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Disrupted relationship between "resting state" connectivity and task-evoked activity during social perception in schizophrenia

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ABSTRACT

Schizophrenia has been described as a self-disorder, whereas social deficits are key features of the illness. Changes in "resting state" activity of brain networks involved in self-related processing have been consistently reported in schizophrenia, but their meaning for social perception deficits remains poorly understood. Here, we applied a novel approach investigating the relationship between task-evoked neural activity during social perception and functional organization of self-related brain networks during a "resting state".

"Resting state" functional MRI was combined with task-related functional MRI using a social perception experiment. Twenty-one healthy control participants (HC) and 21 out-patients with a diagnosis of schizophrenia (SCH) were included. There were no significant differences concerning age, IQ, education and gender between the groups.

Results showed reduced "resting state" functional connectivity between ventromedial prefrontal cortex and dorsal posterior cingulate cortex in SCH, compared to HC. During social perception, neural activity in dorsal posterior cingulate cortex and behavioral data indicated impaired congruence coding of social stimuli in SCH. Task-evoked activity during social perception in dorsal posterior cingulate cortex co-varied with dorsal posterior cingulate cortex-ventromedial prefrontal cortex functional connectivity during a "resting state" in HC, but not in SCH. Task-evoked activity also correlated with negative symptoms in SCH.

These preliminary findings, showing disrupted prediction of social perception measures by "resting state" functioning of self-related brain networks in schizophrenia, provide important insight in the hypothesized link between self and social deficits. They also shed light on the meaning of "resting state" changes for tasks such as social perception.

1. Introduction

Schizophrenia has been described as being a self-disorder that is expressed in a heterogeneity of symptoms (Northoff, 2014; Nelson, Fornito, et al., 2009; Sass and Parnas, 2003). Among these symptoms, social impairments have been recognized as key features of the illness (Green et al., 2012; Horan et al., 2012; Fett et al., 2011; Eack et al., 2010; Addington et al., 2008; Couture et al., 2006; Minkowski, 1927). However, the exact relation between social impairments and self-disorder as a disturbed sense of self remains unclear.

Self-related processing regards a well-studied aspect constituting our sense of self. It concerns the neural processing of the relation of environmental/exteroceptive and bodily/interoceptive stimuli with one's own person (van der Meer et al., 2010; Northoff 2016). If that is disrupted, such stimuli cannot be properly related to the self.

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Because environmental stimuli include social stimuli concerning other individuals' self, it raises the question how self-related processing in schizophrenia is linked to social deficits (Haug et al., 2014; Nelson, Sass, et al., 2009; Gallese, 2003; Parnas et al., 2002).

Studies in healthy participants suggest that social perception of others' mental and bodily states could be mediated by self-related processing (Schilbach et al., 2008; Fisher et al., 2008; Mitchell et al., 2005). The integration of multiple signals during social perception has recently been associated with self-related processing: congruent social information could increase self-relatedness and facilitate subjective judgments of others' experiences (Ebisch et al., 2016). This is in line with accounts proposing association of self-relatedness with other functions (Northoff, 2016), including integrative information processing (Sui and Humphreys, 2015).

The present study aimed at investigating whether deficits in the integration of multiple signals during social perception can be related to disrupted functional organization of self-related brain networks in schizophrenia.

Self-related processing involves cortical midline structures (CMS), like anterior (ACC) and posterior cingulate cortex (PCC), and medial prefrontal cortex (MPFC) (Qin and Northoff, 2011; van der Meer et al., 2010). These CMS are also known to be involved in social cognition (Schilbach et al., 2008; Mitchell et al., 2005) interacting with sensorimotor and affective systems for social understanding (Molnar-Szakacs and Uddin, 2013; Gallese, 2007). Furthermore, self-related activity within CMS shows strong overlap with spontaneous activity during task-unrelated thought (i.e., “resting state”) in the default mode network (DMN) (Qin and Northoff, 2011; Whitfield-Gabrieli et al., 2011; Bai et al., 2016; Huang et al., 2016).

“Resting state” changes in MPFC and PCC have indeed been shown in schizophrenia (Sheffield and Barch, 2016; Northoff, 2015; Kuhn and Gallinat, 2013; van der Meer et al., 2010). These changes included functional connectivity within CMS as well as with sensorimotor and affective networks (Martino et al., 2017; Berman et al., 2016). However, the meaning of such “resting state” changes for subsequent task-evoked activity during social perception remains poorly understood. Specifically, it is unclear whether the relationship between CMS “resting state” functional connectivity (RS-FC) and task-evoked impairments in social perception is altered in schizophrenia.

