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REVIEW

Exploring the brain network: A review on resting-state fMRI functional connectivity

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Abstract

Our brain is a network. It consists of spatially distributed, but functionally linked regions that continuously share information with each other. Interestingly, recent advances in the acquisition and analysis of functional neuroimaging data have catalyzed the exploration of functional connectivity in the human brain. Functional connectivity is defined as the temporal dependency of neuronal activation patterns of anatomically separated brain regions and in the past years an increasing body of neuroimaging studies has started to explore functional connectivity by measuring the level of co-activation of resting-state fMRI time-series between brain regions. These studies have revealed interesting new findings about the functional connections of specific brain regions and local networks, as well as important new insights in the overall organization of functional communication in the brain network. Here we present an overview of these new methods and discuss how they have led to new insights in core aspects of the human brain, providing an overview of these novel imaging techniques and their implication to neuroscience. We discuss the use of spontaneous resting-state fMRI in determining functional connectivity, discuss suggested origins of these signals, how functional connections tend to be related to structural connections in the brain network and how functional brain communication may form a key role in cognitive performance. Furthermore, we will discuss the upcoming field of examining functional connectivity patterns using graph theory, focusing on the overall organization of the functional brain network. Specifically, we will discuss the value of these new functional connectivity tools in examining believed connectivity diseases, like Alzheimer's disease, dementia, schizophrenia and multiple sclerosis.

1. Introduction

Our brain is a network. A very efficient network to be precise. It is a network of a large number of different brain regions that each have their own task and function, but who are continuously sharing information with each other. As such, they form a complex integrative network in which information

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is continuously processed and transported between structurally and functionally linked brain regions: the brain network.

In the past three decades, a rich history of structural and functional neuroimaging studies have provided an incredible amount of knowledge about the primate and human brain, especially about the role and function of each brain region. Interestingly, recent advances in functional neuroimaging have provided new tools to measure and examine functional interactions between brain regions, catalyzing the examination of functional connectivity in the human brain. Functional connectivity is defined as the temporal dependence of neuronal activity patterns of anatomically separated brain regions (Aertsen et al., 1989; Friston et al., 1993) and studies have been shown the feasibility of examining functional connectivity between brain regions as the level of co-activation of functional MRI time-series measured during rest (Lowe et al., 2000).

Examining the human brain as an integrative network of functionally interacting brain regions can provide new insights about large-scale neuronal communication in the human brain. It provides a platform to examine how functional connectivity and information integration relates to human behavior and how this organization may be altered in neurodegenerative diseases (Bullmore and Sporns, 2009; Greicius, 2008). In the past few years, novel neuroimaging techniques and analysis methods have enabled the examination of whole-brain functional connectivity patterns, enabling the *in vivo* examination of functional connectivity on a whole-brain scale. These studies have examined the level of co-activation between the functional time-series of anatomically separated brain regions during rest, using so-called resting-state functional Magnetic Resonance Imaging, believed to reflect functional communication between brain regions (Biswal et al., 1995; Damoiseaux et al., 2006; Greicius et al., 2003; Salvador et al., 2005a). This review provides an overview of these new imaging and analysis techniques and their implication to neuroscience. We discuss the most commonly used resting-state fMRI acquisition and analysis techniques, discuss how functional connections are likely to relate to white matter structural tracts and how these resting-state fMRI techniques can be used to examine specific as well as whole-brain functional connectivity patterns. Furthermore, we will discuss the upcoming field of applied graph analytical approaches of resting-state data, enabling the exploration of the overall organization of functional communication channels within the brain network. We discuss how the efficiency of functional communication between brain regions might form a new framework to examine complex behavior in the human brain, reviewing recent studies on a direct link between overall functional communication efficiency and cognitive ability. Furthermore, we discuss how resting-state functional connectivity can be used to examine hypothesized disconnectivity effects in neurodegenerative and psychiatric brain diseases.

2. Functional connectivity: resting-state fMRI

Our brain is a complex network of functionally and structurally interconnected regions. Functional communication between brain regions is likely to play a key role in complex cognitive processes, thriving on the continuous integration of information across different regions of the brain. This makes the examination of functional connectivity in the human brain of high importance, providing new important insights in the core organization of the human brain. Functional connectivity is defined as the temporal dependency between spatially remote neurophysiological events (Aertsen et al., 1989; Friston et al., 1993). In the context of functional neuroimaging, functional connectivity is suggested to describe the relationship between the neuronal activation patterns of anatomically separated brain regions, reflecting the level of functional communication between regions. Interestingly, around 15 years after the invention of fMRI, studies started to examine the possibility of measuring functional connectivity between brain regions as the level of co-activation of spontaneous functional MRI time-series, recorded during rest (Biswal et al., 1997; Greicius et al., 2003; Lowe et al., 2000). During these resting-state experiments, volunteers were instructed to relax and not to think of something in particular, while their level of spontaneous brain activity was measured throughout the period of the experiment. Biswal and colleagues were the first to demonstrate that during rest the left and right hemispheric regions of the primary motor network are not silent, but show a high correlation between their fMRI BOLD time-series (Biswal et al., 1995; Biswal et al., 1997), suggesting ongoing information processing and ongoing functional connectivity between these regions during rest (Biswal et al., 1997; Cordes et al., 2000; Greicius et al., 2003; Lowe et al., 2000). In their study (schematically illustrated in Fig. 1), the resting-state time-series of a voxel in the motor network was correlated with the resting-state time-series of all other brain voxels, revealing a high correlation between the spontaneous neuronal activation patterns of these regions. Several studies have replicated these pioneering results, showing a high level of functional connectivity between the left and right hemispheric motor cortex, but also between regions of other known functional networks, like the primary visual network, auditory network and higher order cognitive networks (Biswal et al., 1997; Cordes et al., 2002; Cordes et al., 2000; Damoiseaux et al., 2006; De Luca et al., 2005; Fox and Raichle, 2007; Greicius et al., 2003; Lowe et al., 2000; Lowe et al., 1998; Van den Heuvel et al., 2008a; Xiong et al., 1999). These studies mark that during rest the brain network is not idle, but rather shows a vast amount of spontaneous activity that is highly correlated between multiple brain regions (Buckner et al., 2008; Buckner and Vincent, 2007; Greicius, 2008). To summarize, resting-state fMRI experiments are focused on mapping functional communication channels between brain regions by measuring the level of correlated dynamics of fMRI time-series.

3. Origin of spontaneous resting-state fMRI signals

Of special interest are the low frequency oscillations (~0.01–0.1 Hz) of resting-state fMRI time-series (Biswal et al., 1995; Biswal et al., 1997; Cordes et al., 2001; Lowe et al., 2000; Lowe et al., 1996). The true neuronal basis of these low frequency resting-state fMRI oscillations is not yet fully understood and in the past years there has been an ongoing debate on whether these resting-state BOLD signals result from physiological processes, like respiratory and