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Paolo Brambilla, *Section Editor*

Applying neuroimaging to detect neuroanatomical dysconnectivity in psychosis

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This editorial discusses the application of a novel brain imaging analysis technique in the assessment of neuroanatomical dysconnectivity in psychotic illnesses. There has long been a clinical interest in psychosis as a disconnection syndrome. In recent years graph theory metrics have been applied to functional and structural imaging datasets to derive measures of brain connectivity, which represent the efficiency of brain networks. These metrics can be derived from structural neuroimaging datasets acquired using diffusion imaging whereby cortical structures are parcellated into nodes and white matter tracts represent edges connecting these nodes. Furthermore neuroanatomical measures of connectivity may be decoupled from measures of physiological connectivity as assessed using functional imaging, underpinning the need for multi-modal imaging approaches to probe brain networks. Studies to date have reported a number of structural brain connectivity abnormalities associated with schizophrenia that carry potential as illness biomarkers. Structural connectivity abnormalities have also been reported in well patients with bipolar disorder and in unaffected relatives of patients with schizophrenia. Such connectivity metrics may represent clinically relevant biomarkers in studies employing a longitudinal design of illness course in psychosis.

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Brain dysconnectivity refers broadly to the abnormal integration of brain processes (Stephan *et al.* 2009). Although disrupted brain connectivity has long been considered a core deficit of psychosis on clinical grounds, recent support for the dysconnectivity hypothesis, enabled by technical advances in the acquisition and analysis of non-invasive *in vivo* neuroimaging data, emphasises impaired integration as a core feature in psychosis pathophysiology (Van den Heuvel & Fornito, 2014). Functional connectivity, referring to synchronised physiological activity between two or more spatially separated brain regions, has

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been reported to be abnormal in individuals with schizophrenia – for example reduced in fronto-temporal regions during working memory tasks (Stephan *et al.* 2009). Findings from such neuroimaging investigations demonstrate that schizophrenia is unlikely to arise from disruption to one brain region alone, and provide biological models as a basis for the pathophysiology of positive psychotic symptoms, as well as negative and cognitive symptoms (Stephan *et al.* 2009; Van den Heuvel & Fornito, 2014). Given that functional connectivity between anatomically separated regions indicates the existence of structural connections, and there is also a considerable interest in probing anatomical connectivity using structural neuroimaging techniques.

Structural magnetic resonance imaging (sMRI) investigations of schizophrenia have identified regional abnormalities, predominantly deficits in frontotemporal and subcortical grey matter structures. Diffusion-weighted imaging is a neuroimaging technique that enables investigation of microstructural alterations in the organisation and orientation of white matter tracts, wherein diffusion of water molecules is constrained by the anatomy of myelinated axons. Diffusion imaging findings of schizophrenia and psychotic bipolar disorder report that white matter microstructural alterations are present within callosal and fronto-temporal regions in patients relative to healthy controls (Ellison-Wright & Bullmore, 2009).

Although structural and diffusion imaging have been used to examine focal abnormalities within grey and white matter regions, a novel approach using graph theory can utilise these modalities to assess neuroanatomical connectivity. Graph theory employs parcellations of structural MRI measures of grey matter to model cortical structures ('nodes'), along with diffusion measures of white matter to reconstruct the set of white matter connections ('edges'). One advantage of this approach is that structural and diffusion MR images can be captured in a relatively short timeframe, allowing then for a complete reconstruction of the brain as a network at the macro-scale. Once the brain is represented as a graph with all the series of nodes and edges mapped, topological properties can be investigated to determine patterns of brain communication and efficiency (Sporns, 2011; Van den Heuvel & Fornito, 2014). Such networks are commonly observed across many real world patterns. For example, one can like the anatomical wiring of the brains' connections to other networks such as airline patterns and the internet (Sporns, 2011). Characteristically such networks have 'hub' regions that are more centrally located with many connections passing through them, e.g. an international connecting airport. Mapping the connectivity structure of these systems provides information on how intact the network would remain if a 'hub' was damaged. Deriving graph theory metrics from neuroimaging data in this way can be applied to identify neuroanatomically based abnormalities of connectivity that may be present in psychotic illness.

