European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

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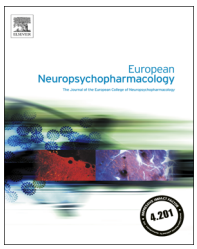

Connectomics: A new paradigm for understanding brain disease

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Received 8 August 2013; received in revised form 20 January 2014; accepted 12 February 2014

KEYWORDS
Graph analysis;
Complex network;
Psychosis;
Dementia;
fMRI;
DTI

Abstract
In recent years, pathophysiological models of brain disorders have shifted from an emphasis on understanding pathology in specific brain regions to characterizing disturbances of interconnected neural systems. This shift has paralleled rapid advances in connectomics, a field concerned with comprehensively mapping the neural elements and inter-connections that constitute the brain. Magnetic resonance imaging (MRI) has played a central role in these efforts, as it allows relatively cost-effective in vivo assessment of the macro-scale architecture of brain network connectivity. In this paper, we provide a brief introduction to some of the basic concepts in the field and review how recent developments in imaging connectomics are yielding new insights into brain disease, with a particular focus on Alzheimer's disease and schizophrenia. Specifically, we consider how research into circuit-level, connectome-wide and topological changes is stimulating the development of new aetiopathological theories and biomarkers with potential for clinical translation. The findings highlight the advantage of conceptualizing brain disease as a result of disturbances in an interconnected complex system, rather than discrete pathology in isolated sub-sets of brain regions.

The brain is vulnerable to a plethora of diseases that vary in terms of clinical expression, severity, causes and outcome. Pathophysiological models of these diseases have largely been cast in terms of two fundamental principles of brain organization: functional segregation and integration (Tononi et al., 1996). Functional segregation refers to the specialization of discrete brain regions or systems in performing specific mental operations. Evidence for segregation can be found across multiple spatial scales in the brain, ranging from the highly selective firing properties of individual neurons through to the large-scale, functionally specialized

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http://dx.doi.org/10.1016/j.euroneuro.2014.02.011
0924-977X

Please cite this article as: Fornito, A., Bullmore, E.T., Connectomics: A new paradigm for understanding brain disease. European Neuropsychopharmacology (2014), http://dx.doi.org/10.1016/j.euroneuro.2014.02.011

and spatially distributed neuronal ensembles underlying higher-order cognitive, emotional and sensorimotor processes. Functional integration is achieved via precise dynamical coordination of these segregated elements and is contingent on intact axonal and synaptic connectivity.

Early clinical observations that focal brain lesions often led to highly specific cognitive and behavioral deficits—exemplified by famous cases such as Broca's Leborgne (Broca, 1861)—offered empirical support for the idea, promulgated in Gall's phrenology, that discrete mental functions could be ascribed to spatially localized and functionally specialized neural elements. This idea laid the foundation for a major emphasis on segregationist accounts of the brain in much subsequent research (Fodor, 1983). Accordingly, pathophysiological models of many brain disorders highlighted the prominence of specific brain regions, such as the striatum in Huntington's disease (Ross and Tabrizi, 2011; Tabrizi et al., 2009), striatonigral neurons in Parkinson's disease (Samii et al., 2004), the medial temporal lobe in Alzheimer's disease (Blennow et al., 2006; Braak and Braak, 1991) and the prefrontal cortex in schizophrenia (Lewis et al., 2005; Weinberger et al., 2001). This regional emphasis may also be construed, in part, as a reflection of technological limitations since the clinical, histopathological and electrophysiological techniques then available only allowed inferences on a limited number of brain regions at any one time. Conceptually, however, the importance of understanding the role of brain connectivity in neuropathology has been recognized for over a century (Geschwind, 1965; Jackson, 1889; Wernicke, 1906).

