	Statistic[a]	p-Value[a]	r	p-Value	r	p-Value
AUC of γ of ventral stream (density range: 0.33–0.44)	0.178 ± 0.029	0.165 ± 0.018	$T = 2.215$	0.030*	$T = 2.215$	0.030[a,*]	−0.029	0.857	−0.020	0.902
AUC of λ of ventral stream (density range: 0.33–0.50)	0.195 ± 0.007	0.191 ± 0.004	$Z = -2.066$	0.039*	$Z = -2.066$	0.039[a,*]	−0.099	0.543	−0.193	0.232
Mean FC variability of dorsal stream	0.676 ± 0.039	0.698 ± 0.036	$T = -2.275$	0.026*	$T = -2.222$[a]	0.030[a,*]	−0.130	0.425	0.122	0.452
Variability of sig. ROI (i.e., right fusiform in dorsal stream)	0.648 ± 0.084	0.727 ± 0.086	$T = -3.576$	<0.001*	$T = -3.322$[a]	0.002[a,*]	0.006	0.969	0.159	0.326

AUC = area under the curve; FC = functional connectivity; ROI = region of interest; FD = frame-wise displacement; data are presented as the mean ± standard deviation.
* Statistical significance (with a threshold of $p < 0.05$; Bonferroni corrections were used for regional measurements).
[a] The p-value was adjusted for age and gender.

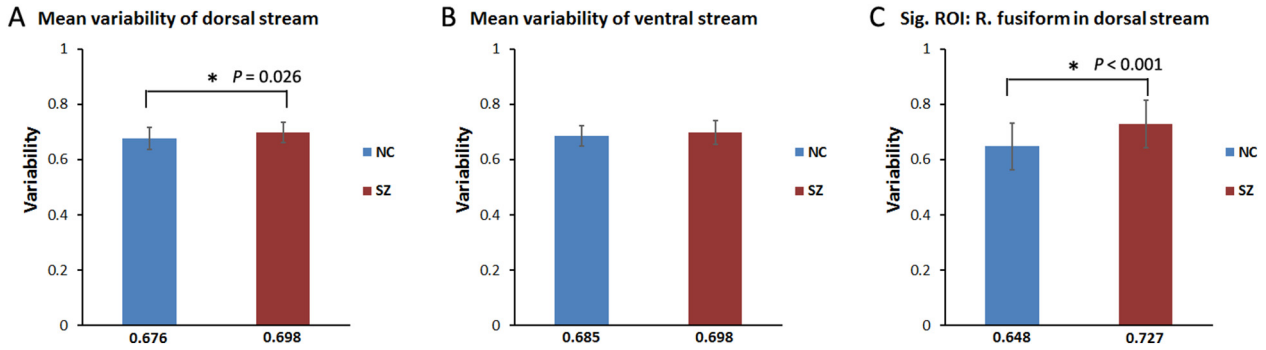

Fig. 3. Comparisons of the variabilities of the ventral and dorsal networks between schizophrenia patients and normal controls (NCs). Mean FC variability of the dorsal visual network was significantly higher in the schizophrenia group than in the NC group (A). Mean FC variability of the ventral visual network was not significantly different between groups (B). For the region-level comparisons, the right fusiform gyrus in the dorsal network showed significantly higher FC variability in the schizophrenia group than in the control group (C).

become impaired under challenging perceptual tasks (Silverstein et al., 2009) or high-demanding ventral functions (Plomp et al., 2013), possibly indicating a compensation limit.

In terms of the dynamic connectivity changes in the dorsal visual network, there was increased temporal variability of whole network and of the right fusiform gyrus. According to a previous study, higher temporal variability reflects decreased stability in the configuration of network communities during dynamic activity (Zhang et al., 2016). This finding is particularly consistent with Zhang's finding (Zhang et al., 2016) that the bilateral visual cortices of the occipital lobe showed symmetric increases in variability in schizophrenia patients. Meanwhile, the current finding of decreased stability in dorsal network activity is also related to a previous finding that the dorsal pathway in schizophrenia patients fails to provide stable coding of spatial location (Plomp et al., 2013). Taken together, these findings imply that unstable dorsal network connectivity perhaps underlies the neurobiological basis for behavioral instabilities and even the deficits in visual perceptual functions in patients with schizophrenia.

