

Reduced intrinsic visual cortical connectivity is associated with impaired perceptual closure in schizophrenia



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ABSTRACT

Sensory perceptual processing deficits, such as impaired visual object identification and perceptual closure, have been reported in schizophrenia. These perceptual impairments may be associated with neural deficits in visual association areas, including lateral occipital cortex and inferior temporal areas. However, it remains unknown if such deficits can be found in the intrinsic architecture of the visual system.

In the current study, we measured perceptual closure performance and resting-state functional connectivity using functional magnetic resonance imaging (fMRI) in 16 schizophrenia patients and 16 matched healthy controls. We estimated intrinsic functional connectivity using self-organized grouping spatial ICA, which clusters component maps in the subject space according to spatial similarity. Patients performed worse than controls in the perceptual closure task. This impaired closure performance of patients was correlated with increased severity of psychotic symptoms. We also found that intrinsic connectivity of the visual processing system was diminished in patients compared to controls. Lower perceptual closure performance was correlated to lower visual cortical intrinsic connectivity overall.

We suggest that schizophrenia is associated with impaired intrinsic connectivity of the visual system, and that it is a potential mechanism leading to impaired visual object perception. These findings contribute to increasing evidence for impairments of higher visual functions in schizophrenia.

1. Introduction

Although schizophrenia has traditionally been conceptualized as a disorder of fronto-limbic-striatal (Meyer-Lindenberg and Weinberger, 2006) or fronto-thalamo-cerebellar (Andreasen, 1999) circuitry, recent research has also zoomed in on dysfunctions of sensory processing systems. Particularly, there is substantial evidence for impaired visual processing in schizophrenia patients. Studies over the recent years have demonstrated deficits in early visual processing pathways in schizophrenia, including dysfunctions in (subcortical) magnocellular pathways and orientation-specificity (Butler et al., 2007, 2005; Martinez et al., 2008; Yoon et al., 2009). Patients also show impaired performance on a number of tasks of visual object recognition, such as visual illusions, Gestalt images and perceptual closure (Doniger et al., 2001; Sack et al., 2005; Uhlhaas et al., 2006a). These findings may point to a particular dysfunction in visual perception, as it has been suggested that the magnocellular pathway may play an important role in the top-down modulation of object-based visual perception (Bar, 2003).

Impairments in visual object processing may be related to core pathological mechanisms in schizophrenia. Many visual tasks on which patients with schizophrenia perform poorly contain elements of contextual processing of sensory information (Javitt, 2009; Silverstein and Keane, 2011). Patients with schizophrenia show impaired performance when contextual information is noisy (Uhlhaas et al., 2006b; Yoon et al., 2009) or incomplete (Doniger et al., 2000; Sack et al., 2005), which indicates that these patients have difficulty integrating top-down contextual processing with bottom-up sensory information. Impaired visual processing has also been observed in sub-clinical at-risk populations (Kim et al., 2010; Oertel et al., 2009), which could indicate that visual impairments share a genetic commonality with other pathogenic mechanisms in schizophrenia. Finally, one study showed improved performance on visual processing tasks after three weeks of clinical treatment, together with alleviation of symptoms (Uhlhaas et al., 2005). Thus, impairments in visual processing may be a core feature in the pathology of schizophrenia.

Impairments in visual object perception can be investigated using

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perceptual closure tasks. Perceptual closure is the ability to recognize visual objects or shapes from incomplete or obstructed visual information (Snodgrass and Feenan, 1990). In perceptual closure tasks, participants must identify visual items that are partially obstructed or that miss visual details. Previous neuroimaging studies showed that performance in such tasks is associated with activity in object-related processing areas, including the lateral occipital cortex and inferior temporal areas (Doniger et al., 2000; Ploran et al., 2007; Sehatpour et al., 2006). Schizophrenia patients have shown impaired perceptual closure performance in a number of tasks (Doniger et al., 2001; Oertel et al., 2009; Sack et al., 2005). For example, in one study (Sack et al., 2005), schizophrenia patients and healthy participants had to identify partially occluded visual objects and written words within a pre-fixed time interval. Patients identified significantly fewer visual items than did healthy controls. In another study, Doniger et al. (2001) used a perceptual closure task in which the occluded visual object was revealed in a step-wise fashion, such that the image appeared more completely with each step. This process stopped when the participant correctly identified the image or when the image was completely revealed. In their task, schizophrenia patients required significantly more visual information to recognize the objects than did healthy controls. An event-related potential (ERP) study further showed that patients' impaired perceptual closure performance was associated with a diminished closure-related negativity, of which the neural source has been attributed to visual association areas (Doniger et al., 2002).

