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Neural networks in psychiatry

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Abstract
Over the past three decades numerous imaging studies have revealed structural and functional brain abnormalities in patients with neuropsychiatric diseases. These structural and functional brain changes are frequently found in multiple, discrete brain areas and may include frontal, temporal, parietal and occipital cortices as well as subcortical brain areas. However, while the structural and functional brain changes in patients are found in anatomically separated areas, these are connected through (long distance) fibers, together forming networks. Thus, instead of representing separate (patho)-physiological entities, these local changes in the brains of patients with psychiatric disorders may in fact represent different parts of the same 'elephant', i.e., the (altered) brain network. Recent developments in quantitative analysis of complex networks, based largely on graph theory, have revealed that the brain's structure and functions have features of complex networks. Here we briefly introduce several recent developments in neural network studies relevant for psychiatry, including from the 2013 special issue on Neural Networks in Psychiatry in European Neuropsychopharmacology. We conclude that new insights will be revealed from the neural network approaches to brain imaging in psychiatry that hold the potential to find causes for psychiatric disorders and (preventive) treatments in the future.

1. Introduction

Over the past three decades numerous imaging studies have revealed structural and functional brain abnormalities in patients with neuropsychiatric diseases. Increases and decreases in brain volumes as well as changes in activity and resting-state related blood oxygen level dependent signals using magnetic resonance brain imaging have been found in patients with schizophrenia (Haijma et al., 2012; Minzenberg et al., 2009; Wright et al., 2000), bipolar disorder (Bora et al., 2010; Chen et al., 2011), depression (Arnone et al., 2012), autism (Nicki-Jockschat et al., 2012), ADHD (Ellison-Wright et al., 2008; Durston, 2010), and Alzheimer's disease (Sexton et al., 2011). These structural and functional brain changes are frequently found in multiple, discrete brain areas and may include frontal, temporal, parietal and occipital cortices as well as subcortical brain areas. Clinical diagnoses show both overlapping and segregating brain changes, such as for example between

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schizophrenia and bipolar disorder (Ellison-Wright and Bullmore, 2010; Hulshoff Pol et al., 2012) and between unipolar and bipolar depression (Kempton et al., 2011; Delvecchio et al., 2012). However, while the structural and functional brain changes in patients are found in anatomically separated areas, these are connected through (long distance) fibers, together forming networks. Thus, instead of representing separate (patho)-physiological entities, these local brain changes in the brains of patients with psychiatric disorders may in fact represent different parts of the same 'elephant', i.e., the (altered) brain network. The 'elephant' refers to the tale "Blind men and an Elephant". This tale originated in India, and was translated in English in the 19th century as a poem by Saxe (1872). In the tale a group of blind men touch an elephant. The first touches its broad and sturdy side and says that the elephant is like a wall; the second touches the tusk and states the elephant is like a spear; the third touches its trunk and concludes that the elephant is like a snake; and so on. In the end, it is concluded, "though each was partly in the right, all were in the wrong." Similarly, the local brain changes in the brain of patients with psychiatric disorders, while correct in their own right, may together mean something else, and in fact represent one (altered) neural network.

Recent developments in quantitative analysis of complex networks, based largely on graph theory, have revealed that the brain's structural and functional networks are topologically complex (Bullmore and Sporns, 2009, 2012; Van den Heuvel and Hulshoff Pol, 2010; Van den Heuvel and Sporns 2011). Graph theory provides a theoretical framework in which the topology of complex networks can be examined, and reveals important information about the local and global organization of structural and functional brain networks. Using these methods, important new insights are currently emerging, showing that neural network changes are underlying structural and functional brain changes in psychiatric diseases, including vulnerability for specific characteristics of the brain network (Van den Heuvel et al., 2010; Bullmore and Sporns 2012). Here we review several of its properties, and discuss the highlights in this emerging field of neural networks in psychiatry, with the aim to sketch its potential in finding causes for and predicting psychiatric disorders and possibly treatments in the future.

2. Brain graphs

The brain consists of networks of neurons. This has been known for a long time. Only a look at the brain's white-matter is required to conclude that these fiber pathways must represent important interconnections between anatomically distant brain areas. However, that these neurons are interconnected does not mean that we understand how the brain network is organized and functioning. It is only recently that the complex brain network characteristics are starting to be deciphered mathematically. By using approaches from network theory in combination with neurobiology, properties of the brain network represented as a graph are now being unraveled. Below we briefly describe some of its main characteristics. For more complete and extensive descriptions several review articles (Bullmore and Sporns; 2009, 2012; Van den Heuvel and Hulshoff Pol, 2010), and a scholarly book on networks of the brain (Sporns, 2011) are available.

A *graph* is a mathematical representation of a real-world network. A graph consists of nodes and edges (Figure 1). *Nodes* may represent anatomical areas at the macroscopic level, and single neurons or glial cells at the microscopic level in the brain. *Edges* represent connections between pairs of nodes, and often represent white matter fiber bundles. Nodes can be linked via a single edge, or via multiple edges and thus via intermediate nodes. The connecting route between two nodes is called a *path*. A path with a short path length means that it has no or few intermediate nodes and this path is considered to provide efficient transfer of information. When for individual edges specific strengths are known, then these individual strengths can be used to weight the edges between two nodes (i.e., the edges are not considered to be binary). For example, the right medial frontal cortex (node) is connected with the right temporal pole (node) through the right uncinate fasciculus (edge) via a direct connection (short path length; efficient connection), that is highly myelinated (strongly weighted connection). If we instead measure the path length of the connection between the left medial frontal cortex and the right temporal pole we find this connection to be somewhat longer and thus less efficient since it goes through the right medial frontal cortex (intermediate node) and then through the anterior corpus callosum (second edge). Please note that the physical distance between nodes (e.g., the length of the

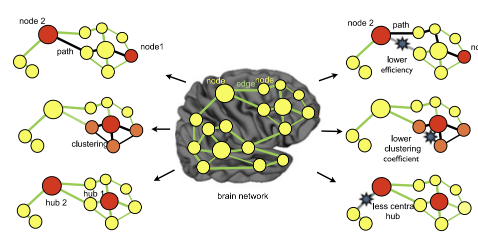

Figure 1 Network representation of the human brain. Shown in the middle is a graphical representation of a network superimposed on the brain surface. Nodes are represented in yellow circles; the edges connecting pairs of nodes are represented in green; stronger connections are represented by thicker green lines; and two modules are shown. On the left, normal network representations of part of this network are shown. The path as connecting route between two nodes 1 and 2 is represented in black lines; clustering is represented by a red node with orange circled neighbors connected through black edges; hub areas are represented by larger circles, with hub 2 representing a connection between the two modules. On the right, changes in the network that may be associated with psychiatric diseases are shown. Disconnections between nodes are represented in gray. A longer path length results in lower efficiency; fewer connections between neighbors results in a lower clustering coefficient; and the disconnection of two modules makes hub 2 a less central hub. The disconnections may represent (progressive) loss and/or differential brain development of structural or functional connections. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)