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Transdiagnostic commonalities and differences in resting state functional connectivity of the default mode network in schizophrenia and major depression

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ABSTRACT

Schizophrenia and depression are prevalent psychiatric disorders, but their underlying neural bases remains poorly understood. Neuroimaging evidence has pointed towards the relevance of functional connectivity aberrations in default mode network (DMN) hubs, dorso-medial prefrontal cortex and precuneus, in both disorders, but commonalities and differences in resting state functional connectivity of those two regions across disorders has not been formally assessed. Here, we took a transdiagnostic approach to investigate resting state functional connectivity of those two regions in 75 patients with schizophrenia and 82 controls from 4 scanning sites and 102 patients with depression and 106 controls from 3 sites. Our results demonstrate common dysconnectivity patterns as indexed by a significant reduction of functional connectivity between precuneus and bilateral superior parietal lobe in schizophrenia and depression. Furthermore, our findings highlight diagnosis-specific connectivity reductions of the parietal operculum in schizophrenia relative to depression. In light of evidence that points towards the importance of the DMN for social cognitive abilities and well documented impairments of social interaction in both patient groups, it is conceivable that the observed transdiagnostic connectivity alterations may contribute to interpersonal difficulties, but this could not be assessed directly in our study as measures of social behavior were not available. Given the operculum's role in somatosensory integration, diagnosis-specific connectivity reductions may indicate a pathophysiological mechanism for basic self-disturbances that is characteristic of schizophrenia, but not depression.

1. Introduction

Impairments of the ability to engage successfully in social interactions are well documented in schizophrenia (SCZ) and major depressive disorder (MDD) (e.g., Billeke and Aboitiz, 2013; Fiszdon et al., 2013; Ladegaard et al., 2014; Lee et al., 2013; Savla et al., 2012; Schilbach, 2015; Schneider et al., 2012). In SCZ, these impairments of social interaction have been related to disturbances of self-related and other-related reasoning, i.e., social cognition (e.g., Frith and Corcoran, 1996). In particular, SCZ patients are thought to attribute more meaning to their social surroundings than usual, reflected in so-called positive symptoms such as delusions and paranoia (Frith, 2004). Alternatively, alterations of social cognition in SCZ have been described as a "loss of natural evidence" for being in a world intersubjectively shared with others, thereby leading to alienation and social withdrawal, which may culminate in a psychotic crisis, in which lost intersubjective meaning is replaced by a 'private' world of delusions (Blankenburg, 1971; Fuchs, 2007; Klosterkotter et al., 2001). The latter changes have been related to the so-called negative symptom dimension of schizophrenia, which is also known to be highly relevant for prognosis and socio-economic outcome (Fulford et al., 2013; Salvatore et al., 2007).

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In depressed patients, impairments of social interaction have similarly been related to attributional biases, which become manifest in abnormally increased, self-defeating, introspective thoughts and self-referential concerns (Marchetti et al., 2012). As in SCZ, disturbances of self-perception and self-referential thought can adversely affect interpersonal relations in MDD and make successful participation in social interaction difficult (Fuchs, 2001; Schilbach et al., 2014). Furthermore, it has been recognized that negative interpersonal experiences throughout the life span constitute an important risk factor for the development of depression and have, thus, become a key target of psychotherapeutic interventions (McCullough, 2003). Since social interactions are normally experienced as intrinsically rewarding (Schilbach et al., 2010), unsuccessful or reduced social interactions can further contribute to depressive symptomatology, but are also known to negatively affect the course of SCZ (Akdeniz et al., 2014; Hooker et al., 2014; Lee et al., 2014; Thomas et al., 2014).

Taken together, impairments of social interaction are well documented in both MDD and SCZ and can therefore be considered as a transdiagnostic symptom. The neurobiology that may underlie these transdiagnostic impairments, i.e., symptoms which fall onto a dimension that cuts across different nosological categories, in otherwise highly dissimilar disorders, however, remains poorly understood. In particular, when considering widespread dysconnectivity in both MDD and SCZ (Hamilton et al., 2013; Stephan et al., 2009), it is not clear whether transdiagnostically observed social impairments are subserved by distinct or common patterns of dysconnectivity. This question of similarities and differences in the neurobiological substrates of transdiagnostic social impairments is of particular relevance in light of current efforts of redefining psychiatric nosology in terms of neurobehavioral systems by taking a dimensional approach to the study of the genetic, neural, and behavioral features of mental disorders (Buckholtz and Meyer-Lindenberg, 2012; Cuthbert and Insel, 2013; Morris and Cuthbert, 2012).