However, to date it remains unknown whether impaired perceptual closure is associated to impaired connectivity of the visual system in schizophrenia patients. One approach to address this issue is to compare intrinsic brain activity in patients and controls to perceptual closure performance. There is growing evidence that the intrinsic functional architecture, which is commonly measured using resting-state paradigms, is disrupted in schizophrenia (Alderson-Day et al., 2016; Bassett and Bullmore, 2009; Menon, 2011; van de Ven, 2012). Many of these studies have focused on higher-order brain networks that are associated with executive functioning and cognitive control. There is very little known about intrinsic abnormalities of visual cortical processing in schizophrenia patients. One resting state study (Liang et al., 2006) found widespread decreases and increases in intrinsic functional connectivity in patients, compared to controls, which included connections between visual and non-visual brain areas. However, no details about altered connectivity within visual cortex were reported. A second study (Hoptman et al., 2010) analyzed differences in low frequency amplitude (< 0.1 Hz) of resting state activity in patients and healthy controls, which strongly contributes to the functional magnetic resonance (fMRI) resting state signal (Cordes et al., 2001; Fox and Raichle, 2007; van de Ven et al., 2004) and may have a neural underpinning (Leopold et al., 2003; Shmuel and Leopold, 2008). Hoptman et al. (2010) found decreased amplitude of low frequency oscillations in visual cortex in patients, compared to controls, which could indicate impaired visual cortex functioning in patients. However, analysis of functional connectivity within visual RSN was not performed.

In addition, several fMRI resting-state studies have also shown that individual differences in connectivity strength within and between RSNs may be associated to individual behavioral performance on a number of tasks. For example, intrinsic connectivity strength of executive and cognitive control RSNs have been found to correlate with behavioral or self-report measures of attentional or executive abilities (Reineberg et al., 2015; Seeley et al., 2007). Other studies have demonstrated that larger improvements after learning a sensory (Lewis et al., 2009; Uner et al., 2013) or motor skill (Albert et al., 2009; Taubert et al., 2011; Zhang et al., 2014) are associated with larger increases in intrinsic connectivity within and between sensory, motor and higher-order RSNs after learning. Thus, it is possible that alterations in intrinsic visual cortical connectivity may be associated with corresponding changes in perceptual closure performance. However, it

remains unknown whether schizophrenia patients show impaired intrinsic connectivity of visual areas and if it is behaviorally relevant for higher-order visual processing.

In the current study, we compared functional connectivity of the visual RSN in schizophrenia patients and healthy controls to perceptual closure performance obtained outside of the scanner environment. We expected to replicate previous findings of impaired perceptual closure performance in schizophrenia patients, compared to healthy controls. Further, we hypothesized that patients show reduced functional connectivity within striate and extrastriate cortex, compared to healthy controls, and that reduced intrinsic visual cortical connectivity is associated with impaired perceptual closure performance.

2. Methods

2.1. Participants

The study included sixteen right-handed schizophrenia patients of the Department of Psychiatry of the University Hospital of Goethe University, Frankfurt, Germany and sixteen control participants matched for handedness, age, gender and parental years of education. The fMRI data have been described in a previous study (Rotarska-Jagiela et al., 2010). Because of the rationale of this previous study, patients were included if they met diagnostic criteria for paranoid schizophrenia according to the DSM IV and had a history of auditory hallucinations. Table 1 lists demographic and clinical data of the participants. Participants with a history of other psychiatric or neurological disorders or drug abuse were excluded. The diagnosis of schizophrenia was confirmed with Structured Clinical Interview for DSM IV (Wittchen et al., 1997). Current psychopathology in the patient group was assessed using PANSS (Fiszbein et al., 1987). The local ethics committee of the University Hospital approved the study. Written informed consent was obtained from all participants.

