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Review

REVIEW

A review of resting-state fMRI and its use to examine psychiatric disorders

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Abstract

Resting-state fMRI (rs-fMRI) has emerged as an alternative method to study brain function in human and animal models. In humans, it has been widely used to study psychiatric disorders including schizophrenia, bipolar disorder, autism spectrum disorders, and attention deficit hyperactivity disorders. In this review, rs-fMRI and its advantages over task based fMRI, its currently used analysis methods, and its application in psychiatric disorders using different analysis methods are discussed. Finally, several limitations and challenges of rs-fMRI applications are also discussed.

Key words: fMRI; resting state; connectivity

Resting-State fMRI

Background on rs-fMRI

Functional magnetic resonance imaging (fMRI), due to its noninvasiveness and high spatial and temporal resolution, has become the method of choice to perform systems-level neuroscience in human and animal models. Most fMRI studies use the BOLD (blood oxygenation level dependent) contrast mechanism first proposed by Seiji Ogawa (Ogawa *et al.*, 1990). When a participant performed a task, there was increased neuronal firing leading to vasodilation and increased blood flow in eloquent regions of the brain. Because this resulted in more oxygenated red blood cells compared to deoxygenated red blood cells, there was less dephasing of the fMRI signal and an increase in activity in the specific brain regions corresponding to the task was observed. Thus, for task activation studies, participants are presented with a stimulus for a short period of time (10–20 seconds) alternating with a control condition for about the same period. Although task-based fMRI has been widely used to identify brain regions corresponding to specific tasks, certain populations, such as infants, patients with Alzheimer's Disease, and patients with other debilitating clinical disorders, may not be able to perform certain tasks required of them.

Resting-state fMRI (rs-fMRI) has emerged as an alternative to task-based fMRI to map brain functions by observing brain signals during rest. This method was first demonstrated in 1995 where it was shown that brain activations in the resting state could exhibit similar correlations between brain regions as activations in the task state (Biswal *et al.*, 1995). It was shown that rs-fMRI signals in the sensorimotor and its associated cortex had significant temporal correlation within the cortex but not with other brain regions. Similar observations

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were also made in other functional regions including the visual cortex (Lowe *et al.*, 1998). Rs-fMRI primarily focuses on measuring the spontaneous activity in BOLD signals, which is measured in a resting state wherein participants do not perform specific tasks that may alter brain activity. These rs-fMRI signals possess very low amplitude fluctuations, resting primarily within the 0.01 to 0.1 Hz range (van den Heuvel and Hulshoff Pol, 2010).

Rs-fMRI possesses several advantages over task-based fMRI. For one, it is a simpler test that does not require stimuli to be presented to a participant, nor does it require the participant to respond to stimuli. It is also easier for certain patient groups, such as the very young or elderly, to undergo imaging as they do not need to perform actions they may have difficulty with (Maknojia *et al.*, 2019). Additionally, it has been found that rs-fMRI can pick up on trends in the brain that task-based fMRI either cannot or cannot pick up on as well. For example, one study used rs-fMRI to classify the social and neurocognitive performance in individuals based on connectivity in the sensorimotor network (SMN). Task-based fMRI was also used for this study but was less sensitive to detecting connectivity in the brain, and the findings did not replicate well across another independent test sample, whereas rs-fMRI did (Viviano *et al.*, 2018). Furthermore, task-based fMRI only reveals brain activity and connectivity elicited by a particular task in which specific brain regions are activated, but not the whole brain. If the focus of a study is on a particular psychological model or process, then this would provide useful information; however, if the focus is on the whole brain, then resting-state fMRI may be a better alternative. It can also be difficult to sort out the associations between brain activity and task performance since the interactions may be complex or nonlinear. On the other hand, resting-state approaches do not make any assumptions on the interaction between brain activity and task performance, since there is no task involved. Because of these advantages, resting-state fMRI has become an important tool in neuroimaging and knowledge of this technique can greatly aid in understanding the human brain.

fMRI analysis

A commonly used method through which connections are established in fMRI is functional connectivity (FC). FC is a measure that correlates two different neuronal activations in the brain by analyzing their time-series data and then using that to determine whether a temporal connection exists (Smitha *et al.*, 2017). Through this, different networks can be established based on specific functions such as the default mode network (DMN). The DMN is a network known for aiding in self-referential thoughts, cognition, and emotional thinking, and is highly active at rest compared to when the brain is performing a task, making it important in rs-fMRI (Smitha *et al.*, 2017).

