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Semi-metric analysis of the functional brain network: Relationship with familial risk for psychotic disorder

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ABSTRACT

Background: Dysconnectivity in schizophrenia can be understood in terms of dysfunctional integration of a distributed network of brain regions. Here we propose a new methodology to analyze complex networks based on semi-metric behavior, whereby higher levels of semi-metricity may represent a higher level of redundancy and dispersed communication. It was hypothesized that individuals with (increased risk for) psychotic disorder would have more semi-metric paths compared to controls and that this would be associated with symptoms.
Methods: Resting-state functional MRI scans were obtained from 73 patients with psychotic disorder, 83 unaffected siblings and 72 controls. Semi-metric percentages (SMP) at the whole brain, hemispheric and lobar level were the dependent variables in a multilevel random regression analysis to investigate group differences. SMP was further examined in relation to symptomatology (i.e., psychotic/cognitive symptoms).
Results: At the whole brain and hemispheric level, patients had a significantly higher SMP compared to siblings and controls, with no difference between the latter. In the combined sibling and control group, individuals with high schizotypy had intermediate SMP values in the left hemisphere with respect to patients and individuals with low schizotypy. Exploratory analyses in patients revealed higher SMP in 12 out of 42 lobar divisions compared to controls, of which some were associated with worse PANSS symptomatology (i.e., positive symptoms, excitement and emotional distress) and worse cognitive performance on attention and emotion processing tasks. In the combined group of patients and controls, working memory, attention and social cognition were associated with higher SMP.
Discussion: The results are suggestive of more dispersed network communication in patients with psychotic disorder, with some evidence for trait-based network alterations in high-schizotypy individuals. Dispersed communication may contribute to the clinical phenotype in psychotic disorder. In addition, higher SMP may contribute to neuro- and social cognition, independent of psychosis risk.

1. Introduction

Dysconnectivity in schizophrenia can be understood as dysfunctional integration of a distributed network of brain regions (Friston, 1999). Meta-analytic reviews of MRI studies of schizophrenia have revealed alterations in gray (Ellison-Wright et al., 2008; Glahn et al., 2008), and white matter organization (Ellison-Wright and Bullmore, 2009) as well as altered functional activation across cognitive tasks (Minzenberg et al., 2009). Furthermore, the resting-state functional MRI (rs-fMRI) literature has described dysconnectivity in schizophrenia in several brain regions, including prefrontal-temporal regions, default mode network (DMN) dysconnectivity and decreased frontoparietal connectivity (FPN) (Friston and Frith, 1995; Rotarska-Jagiela et al., 2010). Also, studies using graph theoretical analyses have shown that functional brain network organization in schizophrenia is typically less small world, less clustered, less efficiently wired and less dominated by hubs (Alexander-Bloch et al., 2010; Bassett and Bullmore, 2009; Bassett et al., 2008; Bullmore and Sporns, 2009; Liu et al., 2008; Lynall et al., 2010; van den Heuvel et al., 2010).

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Here we propose a new graph theoretical methodology to analyze complex functional brain networks in psychotic disorder, based on semi-metric behavior. Generally, brain regions in a network are described as nodes and connections between nodes as edges (Bullmore and Sporns, 2009; Sporns et al., 2005). Weighted networks, such as fMRI connectivity networks are characterized by a high number of transitivity violations. A relation is transitive when a node A is related to a node B, and B is related to C, implying that A is also related to C (i.e., via indirect association). Transitivity violations occur when the sum of weights along an indirect path between two nodes (i.e., involvement of additional regions), is greater than the weight of the direct path between them. In this sense, the indirect path represents the shortest path between the two nodes (Fig. 1), which in the case of weighted graphs is a sequence of correlations that increase the overall correlation between the two nodes, compared to a more direct topological route. This type of network is called semi-metric (Simas et al., 2015). Higher levels of semi-metricity indicate more indirect paths, which may represent a higher level of redundancy (Simas et al., 2015), i.e., interactions between multiple network nodes (Leistritz et al., 2013).

To date, only one study has investigated the amount of semi-metric connections in a sample of adolescents with autism spectrum condition (ASC) and major depressive disorder (MDD). ASC was associated with more semi-metric connections, whereas MDD was characterized by a higher level of metric, constrained connections. It was suggested that constrained connections may be associated with rumination, which is characteristic in depression, whereas dispersed communication (the involvement of multiple regions) in ASC may be associated with a lack of central coherence often seen in this disorder (Belmonte et al., 2004). Thus, semi-metricity is thought to provide information about network communication/information processing, which potentially makes it a useful method to detect and classify a wide range of psychiatric and developmental disorders (Simas et al., 2015).

