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Comparison of large-scale human brain functional and anatomical networks in schizophrenia

Brent G. Nelson[a,*], Danielle S. Bassett[b,c,d], Jazmin Camchong[a], Edward T. Bullmore[e,f,g], Kelvin O. Lim[a]

[a] Department of Psychiatry, University of Minnesota, Minneapolis, MN 55454, USA
[b] Department of Physics, University of California, Santa Barbara, CA 93106, USA
[c] Sage Center for the Study of the Mind, University of California, Santa Barbara, CA 93106, USA
[d] Department of Bioengineering, University of Pennsylvania, Philadelphia, PA 19104, USA
[e] Behavioural & Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK
[f] Cambridgeshire & Peterborough NHS Foundation Trust, Cambridge, UK
[g] GlaxoSmithKline R & D, Cambridge, UK

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ABSTRACT

Schizophrenia is a disease with disruptions in thought, emotion, and behavior. The dysconnectivity hypothesis suggests these disruptions are due to aberrant brain connectivity. Many studies have identified connectivity differences but few have been able to unify gray and white matter findings into one model. Here we develop an extension of the Network-Based Statistic (NBS) called NBSm (Multimodal Network-based statistic) to compare functional and anatomical networks in schizophrenia. Structural, resting functional, and diffusion magnetic resonance imaging data were collected from 29 chronic patients with schizophrenia and 29 healthy controls. Images were preprocessed, and average time courses were extracted for 90 regions of interest (ROI). Functional connectivity matrices were estimated by pairwise correlations between wavelet coefficients of ROI time series. Following diffusion tractography, anatomical connectivity matrices were estimated by white matter streamline counts between each pair of ROIs. Global and regional strength were calculated for each modality. NBSm was used to find significant overlap between functional and anatomical components that distinguished health from schizophrenia. Global strength was decreased in patients in both functional and anatomical networks. Regional strength was decreased in all regions in functional networks and only one region in anatomical networks. NBSm identified a distinguishing functional component consisting of 46 nodes with 113 links ($p < 0.001$), a distinguishing anatomical component with 47 nodes and 50 links ($p = 0.002$), and a distinguishing intermodal component with 26 nodes ($p < 0.001$). NBSm is a powerful technique for understanding network-based group differences present in both anatomical and functional data. In light of the dysconnectivity hypothesis, these results provide compelling evidence for the presence of significant overlapping anatomical and functional disruption in people with schizophrenia.

1. Introduction

Schizophrenia is characterized by a host of observable abnormalities in integrated thought, emotion, and behavior. Lack of integration is hypothesized to stem from multiple abnormalities in the underlying brain circuitry, collectively referred to as *dysconnectivity*. The hypothesis that dysconnectivity drives psychiatric symptoms in schizophrenia is supported by neuroimaging studies utilizing both functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (Friston, 1998; Volkow et al., 1988; Weinberger et al., 1992). Dysconnectivity can manifest separately as either differences in coherent brain activity (functional connectivity) or brain wiring (anatomical connectivity) (Camchong et al., 2011; Skudlarski et al., 2010).

While dysconnectivity can accompany many different disease states, the specific connectivity abnormalities identified in schizophrenia patients remain far from understood. Anatomical connectivity estimated from white matter tracts is altered in schizophrenia in a range of disparate cortical structures including frontal regions (Kong et al., 2011), thalamo-frontal connections (Oh et al., 2009), temporal-frontal connections (van den Heuvel et al., 2010), and temporal tracts (Phillips

* Corresponding author at: Department of Psychiatry, F282/2A West, 2450 Riverside Avenue South, Minneapolis, MN 55454, USA.
E-mail address: nels1741@umn.edu (B.G. Nelson).

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et al., 2009). Alterations in functional connectivity have similarly been identified across a range of brain states, affecting the default mode network (DMN) at rest (Whitfield-Gabrieli et al., 2009; Woodward et al., 2011), multiple cognitive control networks (Repovs et al., 2011), and several independent brain regions (Zhou et al., 2007). However, the focus of much of this previous work has been limited to a few selected regions or tracts and to a single imaging modality, potentially hampering a broader understanding of a distributed pathophysiology.

Anatomical and functional connectivity are inherently related (Schneider et al., 2007; Skudlarski et al., 2010). Evidence suggests that anatomical connectivity patterns underlie resting-state and task-based functional connectivity patterns (Hermundstad et al., 2013; Honey et al., 2009; Teipel et al., 2010). A simultaneous examination of whole-brain anatomical and functional connectivity in a single cohort is necessary for a more comprehensive understanding of putative alterations in brain architecture that underlie abnormal cognition and behavior in schizophrenia.

Multimodal techniques in depression (Hermundstad et al., 2013) and schizophrenia (Jeong et al., 2009; Pomarol-Clotet et al., 2010; Skudlarski et al., 2010) have provided a holistic characterization of these diseases inaccessible from either modality alone. However, the translational impact of these studies has likely been hampered by inconsistent results. Several whole-brain connectivity studies have identified anatomical and functional abnormalities in frontal regions in schizophrenia patients: two studies examining the resting state and one study examining task-based states (Camchong et al., 2011; Jeong et al., 2009; Pomarol-Clotet et al., 2010). Zhou et al. (2008) report converging anatomical and functional connectivity abnormalities between the hippocampus and the rest of the brain in people with schizophrenia (Zhou et al., 2008). The use of divergent analysis methods makes unifying these findings difficult. Skudlarski et al. (2010) described one method to address this challenge and report convergent findings across multiple imaging modalities.

