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Invited review

Resting state functional connectivity: Its physiological basis and application in neuropharmacology

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ABSTRACT

Brain structures do not work in isolation; they work in concert to produce sensory perception, motivation and behavior. Systems-level network activity can be investigated by resting state magnetic resonance imaging (rsMRI), an emerging neuroimaging technique that assesses the synchrony of the brain's ongoing spontaneous activity. Converging evidence reveals that rsMRI is able to consistently identify distinct spatiotemporal patterns of large-scale brain networks. Dysregulation within and between these networks has been implicated in a number of neurodegenerative and neuropsychiatric disorders, including Alzheimer's disease and drug addiction. Despite wide application of this approach in systems neuroscience, the physiological basis of these fluctuations remains incompletely understood. Here we review physiological studies in electrical, metabolic and hemodynamic fluctuations that are most pertinent to the rsMRI signal. We also review recent applications to neuropharmacology – specifically drug effects on resting state fluctuations. We speculate that the mechanisms governing spontaneous fluctuations in regional oxygenation availability likely give rise to the observed rsMRI signal. We conclude by identifying several open questions surrounding this technique.

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Addiction is characterized by the compulsive drug seeking and taking behavior despite significant negative consequences. One theory (Everitt et al., 2008) views drug addiction as the endpoint of a series of transitions from initial voluntary drug use to habitual and ultimately compulsive use, involving neuroplasticity in the glutamatergic pathway from prefrontal cortex to striatum as well as in the dopaminergic pathway mediating the progression from ventral to more dorsal domains of the striatum. Decades of human neuroimaging studies, using both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have identified regional neuroplastic changes resulting from prolonged drug exposure, including orbital and prefrontal cortex, anterior cingulate cortex, striatum, hippocampus and amygdala (Breiter et al., 1997; Childress et al., 1999; Garavan et al., 2000; Grant et al., 1996; Kufahl et al., 2005; Stein et al., 1998; Volkow et al., 1992, 1988, 1997). However, brain regions do not work in isolation; they work in concert, forming neural networks to produce subjective perception, motivation and behavior.

For a long time noninvasive assessment of the spatiotemporal dynamics of network activity has been limited by the availability of imaging tools. The recent development of resting state MRI (rsMRI) offers an attractive methodology to investigate systems-level network activity (Biswal et al., 1995), leading to a paradigm shift in functional brain imaging (Raichle, 2009). Over the last few years, rsMRI has been applied to assess alterations in functional connectivity associated with a range of drug-using cohorts, including cocaine, heroin, morphine, nicotine, alcohol and caffeine (Camchong et al., 2011; Gu et al., 2010; Khalili-Mahani et al., 2012; Ma et al., 2010; Meunier et al., 2012; Niesters et al., 2012; Sutherland et al., 2013; Tal et al., 2013; Tomasi et al., 2010; Upadhyay et al., 2010; Wong et al., 2012). Emerging evidence further suggests a genetic linkage between resting state functional connectivity networks and a circuit level addiction phenotype (Hong et al., 2010), raising the promise that functional connectivity may serve as a systems-level biomarker to identify individual differences in, and provide differential disease diagnoses for, neuropsychiatric disorders (Greicius, 2008).

Like all fMRI techniques, rsMRI measures hemodynamic signal, relying on a still poorly understood neurovascular signal transduction mechanism to infer neuronal activity. Incomplete understanding of these coupling mechanisms gives rise to certain degree

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of ambiguity when interpreting pharmacological MRI data (Jenkins, 2012). This issue is further exacerbated in rsMRI, a technique that is based on ongoing spontaneous activity, and lacks well-defined task events. As the field of rsMRI and its applications in neuropharmacology emerges, understanding its physiological basis, origin and neuronal substrate becomes imperative. Here we review studies of spontaneous fluctuations in electrical, metabolic, and hemodynamic activity that may be most pertinent to understanding the neurobiological bases of the rsMRI signal. We first describe the measurements and frequencies of each of the fluctuations. We then describe recent applications to neuropharmacology – specifically drug effects on resting state fluctuations. From these results we argue for the significance of resting state fluctuations to relevant ongoing neuronal activity. Based on the characteristics of the spontaneous fluctuations measured with different techniques, we propose the hypothesis that mechanisms governing spontaneous fluctuations in regional oxygenation availability likely give rise to the observed rsMRI signal. Finally, we bring forward open questions surrounding rsMRI and discuss critical future experiments.