Previous neuroimaging evidence indicates that aberrations of introspective processes relevant for social interactions are related to changes of functional connectivity (FC) in key nodes of the very robust "default mode network" (DMN) in particular related to social processing (Bastos-Leite et al., 2015; Das et al., 2012; Liston et al., 2014; Meda et al., 2012; Nixon et al., 2014; Schilbach et al., 2014; Yu et al., 2012). The DMN is classically defined as brain regions that show relative neural deactivation when focusing on the external environment and relative activation for internally focused tasks including autobiographic memory retrieval and conceiving the perspectives of others (Buckner et al., 2008). Recently, a large-scale neuroimaging meta-analysis characterized the overlap of the DMN, emotional processing and social-cognitive networks (Schilbach et al., 2012). The spatial convergence was identified in two cortical midline regions, namely the dorsomedial prefrontal cortex (DMPFC) and precuneus including the posterior cingulate cortex (PRC/PCC) representing the anterior and the posterior hubs of the DMN, respectively (Fig. 1). Functionally, the DMPFC is involved in the generation of stimulus-independent thoughts about another person's mental states (Frith, 2008), while the PRC is frequently associated with internally directed attention (Shannon and Buckner, 2004). In order to assess dysconnectivity patterns that might be relevant for transdiagnostic social impairments, we used seed-based FC analyses of these two hubs of the DMN in groups of SCZ and MDD patients relative to cohorts of matched controls.

As the current study is based on the idea that transdiagnostic impairments of social interaction in SCZ and MDD may rely on common circuit dysfunction, we hypothesized to find similarities in functional dysconnectivity patterns, which may represent a common neurophysiological basis of the social deficits observed in both disorders.

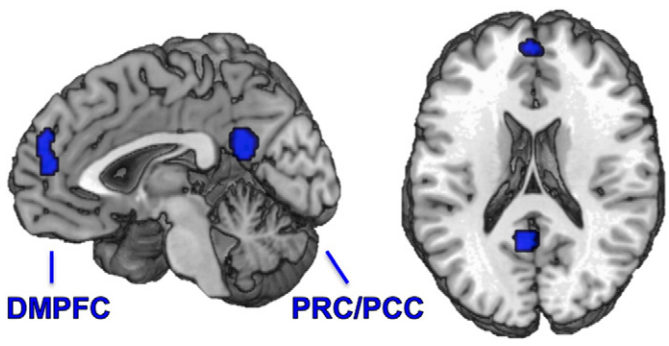

Fig. 1. Meta-analytically defined default mode network. Taken from Schilbach et al. (2012), precuneus including posterior cingulate cortex: PRC/PCC MNI: x −4, y −54, z 24, dorso-medial prefrontal cortex: DMPFC MNI: x −2, y 52, z 14.

2. Material & methods

2.1. Meta-analytically informed seed definition

For the current study, the seed regions of interest for the whole-brain FC analysis were derived from a quantitative meta-analysis on the statistical convergence of task-related neural deactivations in 533 experiments and increased activation in social-cognitive as well as in emotional tasks in 74 and 1474 experiments, respectively (Schilbach et al., 2012).

2.2. Sample description

In order to obtain a sufficient number of participants for robust statistics, samples of SCZ and MDD patients recruited in the hospital setting were pooled over different measurement sites (Table 1) with each subsample being matched to a site-specific group of healthy controls (HC). As pooling over different MR scanners may introduce a systematic confound when comparing BOLD contrasts between scanners, every patient subsample was complemented with a group of closely matched HC of the same site. Thereby, group comparisons were based on a matched contribution of participants from every MR scanner minimizing the influence of MR scanner and EPI sequence parameters on group differences.

Patient and control groups for every site in both diseases were independently matched for age, sex and within scanner movements using the following procedure. For each subsample, 1,000,000 random samples of patient–control combinations were drawn and t-tests were computed for three movement parameters (see below) and age and chi-square tests for sex using MATLAB. Then, the biggest subsample of patients and controls with a p-value > 0.2 in all tests was chosen to rule out any trend towards group difference regarding the applied parameters. Finally, the same matching criteria were used for the whole cohort in SCZ and MDD. Thereby, we assume that group differences in resting-state connectivity would neither be driven by systematically different head motion in the scanning process nor by differences in age or sex distribution. The SCZ sample included 75 patients and 82 controls from 4 scanning sites (Table 2) and the MDD group consisted of 102 patients and 106 controls from 3 sites (Table 3). Diagnosis was confirmed by clinical examination of the attending psychiatrist in accordance with the International Classification of Diseases (ICD-10). The two patient groups did not differ in terms of disease duration (mean duration: SCZ 9.03 ± 8.22; MDD 10.63 ± 10.20; Mann–Whitney U test: $p = 0.72$).

Due to recruitment taking place in a hospital setting and in light of around a decade long disease history, patients were medicated following established medication regimes. 80% of the SCZ patients were treated with second generation antipsychotics (SGA) and only a minority of 6.7% was receiving first generation antipsychotics (FGA) or a combination of the two (8%, Table 4). 50% of the MDD cohort was prescribed selective serotonin reuptake inhibitors (SSRI), serotonin–norepinephrine reuptake inhibitors (SNRI) or norepinephrine–dopamine reuptake inhibitors (NDRI), while 16.7% were additionally taking Tricyclic antidepressants (TCA). TCA alone were taken by 15.7% of