Examples of metrics employed in studies to date include characteristic path length, global efficiency and clustering coefficient (Sporns, 2011). These are graphically displayed in Fig. 1. Specifically, characteristic path length measures the average shortest path of information flow between any pair of brain regions, i.e. the minimum number of edges that must be traversed to go from one node to another, between all pairs of brain regions (Fig. 1*a*). Clustering coefficient measures the frequency with which a node's neighbours are also neighbours of each other – complex networks tending to have high clustering (Fig. 1*b*). Global efficiency is presented mathematically as the inverse of path length, providing a reciprocal relationship whereby a shorter path length reflects increased efficiency in the system (Fig. 1*a*).

A number of studies to date have reported abnormal connectivity metrics in cohorts of patients with psychotic illnesses compared with controls. For example, patients with schizophrenia are reported to display longer path length than controls in frontal and temporal regions (Van den Heuvel *et al.* 2010) and impairment of connectivity in a network connecting medial frontal to parietal and occipital regions (Zalesky *et al.* 2011). Patients with euthymic bipolar disorder display longer path length, lower global efficiency and lower clustering coefficient than controls, with particular deficits in interhemispheric integration (Leow *et al.* 2013). A summary of studies is provided in Table 1.

Further exploration of brain organisational properties has led to the development of social theory measures in network analysis. The term 'rich club' originates from the analogy of being 'rich' in connections, and forming a 'club' because the set of regions are densely interlinked among themselves (Fig. 1*c*). The rich club coefficient metric derived from social theory represents the hierarchy, power distribution and conduction of information flow throughout the brain (Van den Heuvel *et al.* 2013). An association between global efficiency and rich club organisation suggests rich club organisation is affiliated with global brain communication (Van den Heuvel *et al.* 2013). The rich club metric identifies crucial circuits for establishing and maintaining efficient global brain communication (Van den Heuvel & Sporns, 2013). Collin *et al.* (2014) employed this metric and identified substantially reduced connectivity between rich club hubs in patients with schizophrenia compared with healthy volunteers and additionally intermediate levels of rich club connectivity among unaffected relatives of

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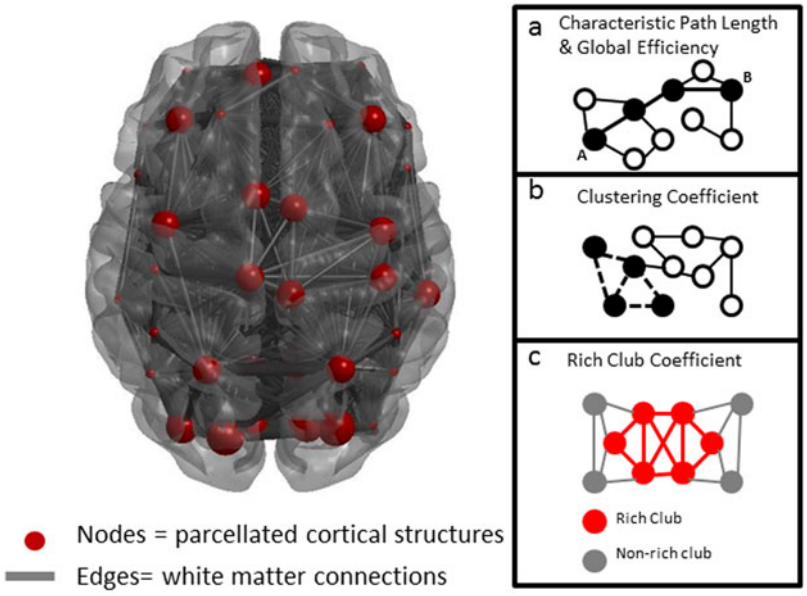

Fig. 1. Graphical representation of some key graph theory metrics. This brain map expresses the series of connections as a network, with white matter connections (edges) linking parcellated cortical regions (nodes). (*a*) Characteristic path length: a measure of the graphs average shortest distance between node A and node B; global efficiency: measured as the inverse of path length; (*b*) clustering coefficient: the number of connections that exist between the nearest neighbours of a node as a proportion of the maximum number of possible connections; (*c*) rich club coefficient: highlights nodes that are more densely interconnected among themselves than with the rest of the nodes in the network.

the patient cohort, suggesting a genetic contribution to impaired rich club connectivity in schizophrenia. These recent investigations implicate rich club dysconnectivity as a core feature of psychosis, in which the rich club coefficient may prove to represent an endophenotype of psychosis (Van den Heuvel *et al.* 2013; Collin *et al.* 2014). Crossley *et al.* (2014) utilised normative DTI data to identify a series of high degree hub nodes that were efficiently interconnected to form a rich club, and linked these maps to a meta-analysis of voxel based morphometry data across a range of brain disorders including schizophrenia, demonstrating that brain disorders tended to involve deficits in hub node regions and that involved hubs demonstrated disorder specificity, incorporating frontal and temporal regions in schizophrenia.