2.2. Assessment of visual perceptual closure

To assess visual perceptual closure, we assessed objective performance on two speed-of-closure tests, which we have used in previous studies (Oertel et al., 2009; Sack et al., 2005). The perceptual closure tests are part of a larger general intelligence test battery (Horn, 1983) that comprises high retest reliability (rtt = 0.95). We assessed object-based perceptual closure speed (OPC, retest reliability, rtt = 0.71) and verbal-based perceptual closure speed (VPC, rtt = 0.88). The OPC consists of 40 sketches of common objects (e.g. car, apple, house), in which some pictorial parts are erased, and participants are required to recognize and name the respective objects. The VPC consists of 40 visually degraded words, in which each word contains one false letter,

Table 1

Demographic variables, symptom ratings and behavioral measures. Numbers in rounded brackets are standard deviations (SD).

	Patients	Controls	Comparison P
Demographics			
Gender (M/F)	8/8	8/8	n.s.
Age in years	36.1 (7.9)	37.0 (7.8)	n.s.
Parental years of education	12.2 (2.0)	13.1 (3.0)	n.s.
Years of education	13.8 (3.5)	17.0 (1.8)	< 0.01
Symptoms (PANSS)			
Positive	14.7 (5.6)		
Negative	15.9 (4.9)		
General	29.9 (10.8)		
Behavioral tests			
Mean perceptual closure (OPC and VPC)	19.3 (5.8)	23.4 (3.2)	0.023
Psychomotor Speed in sec	47.8 (33.6)	30.1 (13.4)	n.s.
Semantic knowledge (items correct)	29.1 (5.1)	28.1 (4.3)	n.s.

which has to be identified and crossed out. Performance for each of the tests is limited to a time constraint of 1 min. Perceptual closure performance is scored as the number of correctly identified items within the restricted time. Because performance on the two speed-of-closure tests are commonly highly correlated, as was the case in our study ($r = 0.65$, $P < 0.001$), the scores were averaged between the two tests to obtain a single measure of perceptual closure.

The perceptual closure tests contain elements of psychomotor speed and semantic knowledge. To control for possible group effects in these cognitive domains, we also assessed the German equivalent (Gaussmann et al., 1978; Oswald, 1986) of the Trail Making Test A (TMT-A (Reitan, 1958)) and the German equivalent (Gaussmann et al., 1978) of the Spot-the-Word-Test (SWT (Baddeley et al., 1993)). In the TMT-A, the material comprises two matrices of numbers that are arranged in random order and participants must connect the numbers in ascending order. Psychomotor speed performance is scored as the mean speed in seconds to complete the matrices. In the SWT, participants must identify a word amongst nonsense-word distractors. Semantic knowledge is scored as the number of correctly identified words. Both psychometric tests possess high test-retest reliability (TMTA: $rtt = 0.95$; SWT: $rtt = 0.87$). All tests were completed within seven days prior to scanning.

2.3. Image acquisition

MRI measurements were performed on a 3 Tesla Siemens Allegra. T1-weighted anatomical data were obtained using 3D Modified Driven Equilibrium Fourier Transform (MDEFT) sequence (Deichmann et al., 2004; Lee et al., 1995) with 176 slices and $1 \times 1 \times 1 \text{ mm}^3$ voxel size. Functional T2*-weighted resting-state images were acquired using an EPI sequence (TR/TE 1000/30 ms, flip angle 60° , 16 slices, 400 volumes, $3.1 \times 3.1 \times 5 \text{ mm}^3$). Participants were instructed to lie still during image acquisition with their eyes open and fixate a white cross presented in the center of the visual field.

2.4. Data preprocessing and analysis

The data were analyzed using BrainVoyager QX (Goebel et al., 2006) and in-house software that used functionalities of the NeuroElf toolbox (www.neuroelf.net) implemented in Matlab (The MathWorks, Natick, MA, U.S.A.). Functional data were preprocessed using slice scan time correction, spatial smoothing with a 6 mm FWHM Gaussian kernel, linear trend removal and high pass filtering of 0.0025 Hz per functional run. The data were aligned to anatomical images and resampled to $3 \times 3 \times 3 \text{ mm}^3$ in a standardized 3D Talairach space. Anatomical images were averaged across participants, and an average brain volume mask was created.