An important challenge for multimodal studies is the identification of methodological approaches capable of unifying disparate types of data. Networks provide a mathematical framework to describe interactions between system entities and can therefore be particularly useful in this context. A powerful and versatile approach, network science can be used to examine the relationships between entities as varied as routers in the internet, friends in a social network, or regions in the human brain (Honey et al., 2007). The network being studied is defined as a graph in which the system's components are represented as nodes in the graph and interactions between the system's components are represented as edges in the graph. This information is encoded in a mathematical data structure called a connectivity matrix, which is composed of rows, columns, and cells, similar to a spreadsheet. Rows and columns represent nodes and cell values represent edges connecting these nodes.

Graph theory has been applied with increasing success to neuroimaging data (Bullmore and Sporns, 2009; Bullmore and Bassett, 2011). Specifically, it is used to quantify the organization of the brain and estimate its information-processing efficiency. In addition to facilitating the examination of healthy brain function, graph theory also provides a means to examine altered brain function in psychiatric disease (Fornito et al., 2012). As a unified approach, network theory can be applied to both anatomical and functional data to derive estimates of connectivity. Its application to schizophrenia in particular has uncovered decreased functional connectivity with increased variation between frontal and temporal regions (Bassett et al., 2012; Lynall et al., 2010; van den Heuvel et al., 2010; Yu et al., 2011; Zalesky et al., 2010). Its application to diffusion imaging has uncovered anatomical connectivity differences between regions including medial frontal, parietal/occipital, and the left temporal lobe (Zalesky et al., 2011).

Statistical inference of significant group differences in network diagnostics of brain connectivity has remained challenging. A common strategy to construct a graph is to threshold a connectivity matrix to retain only the very strongest and/or most statistically significant edges (Bullmore and Bassett, 2011). To compare graphs between two groups, the threshold is often chosen for each matrix independently in order to ensure that all networks, irrespective of group, contain the same number of edges (van Wijk et al., 2010). However, it has been noted that for very stringent thresholds, networks derived from one population can fragment (some nodes become completely disconnected from the graph, having no remaining edges) while networks derived from a second population can remain intact. This phenomenon has been reported to occur in resting state fMRI data acquired from people with schizophrenia (Bassett et al., 2012). In this context, fragmentation has been linked to underlying network developmental abnormalities (van den Berg et al., 2012). Comparing fragmented and non-fragmented networks is problematic because network diagnostic values are highly dependent on the number of nodes present in the network (Bassett et al., 2012; van Wijk et al., 2010). In addition to the challenges of the differential fragmentation processes, this common approach also focuses on only the strongest set of edges although recent evidence suggests that in fact weakly connected portions of the network might be particularly important in distinguishing healthy and diseased resting state function in schizophrenia (Bassett et al., 2012), and uncovering changes in network organization that underlie individual differences in cognitive function (Cole et al., 2012; Santarnecchi et al., 2014). In combination, these methodological factors underscore the potential benefits of developing alternative approaches.

A recently developed methodology known as the Network-Based Statistic (NBS) can be used to circumvent several issues that accompany the comparison of networks extracted from thresholding procedures (Zalesky et al., 2010). NBS uses a permutation-based approach to select sub-networks (also known as network components) formed by edges whose weights are significantly different between the two groups. Importantly, these edges are identified irrespective of whether their weights are strong or weak. A benefit of this technique is that it is safeguarded against the multiple comparisons problem that one faces in the pairwise comparison of all edges between the two groups. While both Bonferroni and false discovery rate (FDR) corrections can be employed, they are arguably overly-conservative for the set of inherently dependent variables that make up connectivity matrices (Zalesky et al., 2010).

Here we apply NBS to both functional and anatomical data to identify connectivity abnormalities. We further develop an extension of NBS for use in the simultaneous examination of multimodal data, which we call NBS_m. This method allows us to statistically test for overlapping regions of dysconnectivity in any two groups, facilitating the identification of an overlapping or “intermodal” set. We apply this method to a clinical population of 29 people with schizophrenia and 29 age- and sex-matched controls. We hypothesize that a subset of regions identified as locations of either functional or anatomical dysconnectivity in schizophrenia will show statistically significant overlap when examined from the perspective of distinguishing sub-networks identified using NBS_m.

2. Methods and materials

2.1. Participants

Data from 29 participants with chronic schizophrenia (11 females; age 41.3 ± 9.3 (SD); 5 left-handed) and 29 healthy participants (11 females; age 41.1 ± 10.6 (SD); 2 left-handed) were included in this analysis. All participants provided written informed consent and received payment for the time they spent participating. The consent process and all procedures were reviewed and approved by the institutional review board (IRB) at the University of Minnesota prior to initiating studies. Schizophrenia patients were diagnosed with the Structured Clinical Interview for *DSM-IV*. Out of the 29 chronic schizophrenia patients: 16 were taking 1 atypical antipsychotic, 8 were