Other resting-state networks have been identified in addition to the DMN, such as the SMN, executive control network (ECN), salience network (SN), auditory network, visual network, frontoparietal network (FPN), and cerebellar network (CN) (Heine *et al.*, 2012). One of the first resting-state networks discovered was the SMN, which includes regions such as the primary and secondary somatosensory cortices, premotor cortex, primary motor cortex, and supplementary motor area (Biswal *et al.*, 1995). In contrast to the DMN, which is involved in contemplative and internalized thoughts, the ECN is associated with more externally driven thoughts (Ng *et al.*, 2016). Another important resting-state network is the SN, which is activated during thoughts specifically important to the individual, encompassing the cognitive, homeostatic, and/or emotional. The auditory and visual networks are activated in response to auditory and visual stimuli, respectively, as their names suggest. A more involved network is the FPN, which has been regarded as a "functional hub" due to its activation in response to a variety of stimuli, involved in attention, executive control, and cognitive control. Last, the CN, composed of the cerebellum, also covers a wide range of functions, such as balance, working memory, emotional learning, and executive functions (Chen *et al.*, 2013). Despite the identification of these resting-state networks, it is important to note that there is still no universally accepted network naming convention, and there is some controversy as to which naming convention to use. However, efforts have been made by Uddin and colleagues toward standardization, proposing six functional brain networks that commonly appear in the literature: the occipital network, pericentral network, dorsal frontoparietal network (D-FPN), lateral frontoparietal network (L-FPN), midcingulo-insular network (M-CIN), and the medial frontoparietal network (M-FPN) (Uddin *et al.*, 2019).

There are many different methods for exploring and finding FC but, in this review, only the most commonly used options will be discussed and explained. A brief outline of the major approaches we discuss is shown in Table 1. First, it is necessary to define the difference between functional segregation and functional integration. Functional segregation is the practice of exploring FC by separating the brain into different regions and networks that appear to share a similar purpose. Then, FC is examined solely within those regions. Functional integration will instead look at the whole brain to examine FC between two different regions or networks and their interactions to find more global trends (Lv *et al.*, 2018). Often, these methods are combined in a way where the regions found through functional segregation can be used in functional integration methods.

Amplitude of low-frequency fluctuations (ALFF) and fractional ALFF (fALFF)

The resting-state signal fluctuations giving rise to significant temporal correlation are found to be dominant in the low-frequency range (<0.1 Hz). The ALFF measures the total signal power in the low-frequency range and can be computed for every voxel or a specific region of interest (ROI). ALFF is computed by averaging the square root of the power of low frequency (0.01–0.1 Hz) BOLD

Table 1: Outline of major RSFC approaches.

Major approaches	Key points
ALFF	• Measures the total power of the BOLD signal in the low-frequency range
fALFF	• Measures the ratio of the power in the low-frequency range over the entire frequency range
ReHo	• Characterizes the relationship between a voxel with nearby voxels using Kendall's coefficient of concordance
Seed-based FC	• Correlates the time series from seeds chosen a priori with every other time series' signals
ICA	• Categorizes signals into independent networks based on statistical independence (data driven)

signals and standardizing the values to a global mean ALFF value. ALFF has been shown to vary across regions of the brain as well across certain clinical populations. One of the limitations of ALFF is that it is sensitive to background noise and voxels in the vicinity of medium to large vasculature. To account for some of the limitations of ALFF, a technique known as fALFF has been proposed. fALFF is defined as the ratio of the ALFF at each voxel divided by the signal power over the entire frequency range (Zou *et al.*, 2008). This approach does not include bandpass filtering, so similar to ALFF, concerns about biological artifacts remain (Cole *et al.*, 2010).

ReHo

Regional homogeneity (ReHo), an example of functional segregation, was developed to explore local connectivity in a specific region. It does this by analyzing a specific voxel and characterizing its relationship with nearby voxels in the region, testing whether their activities are correlated via Kendall's coefficient of concordance. Although useful, its findings are generally limited to the region the ReHo is found in (Jiang and Zuo, 2016). ReHo can also be used to classify brain regions by functions based on correlation. This has become important for certain methods of functional integration, specifically seed-based, or ROI FC.

Seed-based FC

Seed-based FC analysis looks at specific regions (known here as seeds) and correlates the corresponding fMRI time-series signal with every other time-series signal throughout the whole brain to examine connectivity. These regions are usually picked a priori from previously available literature or from the use of functional segregation methods that were used to determine regions (van den Heuvel and Hulshoff Pol, 2010). Seed-based analysis is simple and relatively fast for hypothesis-driven studies, but the need to select seeds a priori makes the findings of this method dependent on selecting the right seeds, which can be difficult for exploratory analyses (Lv *et al.*, 2018).

Independent component analysis (ICA)

An alternative to hypothesis-driven rs-fMRI analyses is data-driven methods. An example of this is ICA. ICA is a multivariate statistical method that utilizes the neural signals already present in the brain to categorize them into independent networks based on signal independence and correlation. That is, signals that seem temporally correlated will be grouped as a unique network and other voxels (or regions) will be left out of the network created (van den Heuvel and Hulshoff Pol, 2010). This iterative process is repeated until a set number of independent networks is determined and all the voxels that do not belong to any of the networks are classified as noise. ICA is a useful method due to not having to select regions before analysis and needing fewer assumptions in general than seed-based analysis (Griffanti *et al.*, 2017). However, some manual input is still required toward the end where independent components must be identified by which network they seem to belong to (Calhoun and de Lacy, 2017). This difference of assumptions makes up a key difference between data-driven and seed-based methods that must be considered before choosing an analysis technique.

