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TECHNICAL REVIEW

Resting developments: a review of fMRI post-processing methodologies for spontaneous brain activity

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Abstract Analytic tools for addressing spontaneous brain activity, as acquired with fMRI during the "resting-state," have grown dramatically over the past decade. Along with each new technique, novel hypotheses about the functional organization of the brain are also available to researchers. We review six prominent categories of resting-state fMRI data analysis: seed-based functional connectivity, independent component analysis, clustering, pattern classification, graph theory, and two "local" methods. In surveying these methods, we address their underlying assumptions, methodologies, and novel applications.

Keywords Resting state · Functional connectivity · Brain networks

Introduction

Entering a cocktail party with three friends, each of us might intermingle—meet new people, loiter by the hors d'œuvres—but throughout the evening we would no doubt exchange glances, watch for indications that all is well, or subtly communicate that it may be time to leave.

Upon exiting, the traditional mapping of new social connections might be discussed as we recount the people we met and the new connections that were formed. However, a much less tangible aspect of the social dynamic is the intermittent communication that maintained the link throughout the party.

These two facets of social connectedness find correlates in models of brain connectivity, which have been roughly categorized as either anatomical or functional. While anatomical connectivity may be understood as the concrete pathways of potential information exchange (such as collected phone numbers and email addresses in the social realm), functional connectivity may be better defined as the intermittent interactions maintaining those lines of communication.

But how would we summarize and describe these dynamic connections? One early definition established functional connectivity as "the temporal correlation of a neurophysiological index measured in different brain areas" [1]; however, over the past two decades, the shift in focus beyond mere correlation has led to the development of increasingly complex frameworks to describe functional relationships between brain regions

In the case of our party, how would we describe the dynamic interactions throughout the evening? Would we choose an individual, perhaps a central figure such as the host, and describe her interactions with each of the guests (*seed-based functional connectivity*)? Would we map out the predominant lines of conversation (*independent component analysis*) or the cliques that formed and disassembled throughout the evening (*clustering*)? Would it be more appropriate to map and abstract the lines of communication (*graph theory*) or search for delineating patterns of activity (*pattern classification*)? Or would we disregard the

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question of connectivity and simply describe the behavior of the guests individually (*"local" approaches*)? Each of these approaches requires a unique methodology, each is based in specific assumptions about the structure of social interactions, and each implies an optimal description. Before beginning an analysis, it would be advantageous to consider these aspects—likewise, with respect to the brain.

Over the past decade, researchers examining functional connectivity using **"resting-state" functional magnetic resonance imaging (fMRI) data** have witnessed a dramatic increase in the analytic options for describing and summarizing the functional organization of the brain. Although, by convention, we will often use the term "resting-state" to denote the data for which these analyses have been largely developed, we also recognize the controversies surrounding this designation [2,3]. While other terms have been adopted to supplant "resting-state" (e.g., "intrinsic" and "spontaneous" [4]), and, when contextually appropriate, have become practically interchangeable, we will maintain the convention of "resting-state" due to its referential role within the field's literature. Nevertheless, it is crucial to recognize that the methods described here are not limited to data acquired during a "resting" condition, and can equally be used as a **model-free** analysis for any **steady-state** fMRI data set (e.g., [5]).

Numerous studies and reviews have explored the implications of various pre-processing steps (e.g., [6–11]); however, only a few to date have broadly addressed post-processing techniques (for a recent review of functional connectivity methodologies with emphasis on the computational aspects, see: [12,13]; or for emphasis on clinical applications, see: [14,15]). In the following review, we will address the diverse array of post-procesing techniques available, with a focus on the theoretical presuppositions of each for exploring brain organization and function (see Fig. 1).

We will identify six analytic categories as they are applied to resting-state fMRI data:

1. seed-based functional connectivity
2. independent component analysis
3. clustering
4. pattern classification
5. graph theory
6. "local" methods[1]

We will discuss their different underlying theoretical assumptions and provide a basic methodological review for their implementation (see also Table 1). Such a framework may also help to highlight analytic techniques that could be further explored and developed. Given the wide scope of this review, we will only attempt a general intuition for the different measures. Thus, the aim of the current review will be to offer an introduction to analytic methodologies for resting-state fMRI data.