The past few decades have witnessed rapid advances in our capacity to map the detailed connectivity architecture of the brain and thus better understand functional integration across multiple spatio-temporal scales. Central to this endeavor is the generation of a comprehensive map of the full set of elements and inter-connections comprising the brain—the so-called connectome (Sporns et al., 2005). Connectomic maps can be generated in different species and at varying resolutions, from the neuronal level (White et al., 1986) through to the macro-scale connections linking large-scale neuronal populations (Kötter et al., 2001; Hagmann et al., 2007; Modha and Singh, 2010; Shanahan et al., 2013). Accordingly, various strategies have been used to generate connectomic maps for species as diverse as the nematode worm *Caenorhabditis Elegans* (White et al., 1986) (the only organism to have its connectome mapped at the level of each and every synapse), fruit fly *Drosophila Melanogaster* (Chiang et al., 2011), mouse (Bota et al., 2012), pigeon (Shanahan et al., 2013), cat (Young et al., 1994), macaque (Modha and Singh, 2010; Stephan et al., 2001) and human (Hagmann et al., 2007; Iturria-Medina et al., 2007; Zalesky and Fornito, 2009). Strictly speaking, a "connectome" refers to a structural description of brain connectivity (Sporns et al., 2005), though similar mapping techniques have been applied to dynamical measures to characterize the inter-regional functional interactions that unfold on this anatomical backbone (Achard et al., 2006; Eguiluz et al., 2005; Salvador et al., 2005).

Attempts to map the human connectome have used magnetic resonance imaging (MRI) because it provides an efficient, cost-effective and non-invasive means for characterizing structural and functional properties of the entire brain (though techniques for comprehensive connectome mapping of *ex vivo* specimens are also being developed; Axer et al., 2011; Chung et al., 2013). In this work, diffusion-weighted imaging (DWI) is typically used to map the macro-scale axonal structure (i.e., physical wiring) of the connectome while functional MRI (fMRI) is used to characterize its dynamical properties (Bullmore and Sporns, 2009; Fornito et al., 2013b). Advances in the acquisition, processing and analysis of MRI data for connectome mapping (e.g., Essen and Ugurbil, 2012; Smith et al., 2013; Sotiropoulos et al., 2013; Uğurbil et al., 2013) are effecting a paradigm shift in imaging neuroscience (Friston, 2011) as the research emphasis moves from mapping regionally discrete changes in activation patterns or tissue integrity to understanding the mechanisms underlying functional integration and their disturbance in disease. Importantly, these approaches are yielding new insights into brain disorders that would not otherwise be possible using a regionally focused, segregationist framework.

In this paper, we review some recent advances in the burgeoning field of imaging connectomics and consider their contribution to understanding disease mechanisms using specific examples taken from the literature. We focus in particular on studies of Alzheimer's disease and schizophrenia as these are disorders in which connectomic methods are making rapid inroads, though we consider studies of other disorders where relevant (extended treatments of other disorders can be found elsewhere: Filippi et al., 2013; Fornito and Bullmore, 2010; Menon, 2011; Zhang and Raichle, 2010). We begin with a brief overview of some basic concepts central to the field.

Figure 1 Schematic pipeline for connectomic analysis with MRI. (a) Images are first parcellated into distinct regions-of-interest to represent network nodes. Shown here are examples of a parcellation based on sulcal/gyral landmarks (left) and functional regions-of-interest (right). (b) Structural connectivity between these regions is then measured using diffusion tractography (left); functional connectivity is estimated as a statistical dependence between regional time courses (right). (c) The connectivity between all regional pairs can be succinctly represented in matrix form. Shown here are examples of an undirected, weighted and unthresholded functional connectivity matrix (right) and the same matrix after thresholding and binarization (left) to retain only the strongest connections. (d) Network connectivity can then be represented in graph form as a set of nodes linked by supra-threshold edges. Shown here are examples of network graphs in an anatomical (left) and topological (right) embedding. The latter illustrates some basic topological properties/measures used to characterize brain network organization: namely the presence of modules of nodes highly connected with each than with other regions (yellow, magenta and cyan node groups); the presence of clustered connectivity, as shown for nodes A, B and C (i.e., both nodes A and B connect to C while also connecting to each other); and the identification of shortest paths between nodes (e.g., the blue path linking nodes A and D). Images adapted from Fornito et al. (2012b) with permission. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)