Graph theory

Another method to consider due to its relatively recent popularity is graph theory. Graph theory is a method of understanding FC by looking at the holistic relationships between voxels, not only within a region but also within the whole brain at the same time. Through this, it can create an FC map of the brain that can give a high level of information regarding certain functions (Smitha *et al.*, 2017). Networks in graph theory are composed of edges and nodes. A node is a point or ROI (such as a brain region in fMRI), while an edge is the connection that node has with the system it is in (such as the FC the brain regions exhibit with other regions). However, as with the other methods, some assumptions need to be made in the analysis step. In this case, one must determine how the network graph theory can be created to obtain the most reliable results. Poor choices lead to results that may not be reliable or repeatable (Wang *et al.*, 2010).

Graph theory has several measures and parameters that can be used in the overall analysis. These measures include global efficiency, local efficiency, nodal efficiency, modularity, path length, degree of centrality, and participation coefficient. Degree of centrality measures the number of edges connected to a node, or in the case of rs-fMRI how much FC is exhibited by a region and its connected regions (Li *et al.*, 2017). The path length is the number of edges connecting two nodes. Global efficiency finds the shortest path length between two nodes in a system, while local efficiency finds the shortest path in the area surrounding a specific node within a system. Network efficiency measures how efficiently information is spread from one node to others in the system. Modularity reflects how many closely connected sets of nodes there are within a global network (Wang *et al.*, 2010). Finally, the participation coefficient measures how much of a specific node's edges are shared with the rest of the regions in the global network (Power *et al.*, 2013).

Preprocessing of rs-fMRI data

As with most neuroimaging analyses, preprocessing is an important part of rs-fMRI analysis. Indeed, it is very important as the small amplitude of rs-fMRI makes it highly susceptible to artifacts, especially those arising from motion (Maknojia *et al.*, 2019). The impact of motion may make certain results unreliable and experiments void. In rs-fMRI, the presence of motion can cause misestimation of connectivity in the brain. This can take the form of either an underestimation of connectivity for long-range connections or an overestimation for short-range connectivity (Power *et al.*, 2012). One of the first and important steps in preprocessing is volume registration, which may reduce the artifacts caused by head motion. This is done by aligning scans obtained from a participant to a certain template scan with minimal motion artifacts (Maknojia *et al.*, 2019). While a powerful technique, this technique may also overcorrect in the sense that minor motion artifacts can be corrected in a way that still leaves an artifact, and in the absence of motion the attempt at correction may further distort the data (Caballero-Gaudes and Reynolds, 2017). In the case of patients with attention deficit hyperactivity disorder (ADHD), micromovements in the MRI scanner are commonly observed, causing motion artifacts in the rs-fMRI data. Fair and colleagues have addressed this issue by using a conservative procedure involving frame-to-frame displacement covariates, which led to improved ADHD characterization (Fair *et al.*, 2012).

An efficient and data-driven form of denoising is using linear regression to remove signals not related to specific neuronal activations. This is done using nuisance regressors that can clean multiple different types of noise, from motion to equipment artifacts and non-neuronal signals. Nuisance regressors compute this by regressing total signals in an area to an average signal obtained (Caballero-Gaudes and Reynolds, 2017). Care must be taken when using nuisance regressors as their use may also result in valuable data being regressed out. For example, in the case where the nuisance regressor and the BOLD signal are of different frequencies due to differences in filtering, new noise may be introduced to the signal (Hallquist *et al.*, 2013). A related method is global signal regression (GSR). GSR is done by taking all of the brain's rs-fMRI time-series data and then averaging it to find a global signal. This global signal has been believed to represent the baseline value of the brain and could therefore be dismissed and regressed out as not containing useful information pertaining to FC in the brain (Maknojia *et al.*, 2019). However, this has been controversial as newer research indicated this global signal could contain valuable information; therefore, it is important to show results without GSR as well, if one chooses to perform GSR (Liu *et al.*, 2017). Although there is no single optimal preprocessing pipeline for all datasets, it may be helpful to consider multiple preprocessing strategies for different datasets, depending on the research question. Parkes and colleagues have shown that the preprocessing pipeline chosen will shape the group comparisons in FC between patients with schizophrenia and healthy controls (Parkes *et al.*, 2018). Thus, when comparing patient groups with healthy controls, one should consider a preprocessing strategy that reports all quality control benchmarks rather than simply following a single preprocessing pipeline.

Rs-fMRI and Psychiatric Disorders

In this section, we give a brief overview of common psychiatric disorders and focus on the use of rs-fMRI in each field.

ADHD

ADHD is characterized by a deficit in behavioral inhibition, poor sustained attention, impulsiveness, and hyperactivity (Barkley, 1997). According to the National Survey of Children's Health (NSCH) in 2016, it is estimated that a total of 6.1 million children ages 0–17 years of age have been diagnosed with ADHD in the USA (Danielson *et al.*, 2018). ADHD can also persist into adulthood, with 40–60% of children diagnosed with ADHD continuing to show symptoms in a longitudinal study (Barkley, 2002). Due to the hyperactivity of individuals with ADHD, the performance of task paradigms in an fMRI scanner may not be feasible or may be contaminated with large motion artifacts. However, with rs-fMRI, individuals with ADHD do not perform any tasks, thus reducing the possibility of large motion artifacts, despite challenges of hyperactivity.