2.5. Functional connectivity analysis

Analysis of resting-state functional connectivity was conducted using self-organized grouping sICA (sogICA) (Esposito et al., 2005; van de Ven et al., 2008) to decompose individual time series into 45 spatial components and temporal profiles (using Infomax algorithm (Bell and Sejnowski, 1995)) and cluster the results in the subject space to obtain group representations of the spatial modes. Spatial components and associated temporal profiles were Z-normalized (McKeown et al., 1998). Component clustering in the subject space was performed using hierarchical clustering with spatial similarity as input to the clustering algorithm to obtain 45 clusters of 32 spatial maps. Each participant contributed one spatial map to a cluster. For each cluster, a representative cluster spatial map was obtained by calculating one-sample *t*-tests of the component values for each voxel (i.e., ignoring group membership of the cluster members). We then selected by visual inspection the spatial cluster map that best represented early visual cortex, referred to here as the visual RSN, for further analysis.

Importantly, this selection was made at the end of the sogICA clustering procedure in order to minimize subjective selection of individual components (Esposito et al., 2005; van de Ven et al., 2008).

We then regressed the temporal profile of the individual components of the visual RSN in a multiple regression analysis for each participant's resting-state time series. Visual RSN regressors were supplemented with fMRI covariates that included time series sampled from the ventricles and from white matter, global signal and six head-volume rotation and translation parameters for each participant (Birn et al., 2006; Fox et al., 2005). The regression fits of the visual RSN were interpreted as linear fits of functional connectivity. Analysis of the absolute values of the six head movement parameters revealed no systematic differences between the two groups ($P > 0.6$).

A multi-subject representation of the visual RSN was calculated by a one-sample *t*-test of functional connectivity maps. The statistical summary map was thresholded for visualization at a false-discovery rate (FDR (Genovese et al., 2002)) of $q = 0.01$ and a minimum region-size threshold of 270 mm^3 (arbitrarily chosen to minimize isolated voxels and bias results towards contiguous clusters surviving the FDR correction). This map also served as a statistical voxel map to empirically restrict voxel-based analysis of functional connectivity to visual RSN areas.

2.5.1. Global and local connectivity

Group differences of connectivity were assessed at the global (that is, map-based) and local level (that is, voxel-based). For the global-level analysis, we calculated a spatial goodness-of-fit (SGI) index (Esposito et al., 2008; Greicius et al., 2004) as the spatial correlation of an individual's visual RSN to a leave-one-out template of the multi-subject visual RSN (Esposito et al., 2008). In the leave-one-out procedure, the template was calculated as the mean of the visual RSNs of all participants with the exception of the one to which the template is compared to. The ensuing correlation values were normalized using Fisher's Z transformation and then used as a dependent variable in subsequent analyses with Group as independent factor.

For the local-level analysis, the distributions of voxel-based connectivity values were analyzed with Group as independent factor in a voxel-by-voxel manner. Only voxels that were tagged by the thresholded multi-subject map were investigated, which amounted to $< 15\%$ of all brain voxels. The resulting statistical map was thresholded at $q(\text{FDR}) = 0.05$.

To simplify the ROI analysis, we pooled voxel clusters according to early vs. higher-level visual areas, which largely coincides with the psychophysical results of visual perceptual deficits in schizophrenia (e.g., (Silverstein and Keane, 2011)). Voxel clusters at or near the calcarine fissure were pooled into an early visual ROI. Voxel clusters in extrastriate and inferotemporal areas were pooled into a higher-visual ROI.

2.5.2. Associations with perceptual closure

We analyzed associations between visual RSN and perceptual closure using correlation analysis at the global and local level. Within the patient group, we also correlated symptom ratings with the perceptual closure scores.

2.5.3. Associations with psychopathology

Finally, we analyzed whether psychopathology was associated with visual RSN connectivity in patients by correlating the symptom ratings for positive, negative and general symptoms to functional connectivity coefficients at the global and local level. This analysis was conducted as an exploratory analysis, following up on previously reported correlations between intrinsic connectivity and psychopathology ratings (e.g., (Oertel-Knöchel et al., 2014; Shinn et al., 2013; Whitfield-Gabrieli et al., 2009)).

3. Results

3.1. Behavioral test performance

Behavioral test scores of one control participant were not logged correctly, and were therefore excluded from analysis. Table 1 provides an overview of the demographic values and behavioral performance on the perceptual closure, psychomotor speed and semantic knowledge tests. Patients did not significantly differ from the control group on age, gender, handedness and parental years of education. However, patients had lower years of education than controls ($P = 0.004$).