1. What is rsMRI?

Compared with task-based fMRI, the acceptance of rsMRI as a research tool experienced a tenuous path. Since the inception of fMRI, most experiments employed either a block-design or an event-related paradigm in which a subject was instructed to perform certain tasks for a fixed duration or at a specific moment followed by a "resting" condition serving as a control state, during which the subjects did not engage in any specific task. However, an interesting phenomenon puzzled imaging physicists: the baseline noise levels of the fMRI time course during the resting condition was much too high to be explained by machine white noise alone (Biswal et al., 1993; Jezzard et al., 1993; Weisskoff et al., 1993). In their seminal paper, Biswal et al. (1995) found that the slow fluctuations (<0.1 Hz) in resting fMRI scans of the sensorimotor, supplementary motor and premotor areas exhibited remarkable temporal coherence, and that the spatial structures of the synchrony closely resembled the activation patterns found during an instructed finger-tapping task. The authors suggested that the ongoing, spontaneously occurring synchrony among brain areas reflected the inherent functional organization of the neural network itself, and dubbed it "resting state functional connectivity." Since subjects did not engage in any specific tasks, the technique was named resting state MRI in contrast to task-based MRI. Many investigators at the time worried that such patterns might be related to respiration and cardiac pulsation, and thus of non-neural origin (Lund, 2001; Mitra et al., 1997; Wise et al., 2004). The identification of the so-called "default mode network (DMN)", first using PET (Raichle et al., 2001), and later by rsMRI (Greicius et al., 2003), lead many to conclude that the ongoing intrinsic activity, as probed by rsMRI, is indeed of fundamental significance (but see (Morcom and Fletcher, 2007)).

Over the last decade, with increasingly sophisticated analysis methods, rsMRI has consistently been able to differentiate multiple distinct cortical and subcortical large scale networks (Beckmann et al., 2005; Bullmore and Sporns, 2009; Salvador et al., 2005; Smith et al., 2009; Tomasi and Volkow, 2010; Wang et al., 2010). These functional connectivity networks have been reported across laboratories (Biswal et al., 2010), and change as a function of brain developmental stages (Dosenbach et al., 2010; Power et al., 2010). Alterations in functional connectivity are implicated in a wide range of neurodegenerative and neuropsychological diseases, such as Alzheimer's disease (Greicius et al., 2004; Li et al., 2002; Lustig et al., 2003), multiple sclerosis (Lowe et al., 2002), spatial neglect syndrome (He et al., 2007), schizophrenia (Bluhm et al., 2007), depression (Anand et al., 2003; Greicius et al., 2007), autism (Jones et al., 2010; Kennedy and Courchesne, 2008), attention deficit/hyperactive disorder (Tian et al., 2006; Zhu et al., 2005), drug addiction (Gu et al., 2010; Ma et al., 2010; Sutherland et al., 2012; Tomasi et al., 2010), and have been identified not only in human, but also in rats (Lu et al., 2007; Zhao et al., 2008) and nonhuman primates (Vincent et al., 2007). Progress in studying structural and functional brain networks has led to a recent National Institutes of Health initiative to create a human connectome (Sporns et al., 2005).

With the large and growing ranges of application using rsMRI, it would seem imperative to better understand its physiological origin and neural basis. These issues are still incompletely understood, and many aspects are very much a work in progress. In the

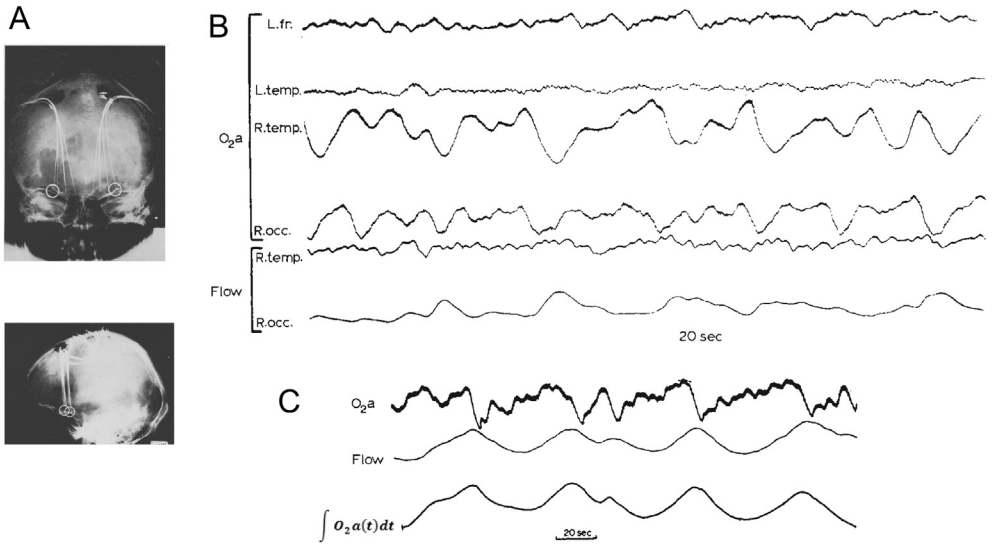

Fig. 1. Spontaneous fluctuations in regional oxygen availability (O_2a) and cerebral blood flow (CBF) measured with the polarographic technique in an awake human. A: Representative posterior/anterior and lateral x-ray photographs showing implanted gold electrodes in a psychiatric patient. White circles indicate micro-thermistors used to measure alteration in CBF. B: Dynamic oxygen availability (O_2a) and CBF recordings measured from electrodes in the frontal, temporal and occipital cortical areas. C: Temporal integral of O_2a curve parallels CBF curve. Abbreviations: L. fr, left frontal area; L. temp, R. temp, left/right temporal area; R. occ, right occipital area. Adapted from Cooper et al. (1966) with permission from publisher.

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