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Review

Resting-state functional connectivity in major depressive disorder: A review

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ABSTRACT

Major depressive disorder (MDD) affects multiple large-scale functional networks in the brain, which has initiated a large number of studies on resting-state functional connectivity in depression. We review these recent studies using either seed-based correlation or independent component analysis and propose a model that incorporates changes in functional connectivity within current hypotheses of network-dysfunction in MDD. Although findings differ between studies, consistent findings include: (1) increased connectivity within the anterior default mode network, (2) increased connectivity between the salience network and the anterior default mode network, (3) changed connectivity between the anterior and posterior default mode network and (4) decreased connectivity between the posterior default mode network and the central executive network. These findings correspond to the current understanding of depression as a network-based disorder.

Contents

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1. Introduction

Major depressive disorder (MDD) is one of the most prevalent psychiatric disorders and is the second leading cause of disability worldwide (Ferrari et al., 2013). Despite almost 60 years of intensive neurobiological research, our current understanding of its pathophysiology is limited, which is reflected in a heterogeneous disease concept and moderate effects of treatment (Arroll et al., 2009; Mojtabai, 2013; Moncrieff et al., 2004). While earlier neuroimaging techniques have investigated focal structural and functional changes (Alcaro et al., 2010; Hamilton et al., 2013; Koenigs and Grafman, 2009; Northoff et al., 2011; Price and Drevets, 2012), depression is increasingly understood as a disorder of distributed effects of aberrant interaction in the brain (Drevets et al., 2008; Hamilton et al., 2013; Mayberg, 1997). Within this framework, brain regions are dynamically organized into functional networks of interconnected areas (or “nodes”) that interact to perform specific tasks (Bressler, 1995).

With the advance of network-based research in system-level neurosciences in general, new techniques allow us to identify these large-scale brain networks, for example by looking at changes in blood-oxygen-level-dependent (BOLD) signal using functional magnetic resonance imaging (fMRI). An important methodological development in investigating these networks was the finding that they can consistently be identified during the “resting-state”, i.e. when a subject is not engaged in any particular task (Biswal et al., 1995). This independence of task-based paradigms offers the important advantage of being reproducible across different populations and study settings. Following this, many recent studies have investigated how the different nodes and networks communicate by investigating synchronous spontaneous activity in different regions of the brain. This so-called “resting-state functional connectivity” (hereafter referred to as “connectivity”) represents the temporal coherence of the BOLD-signal within or between regions or networks during rest and is an important addition to functional imaging techniques in unraveling the neurobiology of depression (Friston, 2011).

In MDD most findings in task-based and resting-state fMRI implicate one of three major neural networks: the default mode network (DMN), the central executive network (CEN) and the salience network (SN) (Hamilton et al., 2013; Menon, 2011; Raichle et al., 2001; Seeley et al., 2007). Two recent papers have reviewed studies on functional connectivity in depression (Smith, 2014; Wang et al., 2012), but either included only a limited number of eligible studies (Smith, 2014) or rather divergent methods which makes comparison of results problematic (Wang et al., 2012). Because of these limitations, and the large number of connectivity papers published in recent years, we aim to provide a coherent review of the resting-state functional connectivity literature in depression that takes into account the different methods used, and update the current concept of depression as a network-based disorder.

Our review will focus on changes within (1) the default mode network, (2) the central executive network, (3) the salience network and (4) the interactions between these networks. We will start by giving a short overview of these networks and their function. Then, we will provide a critical appraisal of all available studies on resting-state functional connectivity in MDD, taking into account different methods used as well as the relation to clinical characteristics and effects of treatment. Lastly, we will discuss the significance of these findings in the light of current depression hypotheses.

2. Core large-scale networks in major depressive disorder

The default mode network (DMN), the central executive network (CEN) and the salience network (SN) (Fig. 1) (Hamilton et al., 2013; Menon, 2011; Raichle et al., 2001; Seeley et al., 2007) represent the brain’s function during rest, cognition and emotional processes, all of which are essential processes that are altered in depression.

2.1. Default mode network (DMN)

The default mode network (also known as the “task-negative network”) was initially identified as areas that consistently showed synchronized deactivation during tasks and prominent activation during rest (Raichle et al., 2001). The fact that this network is related to processes that are mostly employed during rest such as self-generated thought has gained significant attention, especially in relation to depression (Andrews-Hanna et al., 2014; Buckner et al., 2008; Menon, 2011). The DMN is often divided into an anterior sub-network that centers on the medial prefrontal cortex (mPFC) and a posterior sub-network that centers on the posterior cingulate cortex (PCC) and the precuneus cortex (PCu) (Andrews-Hanna et al., 2010; Buckner et al., 2008). While the anterior and posterior sub-network share similar temporal dynamics, they differ in regards to their specific function (Andrews-Hanna et al., 2010, 2014). In general, both the anterior and posterior parts of the DMN are related to spontaneous or self-generated cognition. The anterior DMN is more related to self-referential processing and emotion-regulation, partly through its strong connections with limbic areas such as the amygdala. The posterior DMN has been implicated in both consciousness and memory processing through its relation to the hippocampal formation (Andrews-Hanna et al., 2014; Cavanna and Trimble, 2006; Leech and Sharp, 2014).

In addition to the core regions, associated DMN areas include the inferior parietal lobule (IPL) and the lateral temporal cortex (LTC) (Buckner et al., 2008; Greicius et al., 2003). Although not