Patient performance on perceptual closure was worse (mean [SD] = 19.3 [5.8]) compared to control participants (23.4 [3.2]), and this difference was significant ($T[29] = 2.4$, $P = 0.023$). Perceptual closure scores did not correlate with years of education ($P > 0.4$). Further, patients performed slower on the psychomotor speed test (mean [SD] = 47.8 [33.6]) compared to controls (30.1 [13.4]), but this difference did not reach significance ($P = 0.068$). Finally, performance on the semantic knowledge test was not significantly different ($P = 0.59$).

Because of the significant difference in years of education and the close-to-significant effect on psychomotor speed, we removed the covariance of these measures from the subsequent functional connectivity analyses by means of least squares regression.

3.2. Visual RSN

A multi-subject map of the visual RSN of patients (one-sample t -test, thresholded at $q = 0.05$ and minimum region-size threshold of 270 mm^3) showed significant functional connectivity in bilateral striate and extrastriate visual cortex, including medial and lateral occipital gyri, inferior temporal areas and parahippocampal gyri (see Fig. 1). This map was very similar to the multi-subject map of the control participants, as indicated by the high spatial correlation between the two maps ($r = 0.70$). We used the one-sample t -test map of all participants combined as a voxel mask for subsequent analyses.

We assessed between-group effects on a global and local level. For the global level, the spatial goodness-of-fit index (SGI) was significantly ($T[29] = 2.5$, $P = 0.017$) lower for patients (mean [SD] = 0.47 [0.22]) compared to controls (0.65 [0.17]) (see Fig. 2A). This result indicated that within the visual RSN the degree of network-wide functional connectivity in patients was less strong or consistent than

in controls.

At the local level, the voxel-by-voxel group comparison within the visual RSN revealed several voxel clusters of significant difference in connectivity around the calcarine fissure, the anatomical marker for striate cortex, lateral occipital cortex and inferior temporal gyri, extending into parahippocampal regions. Table 2 lists the coordinates and sizes of the clusters. The regional results reflected widespread changes within the visual RSN, which mostly was in the direction of decreased connectivity in patients compared to controls, thereby corroborating the global connectivity results. That is, visual cortex connectivity in schizophrenia is reduced in strength, rather than increased network heterogeneity. To focus the analysis on key visual sensory processing areas, we pooled areas according to homologue location in the left and right hemisphere for cuneus (region-of-interest for early visual processing) and inferior temporal gyrus (region-of-interest for higher order visual processing), which we used for further analysis.

3.3. Association with perceptual closure

Initial correlation analysis between perceptual closure scores and the global network index showed that higher global connectivity was associated with increased perceptual closure performance across both groups (SGI, $r = 0.55$, $P = 0.002$). However, because both measures significantly differed between the two groups, we regressed out the Group factor from both measures. The correlation between the two corrected measures remained significant ($r = 0.41$, $P = 0.011$) (see Fig. 2B).

We also correlated the perceptual closure scores with the functional connectivity values of the two bilateral visual RSN regions. A significant correlation was found for bilateral ITG ($r = 0.53$, $P < 0.001$) and for bilateral cuneus ($r = 0.39$, $P = 0.014$), indicating that higher connectivity was associated with better perceptual closure performance. To rule out the possibility that these correlations were confounded by Group factor, we regressed out Group factor and recalculated the correlations for both regions. We again found a significant correlation corrected for Group in bilateral ITG ($r = 0.40$, $P = 0.014$; see Fig. 2D) but not for early visual cortex (Fig. 2C).

Finally, we assessed how perceptual closure performance correlated with symptom ratings. Perceptual closure performance in patients correlated negatively with positive symptom severity ($r = -0.66$,

