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Resting-state functional network correlates of psychotic symptoms in schizophrenia

Anna Rotarska-Jagiela [a,b,c,*,1], Vincent van de Ven [d,1], Viola Oertel-Knöchel [c], Peter J. Uhlhaas [a,c], Kai Vogeley [b], David E.J. Linden [e]

[a] Max Planck Institute for Brain Research, Department of Neurophysiology, Deutschordenstr. 46, 60528 Frankfurt a.M., Germany
[b] University of Cologne, Department of Psychiatry and Psychotherapy, Kerpenerstr. 62, 50924 Cologne, Germany
[c] Johann Wolfgang Goethe University, Department of Psychiatry, Neurophysiology and Neuroimaging Lab and Brain Imaging Center, Heinrich-Hoffmann-Str. 10, 60528 Frankfurt/Main, Germany
[d] Maastricht University, Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, PO Box 616, 6200 MD, Maastricht, The Netherlands
[e] Bangor University, School of Psychology and North Wales Clinical School, Adeilad Brigantia, Penrallt Road, Gwynedd LL57 2AS, United Kingdom

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ABSTRACT

Schizophrenia has been associated with aberrant intrinsic functional organization of the brain but the relationship of such deficits to psychopathology is unclear. In this study, we investigated associations between resting-state networks and individual psychopathology in sixteen patients with paranoid schizophrenia and sixteen matched healthy control participants.

We estimated whole-brain functional connectivity of multiple networks using a combination of spatial independent component analysis and multiple regression analysis. Five networks (default-mode, left and right fronto-parietal, left fronto-temporal and auditory networks) were selected for analysis based on their involvement in neuropsychological models of psychosis. Between-group comparisons and correlations to psychopathology ratings were performed on both spatial (connectivity distributions) and temporal features (power-spectral densities of temporal frequencies below 0.06 Hz). Schizophrenia patients showed aberrant functional connectivity in the default-mode network, which correlated with severity of hallucinations and delusions, and decreased hemispheric separation of fronto-parietal activity, which correlated with disorganization symptoms. Furthermore, the severity of positive symptoms correlated with functional connectivity of fronto-temporal and auditory networks. Finally, default-mode and auditory networks showed increased spectral power of low frequency oscillations, which correlated with positive symptom severity. These results are in line with findings from studies that investigated the neural correlates of positive symptoms and suggest that psychopathology is associated with aberrant intrinsic organization of functional brain networks in schizophrenia.

1. Introduction

Bleuler (1911) coined the term schizophrenia or "fragmented mind" to suggest that the disorder may be caused by a dysfunction in the integration of cognitive processes. This intuition has been conceptualized in neurobiological frameworks that propose a disruption of the anatomical and functional connectivity between brain areas as the neurobiological correlate of the cognitive dysfunctions (Friston, 1998). This hypothesis has been further supported by evidence from structural (Kubicki et al., 2007; Rotarska-Jagiela et al., 2009; Rotarska-Jagiela et al., 2008) and functional connectivity studies (Meyer-Lindenberg et al., 2001; Uhlhaas et al., 2006). However, much remains

* Corresponding author. Max Planck Institute for Brain Research, Department of Neurophysiology, Deutschordenstr. 46, 60528 Frankfurt a.M., Germany. Tel.: +49 69 6301 83782; fax: +49 69 6301 3833.
E-mail address: rotarska@mpih-frankfurt.mpg.de (A. Rotarska-Jagiela).
[1] These authors contributed equally to this work.

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unknown about how, for example, symptoms are associated with the functional organization in schizophrenia.

Functional organization of neural networks in schizophrenia has often been addressed using the concept of functional connectivity, which is formalized as temporal covariation of neural signals between two (or more) spatially disparate brain areas (Friston et al., 1993). A number of studies have reported altered functional connectivity in schizophrenia. For example, functional connectivity between prefrontal and temporal regions during a working memory task was decreased in patients (Meyer-Lindenberg et al., 2001), and functional connectivity between auditory areas was altered during an auditory oddball task (Calhoun et al., 2004b).