In adolescents with ADHD, abnormal resting-state FC patterns are observed in the dorsal anterior cingulate cortex, in which RSFC is significantly increased compared to that of adolescents without ADHD (Tian *et al.*, 2006). This suggests deviations in autonomic control in children with ADHD since the anterior cingulate cortex is highly involved in autonomic control, such as the sympathetic regulation of the heart rate (Critchley *et al.*, 2013). Similarly, Zang and colleagues observed altered resting-state activity in children with ADHD, using ALFF measures, and found increased ALFF in the right anterior cingulate cortex, left sensorimotor cortex, and bilateral brainstem, while there were decreased levels of ALFF in the right inferior frontal cortex, left sensorimotor cortex, and bilateral cerebellum (Zang *et al.*, 2007). Despite the use of different rs-fMRI analysis methods, we see an overlap in results in which activity in the anterior cingulate cortex is altered in children with ADHD. Another approach to observing regional resting-state activity is using ReHo, which was found to be decreased in the frontal-striatal-cerebellar circuits, while it increased in the occipital cortex of boys with ADHD (Cao *et al.*, 2006). Measures of resting-state brain activities can also be combined, as seen in Tian and colleagues' work in defining a resting-state activity index (RSAI) that combined ReHo measures with the standard variance of low-frequency fluctuations to account for both spatial and temporal characteristics of brain voxels, respectively (Tian *et al.*, 2008). In this study, a greater RSAI was found in the basic sensory and sensory-related cortices of patients with ADHD compared to matched controls.

Using rs-fMRI, one could even classify different subtypes of ADHD, as Fair and colleagues have shown by using support vector machine (SVM)-based multivariate pattern analysis (MVPA), which is a machine learning algorithm that can identify different patterns inherent in the brain (Fair *et al.*, 2012). This study observed unique connectivity characteristics between combined (ADHD-C) and inattentive (ADHD-I) subtypes. ADHD-C is characterized by a combination of both inattention and hyperactivity impulsivity, while ADHD-I is predominantly defined by inattention and not hyperactivity impulsivity, according to the Diagnostic and Statistical Manual of Mental Disorders (Association, 2013). Altered connectivity was observed in the midline DMN and insular cortex for the ADHD-C groups, while atypical connectivity patterns were observed in the dorsal-lateral prefrontal cortex (dlPFC) regions and cerebellum for the ADHD-I group (Fair *et al.*, 2012). Classification of ADHD patients using rs-fMRI can also be performed using convolutional neural networks. In a study by Zhang and colleagues, a method of separated channel attention convolutional neural network (SC-CNN-Attention) was used, which consisted of two main stages: using an SC-CNN to learn the temporal features among brain regions and then capturing the temporal features among brain regions using an attention network (Zhang *et al.*, 2020). This study used multi-site rs-fMRI data and achieved a mean classification accuracy of 68.6% on five different sites.

The atypical RSFC observed in patients with ADHD could also be studied from a dynamical systems point of view, as FC may fluctuate over time. Kaboodvand and colleagues assessed time-varying FC to study the different network configurations recruited by the DMN in ADHD patients (Kaboodvand *et al.*, 2020). This study found that the recruitment rate and topology of specific resting-state network synergies are altered in patients with ADHD. The synergies were defined by instances where patterns of connectivity associated with the DMN were stable for at least 4 s, and the study found a significantly lower recruitment rate within the DMN in patients with ADHD for the first identified synergy. The DMN is a widely studied network in rs-fMRI, particularly for studies involving ADHD populations, with reduced network homogeneity being found in the DMN of patients with ADHD (Uddin *et al.*, 2008).

ASD

Autism spectrum disorder (ASD) is comprised of several different disorders, which share characteristics in deficits of social behaviors and interactions, such as prototypic autistic disorder, Asperger syndrome, and pervasive developmental disorder-not otherwise specified (PDD-NOS) (DiCicco-Bloom *et al.*, 2006). Prototypic autistic disorder is defined by impairments in communication and restricted repetitive patterns of behaviors or interests observed before the age of 3 years (Faras *et al.*, 2010). Patients with Asperger syndrome exhibit problems in social communication as well as restricted repetitive forms of interests, however, they can retain linguistic and cognitive development (Faridi and Khosrowabadi, 2017). In cases where the typical symptoms are present but specific pervasive developmental disorder criteria are not met, patients are diagnosed with PDD-NOS (Faras *et al.*, 2010). In 2014, it was found that approximately one in 59 children aged 8 years had ASD in the 11 Autism and Developmental Disabilities Monitoring sites across the United States, and males were four times more likely than females to be diagnosed with ASD (Baio *et al.*, 2018).

From rs-fMRI scans, it has been observed that the resting-state networks of those with high-functioning autism or Asperger syndrome exhibit "underconnectivity" in the anterior–posterior connections of the brain (Cherkassky *et al.*, 2006). In addition to decreased RSFC, decreased ReHo has been observed in patients with ASD, particularly in the right superior temporal sulcus region, right inferior and middle frontal gyri, bilateral cerebellar crus I, right insula, and right postcentral gyrus (Paakki *et al.*, 2010). Paakki and colleagues note that these alterations are observed to be right-hemisphere dominant, possibly due to language domain deficits. Another method used to study connectivity alterations in rs-fMRI is ICA, which was used by Starck and colleagues to identify subnetwork connectivity alterations in the DMN for patients with ASD (Starck *et al.*, 2013). Using ICA, the authors observed decreased connectivity between the anterior and posterior DMN subnetworks in the ASD group. This similarly reflects the "underconnectivity" model between the anterior and posterior connections observed by Cherkassky and colleagues (Cherkassky *et al.*, 2006).