Regarding the regional finding in the right fusiform gyrus, it's worth noting that increasing evidences have supported the involvement of the fusiform region in the functionality of dorsal pathway (e.g., processing of the motion perceptual visions (Jackson et al., 2006; Jastorff and Orban, 2009; Jeannerod, 2004)). This overlapped recruitment of fusiform gyrus in both dorsal and ventral pathways was noted in previous researches, and possibly relating to the "crosstalk" mechanism between the two networks for integrated information processing of visual perceptions (de Haan and Cowey, 2011). Specific to our data, besides the current finding in the right fusiform gyrus in dorsal visual network, the right fusiform region in ventral network was actually also observed with a similar tendency of FC variability increase (0.716 ± 0.088 in SZ group vs. 0.667 ± 0.094 in NC group). Although this tendency observed in the fusiform gyrus of ventral network was not significant at regional level ($p = 0.038$), it may lead to the speculation that the disrupted dynamic FC in the right fusiform gyrus is perhaps a convergent abnormality in both dorsal and ventral pathways, and possibly relating to the impaired integration of dorsal-ventral visual functions in SZ patients (Martinez et al., 2012). On the other hand, being consistent with our results, a series of previous studies have revealed the abnormal activity of fusiform gyrus in SZ patients during performing dorsal visual functions (Martinez et al., 2012; Silverstein et al., 2010), as well as decreased FC in fusiform gyrus in SZ patients relating to the integrated information processing of dorsal-ventral functions (Kang et al., 2011). These evidences may directly support that the fusiform gyrus could exhibit deficiency as a component of dorsal visual network in SZ patients. Moreover, we also found a significant correlation between regional variability increases in the right fusiform gyrus and symptoms of schizophrenia. This finding may further support that the functional instability of right fusiform gyrus in the dorsal visual network might be of behavioral relevance in patients with schizophrenia.

Several limitations of this study should be noted. Due to the limited sample size and the lack of replication analysis, the findings of this study are preliminary. Similarly, although we have testified that the influence of antipsychotic dosage was statistically of no significance based on our sample size, the influence of anti-schizophrenia medicine on the visual

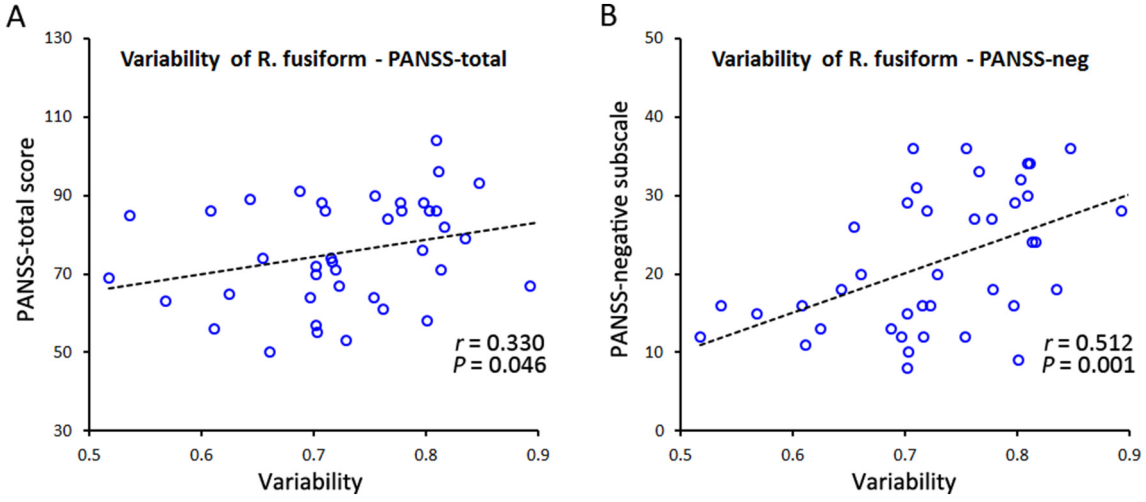

Fig. 4. Significant correlations between the clinical symptoms of schizophrenia patients and the connectivity variability of the right fusiform gyrus. The connectivity variability of the right fusiform gyrus was positively correlated with the total score (A) and the negative score of the Positive and Negative Syndrome Scale (PANSS).

network changes in the patients cannot be completely excluded. Thus, further observation with larger sample size of drug naïve participants is highly encouraged. Moreover, since the dorsal/ventral visual functions are difficult to be comprehensively measured at behavioral level, we didn't introduce a corresponding neuropsychological test in this study. Thus, the behavioral significance of the current visual network findings is limited and should be taken with caution.