For this purpose, we combined “resting state” RS-FC functional magnetic resonance imaging (fMRI) with task-related fMRI using a social perception experiment in schizophrenia.

RS-FC analysis provides a basic index of functional network structure in terms of long-range communication between brain regions based on low-frequency fluctuations of the Blood Oxygen Level Dependent (BOLD) signal. We focused on RS-FC of the regions of interest (ROIs) ventral MPFC and PCC showing overlap with self-related processing and high “resting state” activity according to meta-analyses (Qin and Northoff, 2011). The social perception experiment addressed integrative processing of visual social stimuli allowing to compare the processing of congruent and incongruent information from multiple sources (others' sensorimotor experiences and facial expressions of emotion).

Analyses preliminarily tested the hypotheses that patients with schizophrenia, compared to healthy control participants, are characterized by (i) decreased RS-FC of vMPFC and PCC with CMS, sensorimotor or affective networks; (ii) impaired performance and task-evoked activity in nodes of self-networks during a social perception task requiring the integrative processing of congruent versus incongruent social stimulus content; (iii) a decreased relation, that is correlation, between RS-FC and task-evoked activity during social perception including their relation to psychopathological symptoms.

2. Material and methods

2.1. Participants

Twenty-one adult, healthy, right-handed control participants (HC) and twenty-one adult, right-handed out-patients with a diagnosis of schizophrenia (SCH) according to DSM-IV criteria were included in the present study. Detailed evaluation procedures are described in the Supplementary material. Demographic and clinical data are provided in Table 1. *t*-Tests did not show significant differences between the HC and SCH groups for age, education (years) and intelligence quotient (IQ) (see Table 1). A Chi-square test showed no significant difference in gender distribution between the groups.

All participating patients were rated for symptom severity with the Positive and Negative Symptom Scale (Kay et al., 1987). Exclusion criteria for all participants included physical health problems and neurological hard signs, standard contraindications for fMRI, a history of severe head trauma, loss of consciousness, drug abuse, IQ < 70, lifetime intake of neuroleptic/typical antipsychotic drugs, and, specifically for the HC group, a personal history of Axis I/II disorders or a history of psychosis in first-degree relatives.

The experimental protocol was approved by the local institutional ethics committee. Written informed consent was obtained from all participants prior to participation, in line with the Declaration of Helsinki.

2.2. fMRI procedures

Each participant underwent BOLD contrast fMRI scanning at 3 T and completed two task-free fMRI scanning runs (“resting state” 2 × 5.2 min) and four “task-related” fMRI scanning runs (4 × 7.7 min). Scanning details and fMRI preprocessing procedures are described in the Supplementary material.

To control for effects due to motion inside the scanner, FMRI preprocessing included regression of fMRI motion parameters and scrubbing of motion affected functional volumes (Power et al., 2012). FMRI runs with movements exceeding 3 mm were excluded from analysis. Finally, the HC and SCH groups were compared for motion inside the scanner: no significant differences were found (Table 1).

Table 1
Participant characteristics.

	Healthy control group	Schizophrenia group
Gender[a] (male/female)	16/5	16/5
Age[b] (mean years, standard deviation)	30.84 ± 4.59	32.24 ± 7.33
Intelligence quotient[c] (mean IQ, standard deviation)	117 ± 13	111 ± 14
Education level (mean years of education, standard deviation)[d]	13.19 ± 2.25	12.95 ± 2.67
Illness duration (mean years, standard deviation)	n.a.	5.19 ± 2.36
Psychotic episodes (mean number, standard deviation)	n.a.	1.76 ± 1.45
Chlorpromazine equivalences (mean CZP, standard deviation)	n.a.	265.25 ± 136.63
PANSS positive symptoms (mean score, standard deviation)	n.a.	15.57 ± 3.71
PANSS negative symptoms (mean score, standard deviation)	n.a.	19.43 ± 3.78
Root mean square error of head motion parameters during resting state fMRI (mean RMSE, standard deviation)[e]	0.21 ± 0.16	0.21 ± 0.1
Root mean square error of head motion parameters during task fMRI (mean RMSE, standard deviation)[f]	0.22 ± 0.15	0.26 ± 0.21

Between-group comparisons:

[a] HC vs. SCH: $\chi^2 = 0, p = 1$.

[b] HC vs. SCH: $t = -0.84, p = 0.41$.

[c] HC vs. SCH: $t = 1.78, p = 0.08$.

[d] HC vs. SCH: $t = 0.31, p = 0.8$.

[e] HC vs. SCH: $t \leq 0.01, p = 0.8$.

[f] HC vs. SCH: $t = 0.85, p = 0.2$.

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