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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 completed 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; Urner 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.