Due to the prevalence of ASD being four times greater in males than females, resting-state fMRI has been used to investigate the sex differences in the brains of patients with ASD. The neural expression of ASD is shown to be hypo-connected in males with ASD and hyper-connected in females with ASD, in comparison to typically developing males and females, respectively (Alaerts *et al.*, 2016). Furthermore, cortico-cerebellar hyperconnectivity and hypoconnectivity are also observed for females and males with ASD, respectively (Smith *et al.*, 2019). The neurobiological mechanism behind these sex differences observed in the RSFC of males and females with ASD is still unclear. This is a particular challenge in ASD research since some studies exclude females altogether due to the highly unbalanced ratio of ASD in males to females (Hull *et al.*, 2017).

A recent area of development in ASD research is the classification of ASD based on resting-state data in conjunction with machine learning and deep learning techniques. Classification has been performed using 3-D convolutional neural nets (3-D CNN) with summary measures such as ALFF and ReHo used as inputs to a 3-D CNN (Thomas *et al.*, 2020). The classification of ASD is also dependent on the sample heterogeneity. Grouping ASD populations into more homogeneous subgroups based on gender and severity range has been shown to yield more accurate classification results (Reiter *et al.*, 2020). Furthermore, machine learning classifiers appear to perform with higher levels of accuracy when the temporal dynamics of rs-fMRI data are taken into account, by using brain dynamic networks and feature extraction methods, with an accuracy of 88.8% achieved in Guo's paper on the classification of ASD (Guo, 2020).

Resting-state fMRI has allowed for the ease of large-scale aggregation of data from multiple imaging sites due to the simplicity of scanning protocol, which has greatly helped in better understanding ASD. A particular initiative is the Autism Brain Imaging Data Exchange, which openly shares 1112 rs-fMRI data sets from 539 individuals with ASD and 573 typical controls (Di Martino *et al.*, 2014). This initiative not only helps in providing greater replicability of studies, but also accelerates the discovery pace for future ASD studies.

Bipolar disorder (BD)

BD is a psychiatric condition defined by alternating periods of mania (a period of elevated mood) and depression. Individuals with BD are at a high risk of suicide at approximately 20 to 30 times higher than the general population (Miller and Black, 2020). BD is split into several subtypes; primarily, these are bipolar disorder I (BD-I) and bipolar disorder II (BD-II). The difference in diagnosis primarily comes from the intensity of the mania period. Another form of BD is bipolar disorder-not otherwise specified (BD-NOS); a diagnosis given when a patient experiences some symptoms of BD but cannot be diagnosed as possessing the condition (Price and Marzani-Nissen, 2012).

A common challenge in diagnosing BD comes from its similarity to major depressive disorder (MDD) when a patient with BD is in a depressive episode, which could result in treatment for the wrong disorder. One study aimed to quantitatively differentiate between the two conditions by examining the resting-state FC of different brain regions with rs-fMRI (Li *et al.*, 2017). The study observed both similarities and differences in the FC of the brain of participants with BD compared to healthy controls. Their findings reported that the degree of connectivity, also known as the degree of centrality (DC), was decreased for both conditions in the areas of the brain responsible for sensory processing, that is, the lingual and fusiform gyrus. They posited that these findings may be related to several negative symptoms seen in depressive states such as apathy and dull perception. However, patients with BD exhibit a loss of DC in the insula and an increase in the precuneus compared to patients with MDD. Differences in DC are clear enough that Li and colleagues were able to differentiate between the two disorders with 86% accuracy.

Mania in patients with BD has been studied extensively with rs-fMRI. These studies have reported abnormal brain activity in areas of the brain associated with emotion regulation. One study found decreased 2dReHo in the left ventral visual stream (VVS) cortex compared to healthy controls (Zhang *et al.*, 2019). The VVS has been noted to respond to emotional stimuli, among other stimuli, which Zhang and colleagues considered to possibly be related to mood swings in patients with BD. Another ReHo study showed low ReHo within children with BD regarding the insula region of the brain, which may play a strong part in emotional perception (Xiao *et al.*, 2019).

In between mania and depression lies a euthymic state, which is not recognized as either but is also not comparable to healthy controls. Euthymic patients may develop mania at any time, and this is paralleled by similarly low ReHo in the right superior temporal gyrus, which, while not as low as that of mania, was still noticeably lower than in healthy controls (Xiao *et al.*, 2019). Another study found that patients in euthymia also exhibited a low level of FC between the anterior cingulate cortex and amygdala compared to healthy controls, almost as low as patients in a maniac state (Brady *et al.*, 2016). The researchers suggested possible compensation for abnormal brain activity in other regions, a method that is disrupted by mania.

Abnormal brain activity has been found in patients with BD-II that is not always reflected in patients with BD-I. For example, lowered connectivity has been observed between the posterior cingulate cortex and the medial prefrontal cortex (mPFC) (Gong *et al.*, 2019). Another study found significantly lowered ReHo in the left occipital frontal cortex within patients with BD-II in a depressive state (Qiu *et al.*, 2019). All of these regions are associated with emotional control, consistent with findings of emotional trauma experienced by patients with BD-I, but the exact regions differ in terms of what is being affected.