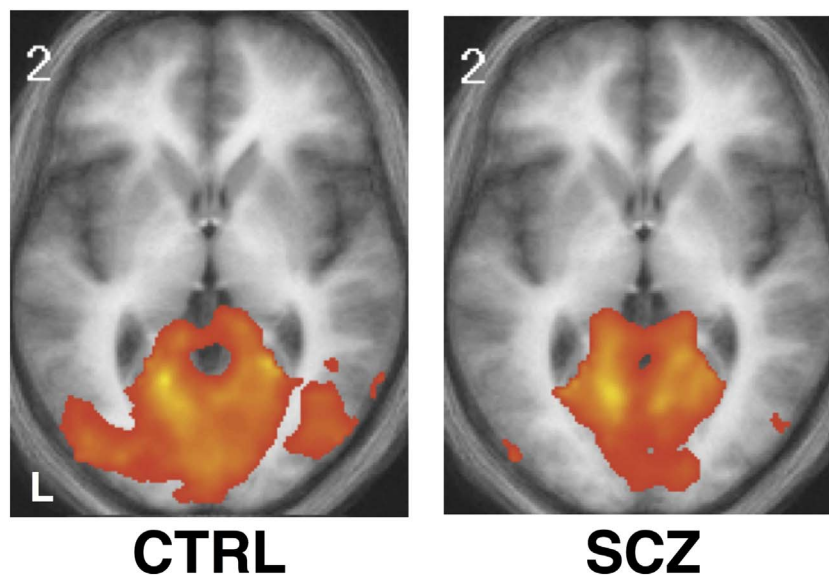


Fig. 1. Visual RSN group maps. Shown are the thresholded ($q(\text{FDR}) = 0.05$) one-sample t -test maps of the visual RSNs for healthy control participants (A) and schizophrenia patients (B) superimposed on the average anatomical image of all participants. White number at left-top of each panel indicates Talairach Z coordinate. Left hemisphere is depicted on the left of each image.

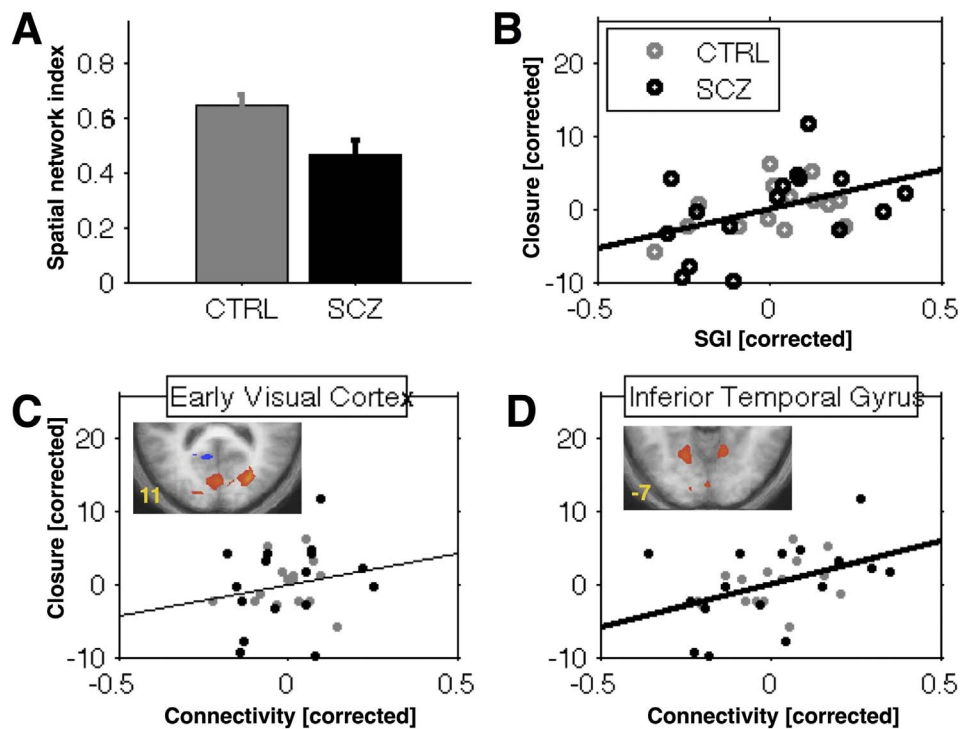


Fig. 2. Visual RSN and perceptual closure. (A) Spatial Goodness-of-fit index (SGI) of visual RSN was lower for patients (black bar) than for healthy controls (gray bar). (B) SGI values correlated with perceptual closure performance across both groups. SGI and perceptual closure scores were corrected for Group because both showed a significant difference between groups (see main text). (C, D) Regional functional connectivity values in inferior temporal areas (D), but not in early visual areas (C), correlated with perceptual closure performance. Connectivity values and perceptual closure scores were corrected for Group. Error bars indicate 1 SEM. Thick regression line indicates a significant linear association ($P < 0.05$).