Seed-based functional connectivity

Seed-based functional connectivity analysis is the correlation between activity in an *a priori* region-of-interest (ROI), or "**seed region**", and activity in all other voxels in the brain. Another widely used approach is to correlate the activity of several distributed ROIs.

The technique was initially applied to resting-state fMRI data by Bharat Biswal et al. in 1995 [16]. Using a seed region in the motor cortex, resting-state functional connectivity was shown to replicate patterns of motor task activation.

The straightforward statistics and comprehensible results have made seed-based functional connectivity a popular technique. But despite the statistical transparency, the technique suffers from the primary drawback of requiring *a priori* selection of seed regions or reduction to a limited number of ROIs. Among the predominant techniques for determining functional connectivity, seed-based procedures are the most explicitly model-based [12].

Techniques

Seed-based analysis comprises two basic steps:

1. extraction of a model time-series from a specified area; and,
2. quantifying the similarity between the model time-series with the time-series from other voxels or ROIs.

In its simplest form, the correlation of an averaged ROI time-series with all other voxels is clear-cut and easily implemented. Long-facilitated by general fMRI data processing **software** such as AFNI[2] and SPM,[3] other software packages have recently emerged focusing specifically on streamlined processing of resting-state functional connectivity using MATLAB in conjunction with SPM: "REST"[4] and "MATLAB Toolbox for Functional Connectivity"[5] [17].

Over the past decade, assessing functional connectivity with seed-based approaches has expanded to include

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[1] We use the term "local" to denote methods that do not address long-distance functional connectivity, but rather assess local voxelwise activity.

[2] http://afni.nimh.nih.gov/afni/.

[3] http://www.fil.ion.ucl.ac.uk/spm/.

[4] http://sourceforge.net/projects/resting-fMRI/.

[5] http://groups.google.com/group/fc-toolbox.

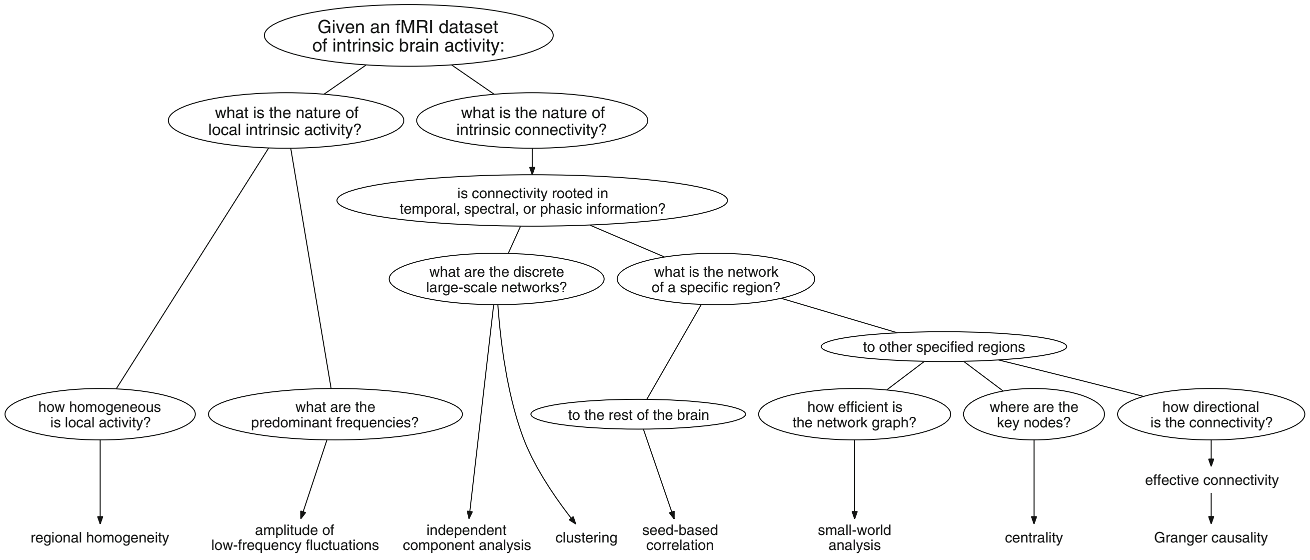

Fig. 1 A flowchart of possible questions that could be addressed with current methodologies given a resting-state fMRI data set

assorted signal processing and statistical techniques aimed at extracting more refined and considered relationships between regions. The following overview will address several of the innovations developed for both steps of the seed-based analysis.