BD-NOS is often similar to BD-I in which the same brain regions display abnormal brain activity. Generally, brain regions associated with sensorimotor functions display altered connectivity. An example is the increased connectivity between the sensorimotor RSN and left precentral gyrus that was found in young adults with BD-NOS (Thomas *et al.*, 2019). The abnormal brain activity in the sensorimotor systems is similar to that of patients with BD-I, suggesting a link in the progression from BD-NOS to regular BD. This is consistent with a growing field of literature on the subject, with one study finding that

45% of patients with BD-NOS progressed to BD-I or BD-II (Axelson *et al.*, 2011).

Schizophrenia

Schizophrenia is a mental condition characterized by a variety of disorders such as hallucinations, loss of emotion, and delusions (Kay *et al.*, 1987). Resting-state fMRI studies have found many signs of abnormal brain activity in patients with schizophrenia. This has led to a greater theory of schizophrenia arising from dysconnectivity in the FC of different brain regions. Despite this, the exact nature of the dysconnectivity is unclear as the abnormalities appear to be diverse in their origin.

Much of the literature in rs-fMRI studies for schizophrenia have focused on attempting to find the functional localization of the brain regions corresponding to certain symptoms of the condition. These symptoms are usually grouped into two categories, positive and negative symptoms. Positive symptoms refer to the presence of abnormal behavior such as hallucinations or other delusions, and negative symptoms refer to the absence of usual behavior such as a lack of happiness (Kay *et al.*, 1987). One study found that decreased connectivity between regions of the DMN network, such as the medial parietal and temporal regions, was correlated with positive symptom severity in patients (Venkataraman *et al.*, 2012). The study also found increased connectivity between the medial parietal and frontal lobes, also located in the DMN, was strongly associated with negative and general symptom severity. These two different abnormalities in the same brain network highlight the difficulty in identifying specific causes of disorders. Even when abnormalities in a network are detected, there may be heterogeneity in FC within the brain regions.

Another study by Lee *et al.* also found DMN FC to be related to positive symptoms. Specifically, they saw the FC between the DMN and brain networks such as the central executive network and SMN to heavily contribute to the severity of positive symptoms (Lee *et al.*, 2018). In terms of negative symptoms, they found a correlation with the salience network (SN), with SN contributing to symptoms such as anxiety and depression. Brady *et al.* also reported a connection between negative symptom severity and sections of the default network. Here the connection was between the dorsolateral prefrontal cortex and the cerebral and cerebellar nodes of the DMN (Brady *et al.*, 2019).

An interesting application of rs-fMRI is the evaluation of treatment response in patients with schizophrenia. A study by Chan *et al.*, 2019 noted that it was possible to differentiate between patients with treatment-resistant symptoms and patients whose symptoms are not treatment resistant by identifying FC in specific brain regions. This connectivity arises between striatal subregions and the anterior cortical loci, and the degree of connectivity was suggested as a potential biomarker for the feasibility of treatment (Chan *et al.*, 2019). Besides the prediction of a treatment response, attempts have also been made to measure FC as treatment is given to monitor changes.

For example, Brady *et al.*'s previously mentioned study saw an increase in FC between the cerebellar node and the right dorsolateral prefrontal cortex after transcranial magnetic stimulation (TMS) was applied to the cerebellar midline. As the FC increased, the patient's negative symptoms also decreased in severity (Brady *et al.*, 2019). A similar study sought to reduce auditory verbal hallucinations (AVH) in patients by using transcranial direct current stimulation (tDCS) on the left temporal-parietal junction (TPJ) (Mondino *et al.*, 2016). This caused a decrease in FC between the left TPJ and interior frontal areas, which came alongside a reduction in AVH.

An increasing number of studies have suggested a theory of continuum between BD and schizophrenia. Through the observation of several measures such as genes, outcome, symptoms, and treatment response, many similarities have been observed between the two disorders (Yamada *et al.*, 2020). Some work has been done using rs-fMRI to examine this proposed continuum with interesting results. One study found clear trends in global connectivity (GC) where patients with BD exhibited lower GC compared to controls, and patients with schizophrenia exhibited lower GC compared to those with BD (Argyelan *et al.*, 2014). This finding supports the theory of continuum where schizophrenia sits on the far end of a spectrum and BD is in the middle compared to healthy controls. However, while global trends could be identified, similar trends in local FC within brain regions was not observed.

MDD

MDD is a disorder characterized broadly by a high level of negative emotions, and a lower level of positive emotions. Specifically, lower levels of emotions such as happiness and hope, and higher levels of emotions such as sadness and guilt (He *et al.*, 2019). It is a widespread disorder that affects as many as 16.2% of the US adult population. Of that population, over half say their lives have been moderately or severely impacted by the disorder (Kessler *et al.*, 2003). With its wide impact and symptoms, MDD has been a focus of study in the field of rs-fMRI for a long time.