Furthermore, recent models have proposed that schizophrenia symptoms may be associated with aberrant functional connectivity of multiple functional networks, including networks that subserve speech perception and production, as well as social processing and agency (Friston, 1998; Frith, 2005; Wible et al., 2009). There is increasing empirical support for these models. For example, several studies have found evidence for impaired communication between motor and speech perception areas in hallucinating schizophrenia patients (Ford et al., 2001; Lawrie et al., 2002; Shergill et al., 2005), which is in line with the suggestion that hallucinations are misinterpreted or misattributed speech intentions (Frith, 2005). A recent study investigated the relation between symptom severity and functional connectivity in one of the resting-state networks, the "default-mode network" (DMN) (Garrity et al., 2007). In healthy subjects, the DMN shows increased baseline activity (Gusnard and Raichle, 2001), and has been associated with self-referential mental activity (Gusnard et al., 2001), mind-wandering (Mason et al., 2007) and social cognition (Schilbach et al., 2008). Garrity et al. (2007) reported that in schizophrenia patients increased severity of positive symptoms correlated with increased functional connectivity in posterior cingulate and middle temporal regions. At the same time, disorganization symptoms may be correlated with impaired functioning of fronto-parietal networks (MacDonald et al., 2005), which can be associated with working memory impairments (Linden, 2007).

Importantly, many reports of aberrant functional connectivity in schizophrenia pertain to regional effects. These findings reflect a special case of dysconnectivity in which particular regions of a network are affected in a systematic and consistent manner. However, patterns of aberrant regional connections within a network could vary across patients, depending on individual psychopathology, medication or compensatory mechanisms. Moreover, aberrant connectivity may be diffuse or widespread, resulting in a network with a "noisy" spatial distribution in patients compared to controls (Callicott and Weinberger, 1999; Winterer et al., 2006), which could impair information processing (Bassett et al., 2008). In these cases, whole-network analyses may complement regional analyses to characterize group differences in network connectivity. A particular form of dysconnectivity in schizophrenia on a whole-network level has been suggested to reside in decreased hemispheric laterality. Crow and others suggested that schizophrenia symptoms may be associated with decreased leftward asymmetry of speech perception areas in the temporal lobes (Ceccherini-Nelli et al., 2007; Crow, 1997; Hugdahl et al., 2007; Sommer et al., 2001). In addition, several studies reported decreased functional laterality of prefrontal or parietal areas during verbal working memory performance (MacDonald et al., 2005; Quintana et al., 2003). These approaches underscore the importance of investigating whole-network connectivity in schizophrenia to complement regional approaches.

Most previous functional connectivity studies in schizophrenia analyzed differences in inter-regional covariations during performance of an experimental task (Calhoun et al., 2004a; Garrity et al., 2007; Lawrie et al., 2002; Meyer-Lindenberg et al., 2001). Recently, however, there has been an increased interest in using resting-state measurements to investigate aberrations of functional connectivity. The examination of brain activation in the absence of a specific task crucially complements task-related investigations because intrinsic functional organization can be measured in the absence of possibly differential task performance between diagnostic groups. Furthermore, it has been amply documented in other fields of neuroscience that spontaneous activity provides important information about the intrinsic neurophysiological architecture (Buzsaki and Draguhn, 2004; Uhlhaas et al., 2008). Resting-state networks measured with functional magnetic resonance imaging (fMRI) are commonly characterized by strong contributions of very low temporal BOLD oscillations, commonly below 0.1 Hz (Biswal et al., 1995; van de Ven et al., 2004). Recent neurophysiological studies showed that spontaneous resting-state oscillations may subserve cognitive functioning or information processing efficiency (Buzsaki and Draguhn, 2004). A growing number of studies have addressed resting state in schizophrenia, and found widespread abnormal functional connectivity in patients (Bluhm et al., 2007; Liu et al., 2006; Zhou et al., 2007). However, it is currently unknown if and how spatial and temporal dynamics of resting state networks contribute to individual psychopathology in schizophrenia.

In the current study, we examined resting-state functional connectivity in schizophrenia and healthy control participants across key networks and investigated both their spatial and temporal features. Specifically, we selected five functional networks that, according to current neuropsychological models (Friston, 1998; Hashimoto et al., 2010; Wible et al., 2009), may be associated with symptoms in schizophrenia, which included DMN, left and right fronto-parietal (lFP and rFP), left fronto-temporal (lFT) and bilateral auditory networks (AC), and examined their spatial and temporal characteristics. Contributions of resting state connectivity to differences across groups and individual psychopathology were investigated on a regional as well as a whole-network level. For the patient group, we also compared network features to psychopathology ratings as assessed by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). We hypothesized that connectivity of the DMN, lFT and AC would correlate with the severity of positive symptoms, especially hallucinations and delusions. We also hypothesized that left and right FP network connectivity would correlate with severity of disorganization symptoms because of their close relationship with working memory. Finally, we explored whether the low frequency temporal dynamics of these functional networks would covary with symptom severity.