



# Disrupted modular organization of primary sensory brain areas in schizophrenia

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## ABSTRACT

Abnormal brain resting-state functional connectivity has been consistently observed in patients affected by schizophrenia (SCZ) using functional MRI and other neuroimaging techniques. Graph theoretical methods provide a framework to investigate these defective functional interactions and their effects on the organization of brain connectivity networks. A few studies have shown altered distribution of connectivity within and between functional modules in SCZ patients, an indication of imbalanced functional segregation and integration. However, no major alterations of modular organization have been reported in patients, and unambiguous identification of the neural substrates affected remains elusive. Recently, it has been demonstrated that current modularity analysis methods suffer from a fundamental and severe resolution limit, as they fail to detect features that are smaller than a scale determined by the size of the entire connectivity network. This resolution limit is likely to have hampered the ability to resolve differences between patients and controls in previous studies. Here, we apply Surprise, a novel resolution limit-free approach, to study the modular organization of resting state functional connectivity networks in a large cohort of SCZ patients and in matched healthy controls. Leveraging these important methodological advances we find new evidence of substantial fragmentation and reorganization involving primary sensory, auditory and visual areas in SCZ patients. Conversely, frontal and prefrontal areas, typically associated with higher cognitive functions, appear to be largely unaffected, with changes selectively involving language and speech processing areas. Our findings support the hypothesis that cognitive dysfunction in SCZ may involve deficits occurring already at early stages of sensory processing.

## 1. Introduction

Schizophrenia has been associated with aberrant functional connectivity as measured by neuroimaging methods in a number of studies (Friston and Frith, 1995; Liang et al., 2006; Liu et al., 2008; Calhoun et al., 2009; Karbasforoushan and Woodward, 2012; Garrity et al., 2007). This growing evidence is in keeping with the disconnectivity hypothesis of schizophrenia (Friston and Frith, 1995) that posits that the core dysfunction of this disease may correspond to alterations of the functional interactions between specialized brain areas (Bullmore et al., 1998; Ellison-Wright and Bullmore, 2009; Fornito et al., 2009; Kubicki et al., 2005), resulting in defective integration of activity in distributed networks and in cognitive disintegration (Tononi and Edelman, 2000). Indeed, psychotic symptoms akin to those of schizophrenia, including hallucinations and delusions, are also observed in certain neurological disorders that involve disruption of corticocortical and corticosubcortical connections (Hyde et al., 1992; Su et al., 2015; Bullmore et al.,

1998). Understanding the nature of connectivity alterations in SCZ patients and their effects on brain functional integration may provide important insights into the etiology of this devastating disease, as well as potential diagnostic or prognostic markers.

To this end, graph theoretical approaches have been proposed as a powerful framework to assess topological features of functional connectivity networks (Bassett and Bullmore, 2006; Bullmore and Sporns, 2009; Kaiser, 2011; Stam and Reijneveld, 2007; Reijneveld et al., 2007), in which nodes correspond to anatomically defined brain regions and the edges to interregional correlations. Several alterations in graph-related metrics of resting state connectivity have been identified in schizophrenia patients, including reduction in global network efficiency (Bassett et al., 2008; Liu et al., 2008; Bullmore and Sporns, 2009), small worldness (Anderson Ariana and Cohen, 2013; Yu et al., 2011; Liu et al., 2008) and rich-club organization of high-connectivity nodes (van den Heuvel et al., 2013).

Recently, graph analyses of resting state brain connectivity

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networks have been applied to study the brain modular organization, i.e. the presence of functionally segregated module, or “communities”, within large-scale, integrated functional connectivity networks (Salvador et al., 2005; He et al., 2009; Meunier et al., 2009). Typically, these methods assess patterns of edges in the graph to identify clusters of nodes that are more densely connected, denoting stronger interactions among themselves than with the rest of the system. This mathematical formulation embodies the notion of segregation and integration, as the emergence of modules reflects the balance between intra- and inter-cluster connections. Hence, community detection methods enable investigation of the interplay between functional segregation and integration in the healthy and diseased brain, and provide a means to map the brain's modular organization. Changes in the structure of specific modules in patients may highlight specific circuits or neural substrates affected by the disease. Moreover, modularity analyses make it possible to identify the brain connector hubs, i.e. the regions that are responsible for the integration of the activity of different modules, and to assess the effects of disease on these hubs (van den Heuvel and Sporns, 2013; Crossley et al., 2014). Indeed, there is growing evidence that abnormalities in nodes characterized by high topological centrality and connectivity are implicated in several neuropsychiatric disorders, and that connector hubs may present increased vulnerability to brain disease (Crossley et al., 2014).