While investigations of structural dysconnectivity have been increasingly implemented, few studies have applied graph analysis to both diffusion MRI and functional MRI modalities to study the pathophysiology of schizophrenia. However, one has raised the potential for reduced structural connectivity to contribute to increased functional connectivity (Skudlarski *et al.* 2010). Fornito and Bullmore (2015) discuss the various mechanistic contributions to such de-coupling in connectivity findings in schizophrenia, in which functional hyperconnectivity may represent a neurodevelopmental or compensatory feature. Such decoupling of structural and functional connectivity highlights the need to examine network abnormalities at both anatomical and physiological levels and to incorporate multimodal imaging to develop a deeper understanding of dysconnectivity in psychotic illness.

In summary, cross-sectional studies indicate that graph theory metrics can be applied to MRI data to detect neuroanatomical dysconnectivity in psychotic illnesses, extending neuroanatomical research beyond identifying focal deficits in grey matter regions or white matter tracts, and providing further material evidence from *in vivo* neuroimaging to support the long held clinical construction of psychosis as a dysconnection syndrome. Abnormal connectivity may underpin the development of positive psychotic symptoms, with initial studies identifying short and long range frontal connectivity deficits in schizophrenia, and also widespread dysconnectivity in bipolar disorder that includes intrahemispheric integration. These novel analytical techniques are of considerable interest for application in epidemiological study designs into the aetiopathogenesis of psychotic illness. They can be potentially analysed on large, representative cohorts of patients with psychotic illness since they can be acquired from clinical MR scanners in a reasonable timeframe and processed using automated methodology. Preliminary studies suggest potential utility as biomarkers present at trait level in well patients (Leow *et al.* 2013) and in genetically susceptible relatives (Collin *et al.* 2014) of patients with psychotic

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Table 1. *Studies employing graph theory analyses of structural neuroimaging data in psychotic illness*

Author	Patient group	Graph theory metrics	Findings
Van den Heuvel *et al.* (2010)	Schizophrenia	Betweenness centrality CC Path length Strength	- Longer node specific path lengths of frontal and temporal regions in patients. - Reduced betweenness centrality of frontal hubs in patients.
Zalesky *et al.* (2011)	Schizophrenia	CC CPL Eglobal Nodal degree Small worldness	- Reduced global efficiency in patients. - Impaired connectivity among medial/frontal, parietal/occipital and left temporal nodes in patients.
Van den Heuvel *et al.* (2013)	Schizophrenia	CC CPL Eglobal Rich club organisation	- Reduced rich club organisation in patients. - Global efficiency reduced in patients.
Collin *et al.* (2014)	Schizophrenia, unaffected siblings of patients	CC Global efficiency Rich club organisation Strength	- Rich Club organisation and clustering coefficient reduced in patients, intermediate in unaffected siblings. - Global efficiency and strength reduced in patients.
Crossley *et al.* (2014)	Schizophrenia	VBM meta-analysis of brain hubs Degree	- Brain disorders involve regions identified by connectivity analysis as highly connected hub nodes; with schizophrenia particularly involving frontal and temporal hubs.
Leow *et al.* (2013)	Bipolar disorder	CC CPL Eglobal Interhemispheric and Intrahemispheric integration	- Longer path length and reduced global efficiency in patients. - Reduced clustering coefficient within limbic system in patients. - Impaired interhemispheric integration in frontal lobe in patients.
GadElkarim *et al.* (2014)	Bipolar disorder	PLACE	- Impaired community structure in posterior default mode network regions in patients.

CC, clustering coefficient; CPL, characteristic path length; Eglobal, global efficiency; PLACE, path length associated community estimation.

illness. Investigations are underway to assess their utility as clinically relevant biomarkers in studies employing a longitudinal design tracking these network based metrics through development of and recovery from psychosis.

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Whole brain network figure was visualized with the BrainNet Viewer (Xia et al., 2013, http://www.nitrc.org/projects/bnv/). Xia M, Wang J, He Y (2013) BrainNet Viewer: A Network Visualization Tool for Human Brain Connectomics. PLoS ONE 8: e68910.

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Conflict of Interest

None.

Ethical Standard

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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