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Review

Large-scale functional connectivity networks in the rodent brain

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ABSTRACT

Resting-state functional Magnetic Resonance Imaging (rsfMRI) of the human brain has revealed multiple large-scale neural networks within a hierarchical and complex structure of coordinated functional activity. These distributed neuroanatomical systems provide a sensitive window on brain function and its disruption in a variety of neuropathological conditions. The study of macroscale intrinsic connectivity networks in preclinical species, where genetic and environmental conditions can be controlled and manipulated with high specificity, offers the opportunity to elucidate the biological determinants of these alterations. While rsfMRI methods are now widely used in human connectivity research, these approaches have only relatively recently been back-translated into laboratory animals. Here we review recent progress in the study of functional connectivity in rodent species, emphasising the ability of this approach to resolve large-scale brain networks that recapitulate neuroanatomical features of known functional systems in the human brain. These include, but are not limited to, a distributed set of regions identified in rats and mice that may represent a putative evolutionary precursor of the human default mode network (DMN). The impact and control of potential experimental and methodological confounds are also critically discussed. Finally, we highlight the enormous potential and some initial application of connectivity mapping in transgenic models as a tool to investigate the neuropathological underpinnings of the large-scale connectional alterations associated with human neuropsychiatric and neurological conditions. We conclude by discussing the translational potential of these methods in basic and applied neuroscience.

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Introduction

Neuroimaging methods like Magnetic Resonance Imaging (MRI), have greatly advanced our understanding of the large-scale organisation of the human brain. Blood-oxygen level dependent (BOLD) functional MRI (fMRI) methods, initially devised to investigate the functional specialisation of the brain and its modulation by cognitive processes, have more recently been applied to reveal the intrinsic network organisation of the human brain in the absence of explicit tasks. This approach, widely known as resting-state fMRI (rsfMRI), relies on the observation that spontaneous low-frequency oscillations in BOLD fMRI signal exhibit reproducible, anatomically specific, patterns of correlations between different brain areas, leading to the use of this readout as an index of "functional connectivity" (Damoiseaux et al., 2006; Beckmann et al., 2005). The initial observations of this phenomenon were of bilaterally correlated signals in the motor cortices (Biswal et al., 1995), followed soon after by similar findings in visual and auditory (Cordes et al., 2000) regions. Beyond bilaterally correlated signals in analogous brain regions, the most interesting findings from rsfMRI have involved the identification of large-scale, anatomically distributed cortical networks, some of which have been associated with specific aspects of brain function. For example, temporally correlated signals from dorsolateral areas in the prefrontal and parietal cortices define a network implicated in executive control and attention (Mazoyer et al., 2001). Similarly, functionally connected structures involving the anterior insular and dorsal cingulate cortices are involved in salience processing, defining a "salience network" (Seeley et al., 2007). One of the most investigated large-scale networks of the human brain is the so-called "default mode network" (DMN), a systems involving correlated areas in the precuneus/posterior cingulate cortex, medial prefrontal cortex and lateral parietal and perihippocampal cortices (Buckner et al., 2008). Interestingly, this network was originally identified and named based on properties other than its low-frequency temporal correlations. These structures were observed in a number of functional imaging experiments to exhibit negative signal changes in fMRI and functional PET experiments when the subject engaged in a specific task. This observation led to the notion that this set of brain structures was associated with a "default mode" of brain function – being most active when the brain is idle or unconstrained, and deactivated when a specific mental task is undertaken. DMN structures have since been demonstrated to be strongly temporally correlated in the absence of a task and the DMN has become one of the most widely studied resting state networks in man, although its function remain debated (Buckner et al., 2008).

The study of large-scale brain connectivity networks may provide a key to understanding brain disease. Brain disorders are inherently complex, and are defined clinically in terms their symptomatic presentation, despite their polygenic and multifactorial origins. This makes it difficult to pinpoint the physiological effects of candidate genetic risk variants, and to identify the neuropathological features that may underlie their onset and progression. One strategy to mitigate this complexity is the study of 'endophenotypes', that is, objective and measurable markers that might help identify the genetic or environmental underpinnings of these syndromes (Meyer-Lindenberg and Weinberger, 2006). Abnormalities in the brain's rsfMRI connectivity represent a promising putative endophenotype for certain mental disorders, like autism and schizophrenia, that are not associated with focal neuropathological features, but are rather thought to be developmental disorders characterised by pathological patterns of neural connectivity, or "connectopathies" (Noonan et al., 2009; Lynall et al., 2010). However, for rsfMRI connectional signatures to become clinically relevant, a deeper understanding of their origin and pathophysiological significance is warranted. Experimental research into these aspects can help provide insight into the heterogeneity observed in clinical populations, linking large-scale brain system dysfunction to underlying cellular and neurobiological processes. It could also play an important role in determining whether the observed connectivity alterations are per se causative (possibly resulting from different cellular pathologies), or reflective of specific underlying pathological processes.