Psychotic disorder is characterized by a disruption in thought processes and an altered perception of reality. These symptoms may arise from aberrant communication between multiple brain regions (Calhoun et al., 2009; Repovs et al., 2011; Stephan et al., 2009). It is speculated that the interaction between multiple brain regions along a semi-metric path interferes with information processing and coordination of mental functions. Following this assumption, we expected that patients would have a higher number of semi-metric paths (i.e., more dispersed communication) than controls. Additionally, since there is evidence for rs-functional connectivity intermediate phenotypes (Chang et al., 2014; Fornito et al., 2013; Guo et al., 2014a,b; Repovs and Barch, 2012; Su et al., 2013; Whitfield-Gabrieli and Ford, 2012; Yu et al., 2013b) it was hypothesized that this would also apply to semi-metric paths. As this is the first study that used semi-metricity to measure functional network alterations in patients with (increased risk for) psychotic disorder a whole brain, hypothesis-generating approach, was used.

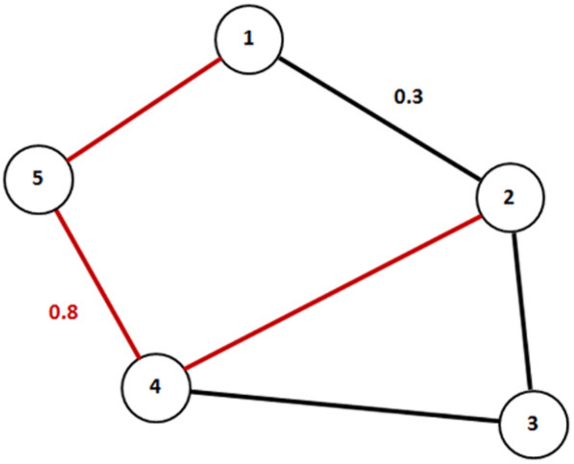

Fig. 1. Example of a semi-metric network. The red line represents the indirect path between node 1 and 2. The sum of weights along this indirect path (i.e., 0.8) is greater than the sum of weights of the direct path between node 1 and 2 (i.e., 0.3). Therefore, the indirect path is semi-metric.

Rs-fMRI studies have shown associations between functional connectivity (in, e.g., DMN, FPN) and symptoms of schizophrenia (Karbasforoushan and Woodward, 2012; van den Heuvel and Fornito, 2014). Only a few studies have investigated such relationships using graph theoretical approaches (Bassett et al., 2012; Shim et al., 2014; Skudlarski et al., 2010). Therefore, exploratory analyses were performed to investigate whether psychotic and cognitive symptoms would be associated with disease-related and risk-related semi-metricity alterations.

2. Methods

2.1. Participants

Data were collected from a longitudinal MRI study in Maastricht, the Netherlands. Recruitment and inclusion criteria have been described elsewhere (Habets et al., 2011). The final sample comprised 73 patients with psychotic disorder, 83 unaffected siblings and 72 controls, after excluding participants from the analyses based on: schizotypy ($n = 3$), movement ($n = 8$), scanner artifacts ($n = 14$), smoking cannabis prior to scanning ($n = 1$) and experimental issues ($n = 20$). The sample contained 46 families: 25 families with one patient and one sibling, three families with one patient and two siblings, one family with two patients, six families with two siblings, and two families with one patient and three siblings. In the control group, there were nine families with two siblings. In addition, 41 independent patients, 34 independent siblings, and 54 independent controls were included.

Diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorder-IV (DSM-IV) criteria (American Psychiatric Association, 2000), assessed with the Comprehensive Assessment of Symptoms and History (CASH) interview (Andreasen et al., 1992). Patients were diagnosed with: schizophrenia ($n = 47$), schizoaffective disorder ($n = 9$), schizophreniform disorder ($n = 4$), brief psychotic disorder ($n = 2$), and psychotic disorder not otherwise specified ($n = 11$). Schizotypy was assessed with the Structured Interview for Schizotypy—revised (SIS-r) (Vollema and Ormel, 2000). Based on the CASH, 16 siblings and 10 controls had a history of MDD.

Before MRI acquisition, participants were screened for the following exclusion criteria: brain injury (unconsciousness >1 h), meningitis or other neurological diseases that might have affected brain structure or function, cardiac arrhythmia requiring medical treatment, and severe claustrophobia. Additionally, participants with metal corpora aliena were excluded from the study, as were women with intrauterine device status and (suspected) pregnancy. The standing ethics committee approved the study, and all participants gave written informed consent in accordance with the committee's guidelines and with the Declaration of Helsinki (Nylenna and Riis, 1991).

2.2. Measures

Psychopathology assessments were done at the time of scanning using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) in all three groups. The five factor model by van der Gaag et al. (2006) was used (van der Gaag et al., 2006).

Educational level was defined as highest accomplished educational level. Handedness was assessed using the Annett Handedness Scale (Annett, 1970).

Attention/vigilance was assessed using a Continuous Performance Test (CPT-HQ) with WM load, also known as CPT-AX (Nuechterlein and Dawson, 1984) (longer reaction times reflecting worse performance). The WAIS-III (Wechsler, 1997) subtest Arithmetic was used to measure WM, which addresses both verbal comprehension and