Time-series extraction for a seed region raises issues regarding the most viable method to purify signal from a set of contiguous voxels. The conceptually basic method is averaging the value at each time point, thus cancelling out extraneous noise. A novel **interactive** implementation has recently been made available with the aforementioned analysis package AFNI. *InstaCorr* allows the selection of a seed region to be virtually simultaneous with the mapping of the correlation map. It is possible to modify the radius of the seed region and the degree of spatial smoothing (traditionally implemented by defining the size of a Gaussian filter that assigns a value to each voxel based on the weighted average of surrounding voxels), thus facilitating the exploration of these decisions on resultant correlation maps. The significance of seed size and spatial smoothing decisions becomes relevant when considering the signal-to-noise ratio of the data, assumptions about hemodynamic response throughout the brain, and the desired anatomical specificity of the resultant functional connectivity maps.

More computationally advanced alternatives, such as **principal component analysis (PCA)** have also been implemented for time-series extraction. Essentially, PCA transforms the seed region time-series into a set of “components” that successively account for the greatest amount of variance in the data. Zhong et al. recently demonstrated that using PCA to extract the signal from an ROI for regression-based functional connectivity analysis could improve the accuracy and true positive rate for detecting the default-mode[6] and motor networks, when compared to averaging over the seed region [21]. Their method has the advantage of combining data-driven optimization of the model time-series with statistically straightforward model-driven regression, thus capitalizing on the strengths of both techniques.

After a model time-series has been extracted, myriad statistical techniques are available for **quantifying the relationship** between the seed region and other voxels or ROIs. As each addresses different aspects of the signal, each also implies specific hypotheses about the mode of communication assessed with functional connectivity. The **blood oxygen-level dependent (BOLD) signal** reflects the response of **deoxyhemoglobin (deoxy-Hb)** concentration to changes in local neuronal activity and is determined by vascular (blood velocity, blood volume: “neurovascular coupling”) and metabolic (oxygen consumption: “neurometabolic coupling”) factors. The analytic tool employed inherently makes certain assumptions about the temporal dynamics of the deoxy-Hb response across the entire brain.

For instance, **temporal correlation** (or **covariance**) can describe synchronous fluctuations, whereas **cross-correlation** can accommodate lags in communication between areas. These approaches would be appropriate if neurovascular coupling were globally consistent; however, if we cannot make

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[6] The “default-mode network” consists of medial prefrontal, posteromedial, and inferior lateral parietal cortex, and received its name due to greater activity during the baseline “resting” condition [18,19]. For a recent review, see: [20].

that assumption, then a statistical method which is insensitive to the temporal domain might be more suitable.

While cross-correlation quantifies the relation between two signals in the time-domain, **coherence** operates equivalently in the frequency-domain. Coherence thus provides a means for assessing functional connectivity that is insensitive to inter-regional differences in neurovascular coupling dynamics [22,23]. Shifts in the frequency spectrum do not alter the degree of coherence (just as lags in the time-domain do not alter cross-correlation coefficients), considering the low-frequency spectral band in which functional connectivity is detected [16,24,25], low-pass filtering at 0.1 Hz (or even lower) is an essential preprocessing step for this method. Higher frequencies due to cardiac or respiratory artifacts would otherwise interfere in coherence analyses. Furthermore, different networks have been shown to correlate at distinct low-frequency bands at rest [26,27], and are modulated in the low-frequency domain during motor [28] and cognitive effort [29].

Another approach, rather than looking at the magnitude of the spectral information, is to explore the **phase-spectrum delay** between regions. For example, Sun et al. developed a novel method of addressing latency between regions in conjunction with connectivity through the combined analysis of phase-delay and coherence [30].

When more than one seed region is analyzed, the *specificity* of functional connectivity to only one of the regions is a critical issue. **Partial correlation** (or **multiple regression**) reveals the functional connectivity between a pair of regions, removing influences from others [31]. For example, partial correlation has been used to parcellate the thalamus with respect to cortical regions, by eliminating the influence of all other cortical regions [32]. The influential role of the posteromedial component of the default-mode network in the networks functioning has also been demonstrated using such methods [33].