While there are ongoing human studies attempting to address these issues, a full disambiguation of the origin and significance of coordinated macroscale functional connectivity and its aberrations requires interventional approaches and controlled experimental conditions only achievable with animal models. The availability of analogous measurement methods in transgenic rodents is in this respect of considerable promise, both in terms of understanding genetic underpinnings of connectional deficits via the ever-increasing repertoire of sophisticated genetically-modified mouse models available, and as a means to more fully understand the complex neurophysiological processes underlying the haemodynamic changes measured with fMRI techniques. Recent advancements in MRI hardware and improvements in the control of animal physiology (Ferrari et al., 2012; Liang et al., 2011a) have recently enabled fMRI methods to be back-translated into rats and mice. Early work investigating functional connectivity in the rodent used cross-subject covariance methods to elucidate brain regions that respond in a coordinated way to an applied stimulus at a population level. This approach dates back to the early days of 2-deoxyglucose (2DG) work (Soncrant et al., 1986), has also been applied to human functional (Horwitz et al., 1984; Vogt et al., 2006) and structural (Evans, 2013) neuroimaging, and found particular application to the investigation of connectivity relationships in the rat brain in response to pharmacological stimuli (Schwarz et al., 2007; Schwarz et al., 2009; Byun et al., 2014). More recently, reliable mapping of distributed rsfMRI functional networks using within-subject temporal correlations has been demonstrated in the rat (van der Marel et al., 2013; Pawela et al., 2008; Schwarz et al., 2013b; Liang et al., 2011a; Becerra et al., 2011; Pan et al., 2015; Hutchison et al., 2010) and in the mouse (Shah et al., 2015b; Sforazzini et al., 2014a; Sforazzini et al., 2014b; Grandjean et al., 2014a; Zerbi et al., 2014). These developments open the possibility of complementing human studies by novel, interventional approaches in genetically engineered laboratory animals and promise to bridge an important translational gap.

Macroscale functional connectivity mapping in rodents

Recently, plausible functional connectivity relationships have begun to be elucidated in the rodent brain, using the same fMRI techniques as employed in human studies. Early experiments in the rat confirmed bilaterally correlated low-frequency BOLD oscillations between homologous regions of the brain (Kannurpatti et al., 2008; Zhao et al., 2008; Lu et al., 2012). Another important early study used an hypothesis-driven approach to confirm functional connectivity relationships within sensorimotor and visual pathways involving midbrain, thalamic and cortical areas (Pawela et al., 2010). Subsequently, several laboratories using independent component analysis (ICA) have consistently reported a number of distinguishable functional components that can be related to specific neurofunctional and neuroanatomical brain systems, including dorsal and lateral somatosensory, basal ganglia, hippocampal and midline cingulate/prefrontal cortex (Becerra et al., 2011; Liang et al., 2011a; Jonckers et al., 2011; Hutchison et al., 2010). A detailed description of these basic cortical and subcortical systems with respect to analogous primate and human networks has been reported in recent rat (van der Marel et al., 2013; Pawela et al., 2008; Schwarz et al., 2013b; Liang et al., 2011a; Becerra et al., 2011; Hutchison et al., 2010; Jonckers et al., 2011; Sierakowiak et al., 2015; Becerra et al., 2011; Hutchison et al., 2010; Liang et al., 2011b) and mouse studies (Sforazzini et al., 2014b; Jonckers et al., 2011; Zerbi et al., 2015; Guilfoyle et al., 2013; Nasrallah et al., 2014b).

Careful seed-based analyses have characterised more distributed functional relationships involving antero-posterior and cortical-subcortical networks and demonstrating a high degree of consistency with established anatomical connectivity within the rat brain. In one exemplar study, connectivity patterns associated with specific nuclei of