Review

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Functional magnetic resonance imaging of intrinsic brain networks for translational drug discovery

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Developing translational biomarkers is a priority for psychiatry research. Task-independent functional brain imaging is a relatively novel technique that allows examination of the brain's intrinsic networks, defined as functionally and (often) structurally connected populations of neurons whose properties reflect fundamental neurobiological organizational principles of the central nervous system. The ability to study the activity and organization of these networks has opened a promising new avenue for translational investigation, because they can be analogously examined across species and disease states. Interestingly, imaging studies have revealed shared spatial and functional characteristics of the intrinsic network architecture of the brain across species, including mice, rats, non-human primates, and humans. Using schizophrenia as an example, we show how intrinsic networks may show similar abnormalities in human diseases and animal models of these diseases, supporting their use as biomarkers in drug development.

Why 'task-independent' functional imaging?

A major obstacle facing psychiatry research is the lack of effective translational biomarkers, or biological indicators of disease state. These assays are not only essential for improving our understanding of the neurobiological mechanisms that underlie disease, but also for providing screening tools to increase the probability of success for investigational compounds as they enter clinical trials.

To that end, investigators have long been interested in using functional magnetic resonance imaging (fMRI) to study neuronal function across species. fMRI is a technique in which the detection of magnetic field disruptions due to the flow of deoxygenated blood is used as a surrogate measure of localized neuronal activity. Great advantages of fMRI are its safety, noninvasiveness, and high spatial resolution. Early attempts at using fMRI as a translational tool were hampered, however, by limitations in its analysis methods. Early fMRI studies in humans were almost entirely 'task' based (e.g., a working memory task), because the fMRI signal – the blood oxygen level-dependent (BOLD) response – could only be interpreted as a comparison between conditions (e.g., task versus no task) using a general linear model (GLM)-based approach. This limitation severely restricted the utility of fMRI in animal studies, not only due to limitations in cognitive ability, but also because many animals (e.g., rodents) were required to be restrained, sedated, or anesthetized during scanning.

Fortunately, recent advances in fMRI analysis methods have enabled researchers to quantify and understand brain function in terms of intrinsic brain networks that are present across all cognitive states, including during rest, sedation, anesthesia, and sleep [1–3]. Intrinsic networks are defined as functionally and (often) structurally connected areas whose activity is thought to reflect fundamental neurobiological organizational principles of the central nervous system. Intrinsic networks are frequently referred to as resting state networks, although they can be extracted regardless of the mental state of the subject. Intrinsic networks are identified methodologically by either seed or independent component analysis (ICA) data-driven based methods (Box 1), and consist of large populations of neurons that demonstrate low-frequency (<0.1 Hz) synchronous BOLD responses [4]. An additional advantage of these techniques is that, unlike traditional GLM-based analysis, they do not impose prior constraints on the time course of the BOLD response, which may vary between individuals [5,6]. This flexibility may help explain why, remarkably, multiple anatomically distinct networks are consistently extracted, reflecting a map of intrinsic functional brain connectivity [7]. These networks may be specialized for functions such as executive function, salience processing, and introspection [8,9]. The activity and functional connectivity of intrinsic networks are dramatically altered in neuropsychiatric diseases such as Alzheimer's disease (AD) [10], bipolar disorder [11], autism [12], attention deficit hyperactivity disorder (ADHD) [13], obesity [14,15], and schizophrenia [11,16], supporting their potential utility as biomarkers.

Perhaps the greatest advantage of task-independent fMRI, however, is its translational utility. Because it does not require animals to perform a task, they can be either sedated or restrained during scanning, providing suitable

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Box 1. Extracting intrinsic networks from fMRI data

Two methods are commonly used to extract intrinsic networks from fMRI data: seed-based functional connectivity and ICA. These methods are conceptually identical across species.

Seed-based functional connectivity. In this technique, the correlation coefficients between one time series of data (the 'seed') and many other time series (the 'targets') are extracted [64]. Higher correlation coefficients imply more synchronous activity and therefore higher functional connectivity between the seed and a target. For example, the time series of the average BOLD response in the hippocampus may be correlated with the time series of the other major brain areas. An averaged correlation coefficient between the seed and all other areas may also be calculated to yield a value for overall connectivity of the seed.