The definition of functional connectivity is often described within the neuroimaging literature in contrast to **effective connectivity**, which addresses the *directionality* of influence between regions. While numerous techniques have been developed to address causal interactions in fMRI data, one popular approach in resting-state analysis is **Granger causality** [34]. The analysis assumes that better *prediction* is an indication of *influence*, and tests whether past values of time-series *A* better *predict* future values of time-series *B* than past values of time-series *B* alone. It has been used to address control of the default-mode network [35,36] and the changing influences between networks with respect to age [37]. Nonetheless, due in part to temporal blurring induced by the hemodynamic response, the potential utility of effective connectivity to resting-state fMRI data, without experimental manipulation, remains a source of debate (see the section *Correlation and Causality* in [13]) and methodological innovation (e.g., [38]). The rest of the current review, however, will focus on methods for the analysis of functional connectivity.

Applications

Early studies of resting-state functional connectivity focused on describing well-charted neural systems from the cognitive neuroscience literature, such as the motor cortical network [39,40], visual network [41–43], a language network, including Broca's and Wernicke's areas [44], a cerebellar-prefrontal network [45], and networks based in the amygdala and hippocampus [40]. Of interest to the emergence of the“resting-state” fMRI research field, Greicius et al. were the first to use seed-based functional connectivity to map the default-mode network in 2003 [46], thus effectively linking the resting-state functional connectivity literature (whose lineage is traced to Bharat Biswal et al. 1995 [16]) with the “resting-state” of cognitive neuroscience (which emerged from Shulman et al. 1997 [18] and several publications in 2001 by Marcus Raichle, Deborah Gusnard et al. [47,48]).

While a significant concern of these initial studies was to establish the validity of studying functional connectivity in the absence of an attributable cognitive or behavioral state, more recent research into resting-state functional connectivity has taken advantage of its strengths in order to address topics that are beyond the practical scope of task-based fMRI. For instance, the detection of functional subdivisions within complex regions usually requires large-scale meta-analysis (e.g., striatum [49], anterior cingulate [50], and cerebellum [51]); however, systematic placement of seed regions throughout such areas has revealed similar subdivisions in striatum [52,53], anterior cingulate [54], and cerebellum [55,56], as well as amygdala [57,58], medial temporal cortex [59], cross-modal auditory-visual connectivity during rest [60], and the red nucleus [61]. Other studies have observed the presence of novel subdivisions with the precuneus [62] and the default-mode network [36], somatotopic organization within the motor cortex [63], differentiation of the dorsal and ventral attention streams [64], a hippocampal-parietal memory network [65], and a fron-to-parietal control network [66]. The efficiency of these approaches for exploring functional neuroanatomy with data sets comprising merely dozens of participants, rather than a meta-analysis of an equal number of studies, is evident.

Furthermore, these approaches have been fruitful in cross-species animal research. The default-mode network is found in the anesthetized macaque monkey [67], as well as the posterior parahippocampal network [68], and posteromedial subdivisions reflecting the anatomical tracing literature [62]. In the rat, the sensorimotor and visual networks have been mapped [69,70]. The general flexibility of resting-state scanning has enabled rapid innovation for addressing cross-species questions using parallel non-invasive techniques.

Amidst these advances, the issue of how to best optimize ROI-selection persists as the most evident weakness of seed-based approaches. Meta-analyses have provided an effective strategy for probing specific distributed systems. For instance, in order to examine the test-retest reliability of resting-state data, Shehzad et al. [71] specified three sets of ROIs, derived from four different and representative studies [72–75]. However, the further development of computationally-oriented, *a priori*-free selection criteria is still much needed.

Discussion

In summary, seed-based approaches constitute one of the primary analytic strategies for resting-state data, and offer an unambiguous means of quantifying functional connectivity. The limitations of *a priori* seed region selection, size, and shape, are a substantial drawback, as these choices can alter findings, and may bias the results. Furthermore, proper delineation of subdivisions becomes a methodological question in itself.

Potential solutions to these issues take the form of several other prominent methodologies (ICA, cluster analyses), which will be discussed in the following sections.

Independent component analysis

Assuming the brain is organized into a number of functionally discrete networks, an optimal analytic technique would determine the signals unique to each network from the data alone. **Blind source separation** (or **decomposition**) techniques address the problem of determining distinct components within a set of signals with minimal *a priori* assumptions. Rather than requiring the specification of seed regions to derive networks, **independent component analysis (ICA)** has gained prominence in resting-state fMRI data analysis as a method to determine the spatial distribution of distinct functional connectivity networks [76–79]. In comparison with the aforementioned seed-based approaches, ICA offers several advantages:

- It does not require assumptions about locations of networks.
- Networks can be distributed, without a focal seed region.
- It can be conducted with minimal preprocessing, as noise is extracted as components during the analysis.