Much of the literature in rs-fMRI has concluded that MDD is a disorder characterized by widespread network dysfunction. This dysfunction has been found primarily in networks and areas relating to emotional regulation. These include the DMN, salience network, affective network, and the prefrontal cortex (Kaiser *et al.*, 2015). Kaiser and colleague's meta-analysis reported hypoconnectivity between the frontal-parietal network and the bilateral posterior parietal cortex. Additionally, hyperconnectivity was found between the default network and much of the medial prefrontal cortex, as well as with the middle temporal gyrus.

Other work has focused on attempting to link the FC in the brain with certain symptoms of MDD. One study reported that positive and negative affect of the disorder could be linked to abnormal FC in the brain (He *et al.*, 2019). Here, having a higher negative affect was correlated with decreased FC between the right posterior hippocampus (HIP) and left dlPFC/mPFC. Lower positive affect, on the other hand, was associated with increased FC between the left striatum and left dlPFC. Given that the HIP and PFC are involved in emotion regulation and that the striatum has been associated with positive feelings, these correlations have strong implications for the source of negative and positive affect in the brain.

Many studies have attempted to find useful biomarkers in the brain that can predict susceptibility to MDD. One of these potential biomarkers may lie in the left middle frontal gyrus. A study using fALFF found that patients with MDD had a level of fALFF in the left middle frontal gyrus that was comparable to their siblings, where both had higher levels relative to healthy controls (Liu *et al.*, 2013). This is not the only area implicated in the heritability of MDD. Another study also found the right insula and left cerebellum to be possible biomarkers (Liu *et al.*, 2010). Here, ReHo was investigated and it was observed that patients with MDD and their first-degree relatives shared lower levels of ReHo in the right insula and left cerebellum relative to healthy controls. Both studies show that rs-fMRI metrics can be useful markers to determine risk.

Attempts have been made to try and distinguish between MDD and healthy controls based on the FC patterns of the brain. A commonly used method in this pursuit is MVPA (Ma *et al.*, 2013; Zeng *et al.*, 2012; Zhong *et al.*, 2017). One study reported an accuracy of 94.3% when applying the method to the whole brain (Zeng *et al.*, 2012). Another study extended this to two independent samples to further confirm these findings with the first episode, drug naïve patients (Zhong *et al.*, 2017). They reported an accuracy of 91.9% in the first sample and 86.4% in the second sample. Both studies reported abnormal connectivity in the cerebellum and cerebellar areas that gave it high discriminatory power. Another study extended the MVPA and applied it to the cerebellum area rather than the whole brain and achieved an accuracy of 90.6% (Ma *et al.*, 2013). This study also confirmed the involvement of the cerebellum in MDD. Another commonality is the abnormal connectivity found in visual areas of the brain inside the cerebellum such as the fusiform gyrus.

Resting-state fMRI has also been used to categorize and predict treatment response in patients with MDD. Due to the heterogeneous nature of the disorder, treatment is a difficult and long process that some do not take to. Areas of the brain that could help differentiate between those who are treatment resistant and those who are treatment sensitive are the frontal and limbic brain regions, and regions involved in visual recognition (Dichter *et al.*, 2015). Specifically, those who responded to treatments well were seen to have higher connectivity between the frontal and limbic brain regions, which are associated with control over emotions. The visual recognition areas such as the lingual gyrus and cuneus also exhibited abnormal connectivity, which may support the growing theory that visual recognition areas of the brain play a part in emotional control. Dichter *et al.* (2015) also found that connectivity in the subgenual cingulate cortex (SCC) was associated with response to treatment from TMS and antidepressants. The SCC has also been implicated in another study on the effectiveness of TMS by Fox and colleagues. Here it was found that the connection between the dlPFC and the SCC was anticorrelated with the effectiveness of TMS (Fox *et al.*, 2012). Taken together, these findings implicate FC in the SCC as being a good predictor for treatment response.

Research Domain Criteria (RDoC)

The National Institute of Mental Health (NIMH) initiated the RDoC project in 2009, which is an integrative framework for investigating mental disorders. Due to the complex nature of the brain, it can be difficult to make psychiatric diagnoses, especially given the incidences of comorbidities or neurobiological heterogeneity within a disorder. Therefore, the RDoC takes a systematic approach to the classification of disorders, with six major domains of human functioning defined: negative valence, positive valence, cognitive, social processes, arousal/regulatory, and sensorimotor systems. Each of these domains contains constructs, or behavioral mechanisms and responses, which are measured using different units of analysis including genetic, behavioral, and self-report assessments. These constructs are also heavily influenced by environmental and neurodevelopmental factors. The RDoC approach was not intended to provide a multifaceted account of disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM), but rather designed to make future revisions to the DSM and International Classification of Diseases (ICD), which are limited by their representation of broad syndromes (Cuthbert, 2015). This may accelerate progress in the field of rs-fMRI and psychiatric disorders, as research groups focus on linking psychiatric phenotypes to RSFC.