Several studies have investigated the modular structure of resting state functional connectivity networks derived from functional MRI in schizophrenia patients compared to healthy controls (Alexander-Bloch et al., 2010; Alexander-Bloch et al., 2013; van den Heuvel et al., 2010; Fornito et al., 2012; Lo et al., 2015; Lerman-Sinkoff and Barch, 2016; Yu et al., 2012; Liu et al., 2008). Reduction in Modularity, a measure of segregation of functional modules within an integrated network, was found in Childhood Onset Schizophrenia (Alexander-Bloch et al., 2010). However, no strong evidence of group differences in the dispersion and structure of brain modules was found in that study (Alexander-Bloch et al., 2010). Reduced Modularity was associated with a proportional increase in inter-cluster edges and decrease in intra-cluster edges in patients (Alexander-Bloch et al., 2012). Lerman-Sinkoff et al. (Lerman-Sinkoff and Barch, 2016) reported similar modular structures in adult schizophrenia patients and healthy subjects under stringent control of potential sources of imaging artifacts, with small but significant alterations of node community membership in specific patient networks. Yu et al. (2012) found reduced overall connectivity strength and a larger, even though very limited, number of communities in the patients' group (6 in SCZ subjects vs 5 in healthy controls). Disturbances in modularity were also observed in subjects with 22q11.2 deletion, a condition associated with cognitive impairment and high risk of developing schizophrenia (Scariati et al., 2016). These pioneering investigations provide important indications that the strength of division of resting-state functional connectivity networks into modules may be altered in patients affected by schizophrenia. However, the partitions per se, i.e. the clustering of different brain regions into modules, appear very coarse, comprising only a few, broad modules that are similarly distributed in patients and controls. Hence, it remains unclear whether schizophrenia affects specific functional modules and how defective connectivity translates into cognitive dysfunction and other symptoms.

Graph theory as applied to the study of brain networks is still in its infancy, and several methodological and conceptual issues that are still open may have affected early studies. An important finding in complex network theory is that most community detection methods, like those applied in previous studies in schizophrenia patients, suffer from a resolution limit (Fortunato and Barthélemy, 2007), as they cannot resolve clusters of nodes that are smaller than a scale determined by the size of the entire network. This limit, first demonstrated for Newman's Modularity, is quite general and affects, to a different extent, all methods that seek to identify the community structure of a network through the optimization of a global quality function (Newman, 2006), including Reichardt and Bornholdt's (Reichardt and Bornholdt, 2006), Arenas and

Gomez' (Arenas et al., 2008), Ronhovde and Nussinov's (Ronhovde and Nussinov, 2010), Rosvall and Bergstrom's (Rosvall and Bergstrom, 2008; Kawamoto and Rosvall, 2015) and others. The introduction of a resolution parameter in the quality function has been proposed as a means to improve detection of smaller clusters (Alexander-Bloch et al., 2010; Reichardt and Bornholdt, 2006). However, this approach introduces a specific scale determined by the choice of parameter values (Thomas Yeo et al., 2011; Reichardt and Bornholdt, 2006; Ronhovde and Nussinov, 2010), enabling detection of smaller clusters at the expense of larger ones, which may be unduly subdivided, resulting in partitions with relatively uniform cluster size distributions (Lancichinetti and Fortunato, 2011).

We have recently demonstrated (Nicolini and Bifone, 2016; Nicolini et al., 2017) that the resolution limit severely hampers the ability to resolve the modular organization of human brain connectivity networks, and to capture their complex community structure. This pervasive limit is likely to have biased previous studies in clinical populations, and may have prevented detection of differences in the organization of functional connectivity in patients and controls at a finer scale. Indeed, even though previous studies in SCZ populations systematically report substantial changes in functional connectivity and modularity strength compared to healthy controls, differences in the number, size and boundaries of functional modules appear to be modest and inconsistent across studies, often dependent on the specific clustering approach that was adopted. The deleterious effects of the resolution limit propagate to the evaluation of important topological parameters that depend on the network's community structure. These include the participation coefficient, a parameter that enables the identification of highly-connected nodes, or hubs, responsible for the integration and efficient exchange of information between modules (Bullmore and Sporns, 2009).

These limitations have made it difficult to unambiguously identify the neurofunctional substrates involved in what is sometimes regarded as a disconnectivity syndrome, and to assess different hypotheses on its etiology. Defective functional interactions may be widespread and affect overall efficiency of the network (Liu et al., 2008; Bullmore and Sporns, 2009; Bassett et al., 2008), or involve more specific circuits, including fronto-hippocampal (Meyer-Lindenberg et al., 2005), fronto-parietal (Garrity et al., 2007), and thalamo-cortical connections (Woodward et al., 2012). On the other end of the spectrum, it's been hypothesized that the complex symptomatology of SCZ may arise from local deficits within primary sensory cortices (Javitt, 2009a, 2009b), and that impairment of higher cognitive functions may result from a bottom-up propagation of these deficits. Overcoming the limitations of current methods might help discriminate between these different scenarios and assess the relative merits of different theories underlying the disconnectivity hypothesis in schizophrenia.

Recently, we have shown that Surprise, a fitness function rooted in probability theory (Nicolini and Bifone, 2016), behaves as a resolution-limit free function for community detection. Extension of this method to weighted networks, dubbed Asymptotical Surprise, was validated in synthetic and real world networks, revealing a heterogeneous modular organization of the human brain, with a wide distribution of clusters spanning multiple scales (Nicolini et al., 2017). The improved resolution afforded by Surprise makes it possible to appreciate differences in the structures of networks from different groups that are undetectable by resolution limited methods (Nicolini and Bifone, 2016), and has led to a refinement of the classification of brain hubs (Nicolini et al., 2017).

Here, we entertain the hypothesis that aberrant brain functional connectivity in the brain of schizophrenia patients affects its modular organization. We apply Asymptotical Surprise to resolve and compare the modular structures of resting state functional connectivity networks in two cohorts of 78 schizophrenia subjects and 91 controls beyond the resolution limit. In contrast with previous studies, we find profound differences in the resting state brain connectivity structure of schizophrenia patients, with a substantial reorganization of functional

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