Nonetheless, ICA is not the perfect answer to functional connectivity analysis, as will become clear from a closer inspection of the methods.

Technique

The aim of ICA is to delineate maximally independent spatial or temporal components. As fMRI data generally consists of more spatial than temporal data points, spatial ICA is more widely applied. ICA assumes that an fMRI data set consists of a mix of independent signals from a number of spatially distributed sources, and decomposes the data into several such independent components.

Many software tools are available to implement ICA. For example, probablistic ICA with MELODIC[7] is available with FSL; GIFT and FIT[8] can be applied using SPM; cortex-based ICA can be conducted in BrainVoyager 2000[9]; and ICASSO offers ICA reliability analysis[10] [80].

Although ICA claims to require no initial assumptions, the approach does require specification of the number of components. While toolboxes such as MELODIC can automatically estimate this number through prior PCA-based estimation, in practice, the dimensions are often estimated by the user.

In deriving independent components, ICA extracts components based in “artifactual” signal such as scanner noise, head movement, and physiological “artifacts” (e.g., cardiac and respiratory signal) alongside functionally meaningful networks. While the extraction of these “noise” components is advantageous—such artifact extraction has even been proposed as a preprocessing step for seed-based correlation analysis [81]—it requires that the user exercises judgment in separating meaningful networks from noise components [82–85], or develop classification techniques [84,86]. Thus, while minimal *a priori* assumptions are required, ICA does require substantial *a posteriori* selection of valid components, whether though visual inspection or automated methods.

Group-level ICA analysis is a substantially more complicated issue due to the difficulty of selecting corresponding components across individuals [87,88]. The order of ICA components is unconstrained, and cannot be used for selection. One approach for classifying a network consistently across individuals is **template matching** [89,90]. Individual-level independent components are first discarded based on temporal criteria (e.g., valid components must consist of characteristic low-frequencies). Then, all remaining individual-level components are compared to a set of researcher-defined spatial templates for “goodness of fit”. Although template matching is an effective means for consistent selection of analogous networks across individuals, it relies on assuming appropriate templates.

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[7] www.fMRIb.ox.ac.uk/fsl/melodic/index.html.

[8] http://icatb.sourceforge.net/.

[9] http://www.brainvoyager.com/BrainVoyager.htm.

[10] http://www.cis.hut.fi/projects/ica/icasso/.

Group-level ICA would seem like the obvious choice for derivation or such templates; however, it too presents significant complications. One proposed solution is to conduct **group-level ICA** on co-registered and concatenated individual datasets. The group-level results of **temporal concatenation ICA (TC-ICA)** can then be used as templates in order to derive individual-level maps. Such approaches have been fruitful in discerning distinct cortico-cerebellar networks [91].

Dual-regression ICA has recently been developed as a method to derive more accurate group-level comparisons based on TC-ICA templates. After creating the templates, spatial regression is conducted on the individual level to extract a temporal model for a second temporal regression. The resultant statistical maps are then used for group-level analysis [25,92,93].

An alternative, proposed by Calhoun et al. [94], addresses the problem of combining components across individuals. Rather than use a template-matching scheme, the individual data sets are entered into a single ICA analysis, and then **back-reconstructed**. This procedure ensures that the components are consistently ordered across individuals.

Other automated group-level approaches aim to cluster components across subjects based on spatial configurations (e.g., **partner-matching** [95]).

Applications

ICA has been responsible for a significant shift in understanding large-scale network structure in the brain. Owing to its exploratory, data-driven aspect, several networks have been consistently classified across studies and subject groups [78,79,96,97]. ICA-derived networks are consistent across participants [79] and scan sessions [98,99], with the default-mode network demonstrating particularly robust reproducibility and cross-research selection reliability [100,101]. ICA has been applied to infants as young as 24 weeks [102] and has also been widely used to study clinical populations (e.g., Alzheimer's disease [89,103], mild cognitive impairment [104], depression [105], schizophrenia [106], Huntington's disease [107], lateral sclerosis [108], temporal lobe epilepsy [109], and non-communicative brain damaged patients [110]).