Limitations and Challenges

Despite the recent advancements in rs-fMRI, some limitations and challenges still exist. One limitation in rs-fMRI is intra-individual variability, which may be due to a variety of causes, such as time-of-day, diet, blood pressure, or cognitive load (Specht, 2019). This results in reduced levels of test–retest reliability of rs-fMRI measures in studies utilizing repeated-measures designs in which the participants are scanned multiple times over a specific timeframe. Variabilities in the resting-state signal within individuals are also region-specific, with brain regions involved in working memory, inhibition, attention, and language showing higher levels of intra-individual variabilities than that of the somatomotor or auditory network (Chen *et al.*, 2015). This poses a challenge in using rs-fMRI for clinical examinations, since various physiological or mental changes could possibly yield unreliable results. On the other hand, differences between individuals are less of a hindrance than differences within an individual, since inter-individual differences have been utilized in functional connectotyping or "fingerprinting" studies, which show that robust inter-individual differences allow for the identification of a single participant from a group (Amico and Goni, 2018; Finn *et al.*, 2015; Miranda-Dominguez *et al.*, 2014). Furthermore, understanding individual differences in RSFC can better aid in uncovering individual susceptibilities to different psychiatric disorders, since brain regions affected by most psychiatric disorders tend to have high individual variability (Mueller *et al.*, 2013).

A limitation of FC methods focusing on the association between brain regions is the lack of information about causal interactions, or the directionality of brain activity. Reid and colleagues suggest redefining FC research to better understand the causal interaction among neural entities, rather than simply describing FC as the statistical associations between brain signals, as is typically described (Reid *et al.*, 2019). Thus, using the term FC as an umbrella term may benefit the field by creating a more unified concept of FC, with causal inference being the main goal. Detailed steps regarding this unified FC framework are discussed by Reid and colleagues, encompassing theoretical, methodological, and confounding properties of the data (Reid *et al.*, 2019).

Challenges are also present in the analysis of rs-fMRI data, in which the analysis methods chosen for one study may not be suitable for another. For instance, if a population of individuals with altered local connectivity is studied, ReHo would be a more sensitive method than ICA to study RSFC, due to ReHo being more robust in extracting local brain information. Therefore, differences in analysis pipelines between studies could lead to variabilities and fewer reproducible results (Griffanti *et al.*, 2016). Another point of concern is the high dimensionality of rs-fMRI data, in which methods such as ICA or principal component analysis are used to reduce the dimensionality by parcellating the whole brain into smaller areas, but the optimal number of brain units to be used is still not clear (Bijsterbosch *et al.*, 2020). This causes further variability in rs-fMRI results. Additionally, challenges may arise in head-motion correction, such that different motion correction techniques may lead to different RSFC results (Maknojia *et al.*, 2019). This is in part due to the various motion correction protocols that exist and lack of an ideal protocol, but can be improved by transparency in reporting the motion correction parameters used in each study. A major challenge in rs-fMRI is the fractionation of the field, as Bijsterbosch and colleagues discuss, due to the many different analysis methods being used by different research groups, which contributes to the formation of research silos (Bijsterbosch *et al.*, 2020). In their review paper, a best-practice guideline is laid out to combat the challenges of rs-fMRI brain representations and move the field forward in a unifying manner.

A major challenge in using rs-fMRI to study psychiatric disorders is the occurrence of comorbidities, in which a participant with one psychiatric disorder may also possess another. Psychiatric disorders such as schizophrenia, BD, ADHD, ASD, and MDD are not only common, but also commonly expressed together, with a clinical overlap in symptoms and shared genetic risk factors (Doherty and Owen, 2014). This poses a difficulty in the development of successful biomarkers using rs-fMRI, since there may be overlapping brain regions affected among the psychiatric disorders. An example can be seen between schizophrenia and BD, which both exhibit dopamine dysregulation and may share susceptibility genes (Murray *et al.*, 2004). Using rs-fMRI, Argyelan and colleagues have shown that in both schizophrenia and BD, significantly lower connectivity in the paracingulate gyrus and right thalamus are observed compared to that of healthy controls (Argyelan *et al.*, 2014). This signifies overlapping FC patterns between schizophrenia and BD. Another example is BD and MDD, in which both reveal increased RSFC between the striatum and dorsolateral prefrontal cortex, in addition to increased cerebral blood flow in the right caudate and putamen for both disorders (He *et al.*, 2019). Even if patients do not exhibit comorbidities of different psychiatric disorders, it may be difficult to classify a psychiatric patient to a particular disorder, due to the shared regional FC patterns of various psychiatric disorders. More research is required to develop robust classification, with possible considerations such as familial history, genetic expression, and psychological exams added to rs-fMRI-based biomarker systems.

Conclusion

The use of rs-fMRI has been shown to be multifaceted and capable of being utilized to measure various brain properties, ranging from FC to graph theoretical measures. From these measures, we can better understand alterations in functional brain connectivity in a range of psychiatric disorders. In this paper, we discussed some roles rs-fMRI has had in better understanding the following psychiatric disorders: ADHD, ASD, BD, schizophrenia, and depression. By using metrics such as RSFC, ReHo, ALFF, and graph theoretical measures, researchers have better understood how different functional brain networks in psychiatric populations deviate from the norm and whether or not specific drug interventions have helped restore specific functional brain properties. Future advancements in rs-fMRI techniques will allow for the development of robust biomarkers for various psychiatric disorders. Despite challenges in rs-fMRI such as intra-individual variability and overlapping psychiatric disorders' resting-state properties, much progress has already been accomplished in the field, as partially outlined here, and technological advances will aid in the development of robust biomarkers.

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