5. Conclusion

This study revealed the differential patterns of connectivity abnormalities in the ventral and dorsal visual networks in schizophrenia patients. Ventral network abnormalities are characterized by decreased network segregation combined with increased network integration in static connectivity, while the dorsal network abnormalities show an unstable network configuration in dynamic connectivity. Moreover, a relationship was found between regional FC variability changes and the symptoms of schizophrenia. In summary, these preliminary evidences may help us better interpret the mechanisms of visual perceptual impairments in patients with schizophrenia and their relationship with psychosis.

Conflict of interest

None of the authors have any conflicts of interest to declare.

Role of funding source

The study was supported by the grants from the National Natural Science Foundation of China (No. 81701674 and No. 81801682), a grant from the Natural Science Foundation of Guangdong Province (No. 2018030310296), a grant from Science and Technology Program of Guangzhou (No. 201607010357), and also supported by the grant from the National Natural Science Foundation of China (No. 31800825).

CRediT authorship contribution statement

Yanjia Deng: Conceptualization, Funding acquisition, Supervision, Writing - original draft. **Kai Liu:** Conceptualization, Funding acquisition, Formal analysis, Methodology, Writing - review & editing. **Dongliang Cheng:** Conceptualization, Data curation, Investigation, Project administration. **Jingyu Zhang:** Validation, Writing - review & editing. **Hui Chen:** Formal analysis, Visualization. **Bingguang Chen:** Conceptualization, Data curation. **Yingjia Li:** Resources. **Wensheng Wang:** Data curation, Resources. **Youyong Kong:** Funding acquisition, Formal analysis, Methodology, Software. **Ge Wen:** Funding acquisition, Supervision, Resources.

CRediT authorship contribution statement

Yanjia Deng: Conceptualization, Funding acquisition, Supervision, Writing - original draft. **Kai Liu:** Conceptualization, Funding acquisition, Formal analysis, Methodology, Writing - review & editing. **Dongliang Cheng:** Conceptualization, Data curation, Investigation, Project administration. **Jingyu Zhang:** Validation, Writing - review & editing. **Hui Chen:** Formal analysis, Visualization. **Bingguang Chen:** Conceptualization, Data curation. **Yingjia Li:** Resources. **Wensheng Wang:** Data curation, Resources. **Youyong Kong:** Funding acquisition, Formal analysis, Methodology, Software. **Ge Wen:** Funding acquisition, Supervision, Resources.

Acknowledgements

The study was supported by the grants from the National Natural Science Foundation of China (No. 81701674 and No. 81801682), a grant from the Natural Science Foundation of Guangdong Province (No. 2018030310296), a grant from Science and Technology Program of Guangzhou (No. 201607010357), and also supported by the grant from the National Natural Science Foundation of China (No. 31800825). We are grateful to all the participants who gave their time and efforts to help us carry out the experiment, and to the reviewers for their insightful comments that improved the quality of this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.12.005.