The impact of data-driven approaches such as ICA were demonstrated in a recent paper by Stephen Smith et al. [111]: 20 ICA components were extracted from resting-state data from 36 individuals, as well as 7,342 peak coordinates from the collection of functional studies contained in the BrainMap database. The sets of components were highly consistent, demonstrating the structural persistence of these functional networks at rest, and suggesting that these networks may provide a foundation for discerning the modular building-blocks of cognitive functions.

Discussion

Blind-source analysis methods are data driven, and do not require specification of seed-regions. However, they are nonetheless hypothesis driven, because the "true" number of components present in the data is not known, and has to be more or less empirically chosen (techniques for the automatic calculation of the number of components exist, and have demonstated high test-retest reliability, but there is poor concordance across the various estimation algorithms [99]). The reproducibility of ICA is another significant challenge. The ICA algorithm begins with a random assumption with each iteration, thus producing results that are variable across analyses.

Secondly, following component identification, the selection of meaningful components remains a problem. Manual selection through visual inspection is prone to human error. While automated methods are promising, they either rely on preexisting templates (i.e., template-matching) or are computationally intensive (i.e., back-reconstruction). Novel methods for automated ICA dimensionality and group-level analysis is an area of ongoing development. Nevertheless, the automaticity and model-independence of ICA makes it a convenient tool for whole-brain functional connectivity analysis.

One dubious assumption at the foundation of ICA is the independence of network signals in the brain. Considering the extraordinary degree of interconnectivity between the entire brain, striving to derive independent networks would not seem to be an effective method at generating a physiologically plausible model of functional organization. Daubechies et al. have recently suggested that the ICA algorithms used in fMRI data analysis are tuned to detect sparsity, rather than independence [112], a more likely model.

Clustering

Although model-free approaches to resting-state functional connectivity, such as ICA, overcome one of the greatest problems associated with model-based (i.e., seed-based) approaches, namely, the dependence of findings on the initial selection of seed ROIs, these model-free approaches still entail a degree of subjectivity and human judgment both in dimensionality estimation and in the selection of "meaningful" components or networks. One approach that is gaining popularity in the attempt to overcome these issues is the application of clustering techniques to resting-state data.

Clustering is essentially a family of mathematical techniques that searches for patterns in data. More specifically, clustering is the unsupervised partitioning (classification) of data into subsets (clusters) so that observations assigned to the same cluster are more similar to one another than they are to observations assigned to another cluster.

Table 1 A select digest of representative "resting-state" research articles for each section

Section	References	Desription
Seed-based functional connectivity	Biswal et al. 1995 [16] Margulies et al. 2007 [54] Sun et al. 2005 [30]	Makes use of temporal correlation from a selected region-of-interest, or "seed" region. Now termed "seed-based" functional connectivity, the technique relies (and expands) on the basic premise, which defines it as "the temporal correlation of a neurophysiological index measured in different brain areas"
Independent component analysis	De Luca et al. 2006 [96] Damoiseaux et al. 2006 [79] Beckmann et al. 2005 [78]	Assumes that resting-state data is composed as a mixture of unknown, but uncorrelated signals. Decomposes rs-fMRI data into spatially or temporally independent components (networks)
Clustering	van den Heuvel et al. 2008 [113] Salvador et al. 2005 [114] Cohen et al. 2008 [115]	A family of statistical techniques that searches for patterns in data. Unsupervised partitioning (classification) of data into subsets (clusters)
Pattern recognition	Craddock et al. 2009 [116] Zhu et al. 2008 [117] Shen et al. 2009 [118]	Involves the application of multivariate pattern classification algorithms. These algorithms use the characteristics of objects to identify classes to which they belong. In fMRI data, these characteristics are generally brain activation or connectivity patterns, and the classes are usually brain or cognitive states
Graph theory	Bassett and Bullmore 2007 [119] Achard and Bullmore 2007 [120] He et al. 2009 [121]	A mathematical tool whose aim is to characterize aspects of a network structure using a variety of measurements. One such approach characterizes the brain as a *small-world network*
Local methods	Zang et al. 2004 [122] Zou et al. 2008 [123] Zuo et al. 2010 [25]	Two measures which quantify the function of the brain locally can be implemented in resting-state fMRI studies: *regional homogeneity* (ReHo) and *amplitude of low frequency fluctuations* (ALFF)