Table 2

Visual RSN regional differences. Clusters were obtained from a between-group voxel-by-voxel analysis of the visual RSN (thresholded at $q(\text{FDR}) = 0.05$). Coordinates are in standardized Talairach space. Contrast specifies the direction of the effect.

ROI	L/R	x y z [mm]	Size [mm]	Contrast
Cuneus	L	6 -79 22	192	C > P
	R	-15 -85 4	99	C > P
ITG	L	-18 -61 -5	27	C > P
	R	12 -58 -8	10	C > P
MTG	R	42 -70 22	46	C < P
PCC	L	-9 -43 7	34	C < P

$P = 0.005$), such that higher positive symptom severity was associated with decreased perceptual closure performance. We did not find significant associations between perceptual closure and negative or general symptom ratings ($P_s > 0.05$). Moreover, perceptual closure performance in patients was not associated with patient age ($P > 0.6$), illness duration ($P > 0.8$) or medication (dosage in chlorpromazine equivalent mg/day, mean [SD] = 651.5 [296.3], $P > 0.9$).

3.4. Association between intrinsic connectivity and psychopathology

We found no significant correlations between positive, negative or general PANSS scores and global or local functional connectivity.

4. Discussion

We compared perceptual closure performance and functional connectivity of the visual RSN in schizophrenia patients to that of matched healthy control participants. We found that patients performed worse on perceptual closure than did healthy controls, independent of psychomotor speed or semantic knowledge. This finding corresponds to previous reports of impaired perceptual closure in schizophrenia (Doniger et al., 2001; Oertel et al., 2009; Sack et al., 2005; Uhlhaas and

Mishara, 2007).

Moreover, we found that strength of functional connectivity was diminished throughout the visual RSN in patients compared to controls, including early and higher-level visual areas. These findings correspond to a previous report of reduced low frequency amplitudes during resting state in patients with schizophrenia and schizoaffective disorder compared to healthy controls (Hoptman et al., 2010). Our results expand on these findings by showing that resting state fMRI can identify aberrant functional connectivity beyond moments of task-related visual perception.

Further, our finding of decreased functional connectivity in early as well as higher-order visual areas fits to previous reports of impaired visual sensory processing. Reports of diminished magnocellular pathway responses (Butler et al., 2007, 2005; Martinez et al., 2008), impaired performance in visual contextual tasks (Dakin et al., 2005; Yoon et al., 2009) and visual illusions (Kantrowitz et al., 2009) indicate deficits in neural pathways at the level of primary visual cortex or before, at subcortical levels. At the same time, schizophrenia patients have also shown impairments for stimuli of higher-order perceptual organization, such as in Gestalt perception of faces (Butler et al., 2008; Uhlhaas et al., 2006a) or perceptual closure of objects (Doniger et al., 2001; Oertel et al., 2009; Sack et al., 2005). The functional relevance of visual cortical connectivity is further supported by the observed correlation between perceptual closure scores and functional connectivity strength in higher-level but not in early visual areas. The perceptual closure tests included degraded visual objects and word forms, which are processed in inferior temporal areas rather than in early visual cortex (Grützner et al., 2010; Ploran et al., 2007; Sehatpour et al., 2006). It is conceivable that performance on perceptual organization tasks that tap into subcortical and early visual processes (e.g., (Butler et al., 2007; Martinez et al., 2008)) may show a stronger correlation with intrinsic connectivity in early visual areas, rather than inferior temporal cortical connectivity. Yet, it is also likely that a deficit at one level of the visual hierarchy influences processing at another level. For example, deficits in magnocellular pathways can result in

noisy processing at higher levels of visual representation (Demb et al., 1998), while top-down processing such as visual attention can alter processing at primary visual (Kastner and Ungerleider, 2000) and even subcortical levels (O'Connor et al., 2002). Our study did not use other perceptual tasks that may be sensitive to higher or lower levels of visual processing, which precludes further insight into this issue. Future studies are required to test the functional specificity of intrinsic visual cortical connectivity and its role in the pathophysiology of schizophrenia.