References

Belge, J.B., Maurage, P., Mangelinckx, C., Leleux, D., Delatte, B., Constant, E., 2017. Facial decoding in schizophrenia is underpinned by basic visual processing impairments. Psychiatry Res. 255, 167–172.
Bennett, D., Dluzniak, A., Cropper, S.J., Partos, T., Sundram, S., Carter, O., 2016. Selective impairment of global motion integration, but not global form detection, in schizophrenia and bipolar affective disorder. Schizophr. Res. Cogn. 3, 11–14.
Bullmore, E.T., Bassett, D.S., 2011. Brain graphs: graphical models of the human brain connectome. Annu. Rev. Clin. Psychol. 7, 113–140.
Butler, P.D., Javitt, D.C., 2005. Early-stage visual processing deficits in schizophrenia. Curr. Opin. Psychiatry 18 (2), 151–157.
Butler, P.D., Silverstein, S.M., Dakin, S.C., 2008. Visual perception and its impairment in schizophrenia. Biol. Psychiatry 64 (1), 40–47.
Calderone, D.J., Hoptman, M.J., Martinez, A., Nair-Collins, S., Mauro, C.J., Bar, M., Javitt, D.C., Butler, P.D., 2013. Contributions of low and high spatial frequency processing to impaired object recognition circuitry in schizophrenia. Cereb. Cortex 23 (8), 1849–1858.
Calhoun, V.D., Miller, R., Pearlson, G., Adali, T., 2014. The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery. Neuron 84 (2), 262–274.
Chen, X., Jiang, Y., Chen, L., He, H., Dong, L., Hou, C., Duan, M., Yang, M., Yao, D., Luo, C., 2017. Altered hippocampo-cerebello-cortical circuit in schizophrenia by a spatiotemporal consistency and causal connectivity analysis. Front. Neurosci. 11 (25).
Damaraju, E., Allen, E.A., Belger, A., Ford, J.M., McEwen, S., Mathalon, D.H., Mueller, B.A., Pearlson, G.D., Potkin, S.G., Preda, A., Turner, J.A., Vaidya, J.G., van Erp, T.G., Calhoun, V.D., 2014. Dynamic functional connectivity analysis reveals transient states of dysconnectivity in schizophrenia. Neuroimage Clin. 5, 298–308.
Danivas, V., Venkatasubramanian, G., 2013. Current perspectives on chlorpromazine equivalents: comparing apples and oranges! Indian J. Psychiatry 55 (2), 207–208.
de Haan, E.H., Cowey, A., 2011. On the usefulness of 'what' and 'where' pathways in vision. Trends Cogn. Sci. 15 (10), 460–466.
Deng, Y., Shi, L., Lei, Y., Wang, D., 2016. Altered topological organization of high-level visual networks in Alzheimer's disease and mild cognitive impairment patients. Neurosci. Lett. 630, 147–153.
Doniger, G.M., Foxe, J.J., Murray, M.M., Higgins, B.A., Javitt, D.C., 2002. Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. Arch. Gen. Psychiatry 59 (11), 1011–1020.
Du, Y., Pearlson, G.D., Yu, Q., He, H., Lin, D., Sui, J., Wu, L., Calhoun, V.D., 2016. Interaction among subsystems within default mode network diminished in schizophrenia patients: a dynamic connectivity approach. Schizophr. Res. 170 (1), 55–65.
Harvey, P.O., Lee, J., Cohen, M.S., Engel, S.A., Glahn, D.C., Nuechterlein, K.H., Wynn, J.K., Green, M.F., 2011. Altered dynamic coupling of lateral occipital complex during visual perception in schizophrenia. NeuroImage 55 (3), 1219–1226.
Hutchison, R.M., Womelsdorf, T., Gati, J.S., Everling, S., Menon, R.S., 2013. Resting-state networks show dynamic functional connectivity in awake humans and anesthetized macaques. Hum. Brain Mapp. 34 (9), 2154–2177.
Jackson, P.L., Meltzoff, A.N., Decety, J., 2006. Neural circuits involved in imitation and perspective-taking. NeuroImage 31 (1), 429–439.
Jastorff, J., Orban, G.A., 2009. Human functional magnetic resonance imaging reveals separation and integration of shape and motion cues in biological motion processing. J. Neurosci. 29 (22), 7315–7329.
Jeannerod, M., 2004. Visual and action cues contribute to the self-other distinction. Nat. Neurosci. 7 (5), 422–423.
Kalkstein, S., Hurford, I., Gur, R.C., 2010. Neurocognition in schizophrenia. Curr. Top. Behav. Neurosci. 4, 373–390.
Kang, S.S., Sponheim, S.R., Chafee, M.V., MacDonald, A.R., 2011. Disrupted functional connectivity for controlled visual processing as a basis for impaired spatial working memory in schizophrenia. Neuropsychologia 49 (10), 2836–2847.
Kaufmann, T., Skatun, K.C., Alnaes, D., Doan, N.T., Duff, E.P., Tonnesen, S., Roussos, E., Ueland, T., Aminoff, S.R., Lagerberg, T.V., Agartz, I., Melle, I.S., Smith, S.M., Andreassen, O.A., Westlye, L.T., 2015. Disintegration of sensorimotor brain networks in schizophrenia. Schizophr. Bull. 41 (6), 1326–1335.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.
Keane, B.P., Silverstein, S.M., Wang, Y., Papathomas, T.V., 2013. Reduced depth inversion illusions in schizophrenia are state-specific and occur for multiple object types and viewing conditions. J. Abnorm. Psychol. 122 (2), 506–512.
Keri, S., Kiss, I., Kelemen, O., Benedek, G., Janka, Z., 2005. Anomalous visual experiences, negative symptoms, perceptual organization and the magnocellular pathway in schizophrenia: a shared construct? Psychol. Med. 35 (10), 1445–1455.
Kong, Youyong, Deng, Yue, Dai, Qionghai, 2015. Discriminative clustering and feature selection for brain MRI segmentation. IEEE Signal Process Lett. 22 (5), 573–577.
Kravitz, D.J., Saleem, K.S., Baker, C.I., Ungerleider, L.G., Mishkin, M., 2013. The ventral visual pathway: an expanded neural framework for the processing of object quality. Trends Cogn. Sci. 17 (1), 26–49.
Kucyi, A., Davis, K.D., 2014. Dynamic functional connectivity of the default mode network tracks daydreaming. NeuroImage 100, 471–480.
Mangelinckx, C., Belge, J.B., Maurage, P., Constant, E., 2017. Impaired facial and vocal emotion decoding in schizophrenia is underpinned by basic perceptivo-motor deficits. Cogn. Neuropsychiatry 22 (6), 461–467.
Martinez, 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. Cereb. Cortex 22 (6), 1282–1293.
Pettersson-Yeo, W., Allen, P., Benetti, S., McGuire, P., Mechelli, A., 2011. Dysconnectivity in schizophrenia: where are we now? Neurosci. Biobehav. Rev. 35 (5), 1110–1124.