In the context of resting-state functional connectivity analysis, clustering algorithms have been used to partition the brain into groups (clusters) of voxels or regions that are functionally connected with one another [113], or that exhibit similar patterns of functional connectivity with the rest of the brain [115]. The former represents a method akin to ICA, aimed at detecting distinct large-scale resting state networks, while the latter is an emerging approach aimed at breaking the brain down into its smallest detectable distinct functional units. The main results of these studies are briefly reviewed below, but it is worth noting that neuroimaging applications of clustering approaches are not restricted to resting-state studies, as clustering has been applied to structural connectivity (e.g., diffusion tensor imaging), task activation and neurotransmitter receptor data with equally impressive results (e.g., [124–129]).

Technique

As we have noted, clustering is a family of techniques, and researchers face a plethora of options with regard to the specific clustering approach to apply to their data. In RSFC applications, those most commonly employed include:

- **hierarchical clustering approaches**, which start by treating each data point as a singleton cluster, then, as K decreases, successively merge previously established clusters (visualized as a dendrogram or tree) (e.g., [114,115,130,131]);
- **partitional clustering (such as *k*-means)**, which determine all K clusters at once, typically by attempting to minimize intra-cluster variance (e.g., [130,132]);
- **spectral clustering approaches**, which perform an eigendecomposition of (the graph Laplacian of) the similarity matrix as an initial data reduction step, then use one of the more standard clustering algorithms (e.g., *k*-means) to perform the final partition of the data on the basis of the resultant matrix of eigenvectors (the data's spectrum) (e.g., [113]).

There are, of course, many other interesting clustering techniques with applications to resting-state fMRI data, including non-metric clustering (e.g, [133]), which hold potential as alternatives to conventional Euclidean distance-based measures. The development and improvement of clustering methods is a topic of intense research in fields such as **machine learning** (e.g., [116]), which will be addressed in the following section on **pattern classification**.

Applications

In the first application of clustering techniques to resting-state functional connectivity data, Cordes et al. [131] applied **hierarchical clustering** using single linkage to frequency-specific inter-voxel correlations. Due to the computational complexity involved, the analysis was limited to four slices covering auditory, motor and visual cortex (1,300–2,400 voxels). They detected several, mostly bilateral clusters that were readily identifiable as functionally distinct areas, including sensorimotor cortex, auditory cortex, fusiform gyrus and primary visual cortex, as well as a number of “nuisance” clusters corresponding to CSF or other artifacts. Furthermore, they demonstrated that, for the majority of clusters detected, cardiac, respiratory and motion-related contributions to functional connectivity between the voxels were minimal.

Salvador et al. [114] used hierarchical clustering and **multidimensional scaling** to identify six networks. However, their methods formed clusters that grouped regions according to anatomical location (e.g., frontal, temporal, subcortical), and thus the resultant networks differ from the resting-state networks with which we are now more familiar. In contrast, Thirion et al. [134] clustered coherence measures of resting-state data using **Gaussian Mixture Models**, and observed several plausible networks, including medial and lateral visual networks, and a bilateral fronto-parietal network, although consistency across the small subject sample was low.

Of course, many of these early clustering studies were limited by the computational capabilities available at the time. As a result, researchers were required to reduce the volume of data entered into their analyses, either by acquiring data from only a limited number of slices, rather than the whole brain [131], or by resampling the brain according to a parcellation scheme (e.g., [114,134]).

More recently however, vast improvements in computational resources have made it possible to perform clustering analyses at the voxel level, permitting the performance of analyses at a finer scale that remains close to that of the original data. Consequently, there is increasing sophistication in the methods employed and, most important, increasing convergence with the results of other resting-state analysis methods (e.g., ICA).

Two exemplars of this increased sophistication and convergence are provided by Van den Heuvel et al. [113] and Bellec et al. [130]. The first of these studies, by Van den Heuvel et al. used spectral clustering, specifically, the **Ncut** method devised by Shi and Malik [135], to partition whole-brain grey matter on the basis of voxelwise functional connectivity (expressed as temporal correlation) in 26 participants. One notable methodological advance detailed in their paper was the computation of a consistency matrix, which quantifies the frequency with which voxels were assigned to the same cluster across participants. In order to determine group-level clustering solutions, spectral clustering was performed on this consistency matrix, the result being a set of cluster solutions (networks) exhibiting the most consistent (stable) functional connectivity across subjects. Their analysis produced seven networks, strikingly similar to those identified using both seed-based analyses and ICA, including the default mode network, right and left fronto-parietal networks, and a sensorimotor/visual network.