Our findings of decreased connectivity in schizophrenia are in line with a growing body of reports that show widespread impairments in intrinsic connectivity in schizophrenia (Alderson-Day et al., 2016; Menon, 2011; Northoff and Qin, 2011). In particular, the default-mode network (DMN), salience network (SN) and the central executive network (CEN) seem to be affected in psychotic patients, compared to healthy controls, and which may be related to symptomatology and higher-order cognitive impairments in patients (Alonso-Solís et al., 2012; Orliac et al., 2013; Palaniyappan et al., 2013; Rotarska-Jagiela et al., 2010; Whitfield-Gabrieli et al., 2009; Woodward et al., 2011). In turn, aberrantly connected networks may impair sensory information processing, thereby playing a role in perceptual impairments as well. For example, one study showed that, in first-episode psychosis patients, the DMN's posterior cingulate cortex was less strongly connected to visual areas, including inferior temporal and cuneus areas, compared to age and gender-matched controls (Alonso-Solís et al., 2012). Yet, aberrant connectivity between visual and other RSNs in schizophrenia is not a common finding. We also did not find aberrant connectivity between the visual and non-visual brain areas in our study. However, we note that differences in patient sample and analytical approaches between the two studies make comparison of results difficult.

It is currently unknown how the association between impaired visual processing and disrupted intrinsic functional connectivity is related to pathogenic factors in schizophrenia. Impairments in perceptual organization are not generally observed in most other mental disorders, such as bipolar disorder (Keri et al., 2005) or non-psychotic disorders (Uhlhaas et al., 2005). Conversely, we and others previously showed impaired perceptual closure performance in clinically unaffected relatives of patients with schizophrenia (Kim et al., 2010; Oertel et al., 2009), suggesting that closure deficits may be associated to the pathogenic mechanism of schizophrenia. Our use of intrinsic connectivity measures may be a useful method in further investigating how perceptual processing impairments are related to schizophrenia. Indeed, several resting-state fMRI studies showed impairments in non-clinical at-risk groups that were similar to those observed in schizophrenia patients (Oertel-Knöchel et al., 2013; Peeters et al., 2015; Whitfield-Gabrieli et al., 2009).

Finally, we found that impaired perceptual closure performance was associated with increased positive symptom severity in patients. It has been suggested that perceptual closure tasks tap into processes that integrate sensory evidence with top-down executive and memory functions (Javitt, 2009; Silverstein and Keane, 2011), which may also play a role in the generation of psychotic symptoms in schizophrenia (Frith, 2000). Our finding appears in line with this postulation. Further support comes from a previous study that used a Gestalt perception task based on inverted faces and reported that decreased Gestalt perception was associated with increased positive symptom ratings, including hallucinations (Uhlhaas et al., 2006a). However, other studies that used comparable tasks reported decreased task performance in association with increased negative (Doniger et al., 2002) or disorganization symptoms (Uhlhaas et al., 2006b), which suggests that the putative link between visual impairments and positive symptoms may not be very specific. A dedicated and high-powered study using one or more perceptual closure tasks and detailed clinical phenotyping in schizophrenia is required to resolve this issue.

We carefully controlled our study for known confounding effects. Our results appear not to be confounded by use of antipsychotic

medication in patients, as correlations between medication dosage and perceptual closure performance were not significant. Also, we carefully matched the two participant groups on various demographic variables, and controlled for confounding effects of differences in years of education and psychomotor speed between the groups. Finally, the confounding effects of head motion in resting state analysis has been fiercely debated over recent years (Power et al., 2012; Turner et al., 2015; van Dijk et al., 2012). Particularly, schizophrenia patients may show more frequent and larger head movements compared to healthy controls, which could spuriously amplify differences between groups (Callicott and Weinberger, 1999). In our study, we found no clear indication of systematically larger head movements in patients than in controls. Also, we controlled for individual head movement in all participants in the functional connectivity analysis, following previous recommendations.

In conclusion, we found impaired functional connectivity in visual RSN in schizophrenia, which was associated with impaired perceptual closure performance. The association was strongest in higher-order visual areas, which fits to the visual object-related nature of the closure task that we used. Visual RSN abnormalities may be a causative factor in explaining visual processing deficits in schizophrenia.

Conflict of interest

D.E.J.L. was an associate editor of NeuroImage: Clinical at the time of this manuscript's original submission and took over as co-editor-in-chief when it had already entered the evaluation process. He has taken no part in the editorial evaluation of this manuscript. The other authors declare no conflict of interest in this work.

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