Plomp, G., Roinishvili, M., Chkonia, E., Kapanadze, G., Kereselidze, M., Brand, A., Herzog, M.H., 2013. Electrophysiological evidence for ventral stream deficits in schizophrenia patients. Schizophr. Bull. 39 (3), 547–554.
Power, J.D., Mitra, A., Laumann, T.O., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2014. Methods to detect, characterize, and remove motion artifact in resting state fMRI. NeuroImage 84, 320–341.
Sergi, M.J., Rassovsky, Y., Nuechterlein, K.H., Green, M.F., 2006. Social perception as a mediator of the influence of early visual processing on functional status in schizophrenia. Am. J. Psychiatry 163 (3), 448–454.
Silverstein, S.M., Keane, B.P., 2011. Vision science and schizophrenia research: toward a re-view of the disorder. Editors' introduction to special section. Schizophr. Bull. 37 (4), 681–689.
Silverstein, S.M., Berten, S., Essex, B., Kovacs, I., Susmaras, T., Little, D.M., 2009. An fMRI examination of visual integration in schizophrenia. J. Integr. Neurosci. 8 (2), 175–202.
Silverstein, S.M., Berten, S., Essex, B., All, S.D., Kasi, R., Little, D.M., 2010. Perceptual organization and visual search processes during target detection task performance in schizophrenia, as revealed by fMRI. Neuropsychologia 48 (10), 2886–2893.
Spencer, K.M., 2008. Visual gamma oscillations in schizophrenia: implications for understanding neural circuitry abnormalities. Clin. EEG Neurosci. 39 (2), 65–68.
Stephan, K.E., Friston, K.J., Frith, C.D., 2009. Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophr. Bull. 35 (3), 509–527.
Vinckier, F., Cohen, L., Oppenheim, C., Salvador, A., Picard, H., Amado, I., Krebs, M.O., Gaillard, R., 2014. Reading impairment in schizophrenia: dysconnectivity within the visual system. Neuropsychologia 53, 187–196.
Watts, D.J., Strogatz, S.H., 1998. Collective dynamics of 'small-world' networks. Nature 393 (6684), 440–442.
Yaesoubi, M., Miller, R.L., Calhoun, V.D., 2015. Mutually temporally independent connectivity patterns: a new framework to study the dynamics of brain connectivity at rest with application to explain group difference based on gender. NeuroImage 107, 85–94.
Zalesky, A., Fornito, A., Cocchi, L., Gollo, L.L., Breakspear, M., 2014. Time-resolved resting-state brain networks. Proc. Natl. Acad. Sci. U. S. A. 111 (28), 10341–10346.
Zhang, J., Cheng, W., Liu, Z., Zhang, K., Lei, X., Yao, Y., Becker, B., Liu, Y., Kendrick, K.M., Lu, G., Feng, J., 2016. Neural, electrophysiological and anatomical basis of brain-network variability and its characteristic changes in mental disorders. Brain 139 (Pt 8), 2307–2321.