ICA. The goal of ICA is to identify statistically independent patterns of BOLD response within the brain [64]. These independent patterns are then classified into networks based on the anatomical localization of their components. Networks identified by ICA show synchronous fMRI BOLD response with each other, as well as asynchronous response with other networks. The level of neuronal activity within an ICA-extracted network can be estimated by the magnitude of the signal fluctuations within that component [65].

conditions for analysis of intrinsic networks using methods analogous to those used for human data. Furthermore, traditional implanted-electrode recordings of brain activity are labor-intensive, invasive, spatially restricted, and only permit the simultaneous study of one or two isolated regions. By contrast, fMRI provides noninvasive whole-brain coverage of neuronal response, allowing the researcher to understand the brain as a dynamic, integrated system of connections within and between networks of many regions. Using fMRI, researchers have analyzed intrinsic brain network activity from a variety of organisms, including mice, rats, and non-human primates. Perhaps the most significant aspect of these findings is that core features of intrinsic networks have been conserved across species, suggesting that their fundamental organization may have been evolutionarily selected for over time. These similarities present the intriguing possibility that disruptions in the networks observed in disease states may be replicated in animal models, highlighting the translational utility of the approach. Ultimately, intrinsic networks may become invaluable biomarkers by which to measure the neurobiological effects of investigational and other compounds of interest.

Accordingly, this review focuses on two major topics. First, it examines recent findings characterizing core intrinsic networks across species to illustrate the degree to which these networks have been conserved. We do not argue that these networks are topographically identical – indeed, large differences in brain size, neocortex/paleocortex ratio, and cognitive function between species preclude any notion of sameness – but rather illustrate that analogous methods can be used across species to identify brain networks that share common features. Second, by using schizophrenia – a devastating disorder with well-known intrinsic network abnormalities – as an example, this review illustrates how task-independent fMRI might be used as a translational tool for drug discovery.

Intrinsic brain networks: from mice to men

The default mode network (DMN)

The DMN is the most widely studied and well-characterized intrinsic network. The DMN was discovered when researchers observed that activity in several brain areas was synchronously reduced during cognitive tasks and consequently increased at rest. Connectivity analyses later confirmed that these regions constituted an intrinsic functional network [17,18]. Due to its tendency to be down-modulated during many tasks, and therefore be active as a default, the network was coined the DMN. The human DMN consists of anterior (medial prefrontal cortex/orbitofrontal cortex/anterior cingulate) and posterior (inferior parietal/posterior cingulate/precuneus) brain areas [17] (Figure 1). The hippocampus/medial temporal lobe is considered an accessory hub of the network. The DMN is readily and reproducibly detectable regardless of the analytic technique used, and irrespective of the cognitive state of the individual, be it during an effortful task, rest, or even during sleep [1]. The functions of the DMN are not completely understood. The network is particularly active during actions that are self-referential: for example, reflecting on the past, planning for the future, or monitoring internal state [17]. Because the network also shows activity while under anesthesia [19,20] and during the early stages of sleep [2], however, its activity does not necessarily imply awake, self-referential thinking.

Based on its hypothesized functions (for example, self-reflection), one might speculate that the DMN is a uniquely human network, without analogs in other species. Surprisingly, however, striking similarities in DMN architecture exist between humans, rats [21,22] and non-human primates [19,23] (Figure 1). An early task-independent fMRI study in macaque monkeys found that temporoparietal and medial prefrontal areas demonstrated correlated response with a posterior cingulate seed [19]. Additional evidence that this network may be functionally analogous to the human DMN was provided by a recent meta-analysis that observed reduced activity of these brain regions across 15 sensory processing and cognitive tasks [24], as well a study that observed down-modulation of the posterior cingulate during an attention task [25]. In rats, Upadhyay and colleagues found correlated response between an anterior cingulate seed and the retrosplenial cortex/posterior cingulate, bilateral parietal cortex, temporal association cortex, and hippocampus [21]. A second study by Lu and coworkers that used ICA found similar results [22], although these researchers found more extensive correlations with the medial ridge of the cingulate cortex. Expansive cingulate involvement in the rat DMN is anatomically distinctive from the non-human primate and human DMN, suggesting that the DMN areas recruited across these species are not identical. Indeed, the primary distinctive feature of the human DMN is increased involvement of anterior regions, possibly indicative of an evolutionary adaptation that facilitates complex spontaneous (stimulus-independent) cognition [17].

The unique features of the DMN in different species, however, do not preclude the translational applications of examining the network. Indeed, the anatomical similarities of the DMN, in combination with the reduced activity