In their paper, Bellec et al. [130] also made use of consistency matrices, in the context of a bootstrap approach to *k*-means clustering of resting-state time series, which sought to identify the most stable large-scale networks (clusters) detectable at both the single-subject and group levels. Interestingly, this approach, named “**bootstrap analysis of stable clusters (BASC)**,” also identified seven networks that were remarkably similar to those identified in other studies, including the default mode, sensorimotor, visual and fronto-parietal networks. In addition, the authors drew attention to the fact that good stability was observable at finer spatial scales (i.e., larger numbers of clusters), and the likelihood of good agreement between solutions at these finer scales and the results of high dimensional ICA analyses, such as that those of Smith et al. [111] and Kiviniemi et al. [97].

Several other papers have directly focused on clustering at finer spatial scales. These studies have demonstrated the ability of clustering methods to identify the organization of the brain at the local level, in terms of its division into functionally distinct regions, rather than at the global level of large-scale networks.

For example, Mezer et al. [132] applied the *k*-means clustering algorithm to time-dependent measures of functional connectivity to identify clusters in grey matter, white matter and thalamus that closely matched known anatomical distinctions in terms of cytoarchitecture/microstructure (e.g., Brodmann’s areas) and morphology. Interestingly, Mezer et al. concluded that their results were primarily driven by non-functional contributions to the BOLD signal, such as head motion, a suggestion that seems overly-pessimistic in the context of their consistency with the resting-state literature.

A more optimistic tone is struck in work by Cohen et al. [115], who performed voxelwise hierarchical clustering on the basis of the eta^2 index, which quantifies the pairwise similarity between voxels’ functional connectivity profiles. Cohen et al. showed that, in a single participant, hierarchical clustering was highly successful at partitioning regions exhibiting different functional connectivity profiles, thus likely constituting functionally distinct areas.

Discussion

In summary, clustering approaches applied to resting-state data have proved highly successful at detecting known functional, anatomical and architectonic subdivisions in the brain. They are not without their flaws however, with the most significant stumbling block being that almost all available techniques require the user to define a number of clusters (*K*) into which to partition the data. Because the true number of clusters is often unknown (referred to as the **“cluster validity” problem**), researchers typically compute multiple solutions, then use some metric of “goodness” to determine the “optimal” cluster solution from those produced. Unfortunately, however, there is no single or best measure of solution optimality, and different studies have employed different methods or sets of methods (e.g., silhouette distance; linkage threshold; between-group similarity of clustering solutions; minimized Ncut cost; information criteria). Ultimately, it is unlikely that clustering will escape the involvement of human judgment, as users have to assess the suitability of the clustering results against known or hypothesized networks or functional subdivisions. However, the advantage of clustering approaches (as well as ICA approaches), is that this human judgment is incorporated at a high perceptional cluster- or network-level, rather than during the early-stage ROI selection, as is required in seed-based approaches.

Pattern classification

In recent years **multivariate pattern analysis (MVPA)** (also referred to as **multi-voxel pattern analysis**) has gained increasing importance in fMRI data analysis (for reviews, see [136,137]). Like other multivariate approaches (e.g., ICA, clustering) MVPA takes into account multi-voxel patterns of brain activity or connectivity. Information contained in these patterns can then be decoded by applying powerful pattern-classification algorithms. This method thus incorporates spatially distributed patterns of activity into the analysis, unlike univariate methods which treat every brain voxel independently.

MVPA has become a valuable fMRI data analysis method for classifying cognitive states and drawing relationships between neural activity (or connectivity) and these states. MVPA was mainly initiated in the domain of visual perception [138–140], but was extended to other types of mental states as well [141]. MVPA has also been applied to the study of neural coding [137,142], and utilized in the field of memory research [143].

Technique

In MVPA, **pattern classification** algorithms assign objects to **classes** using specific **features**. In the analysis of fMRI data, these characteristics are generally patterns of brain activation or connectivity and the classes are brain states or cognitive states. Introductory guides are available [144,145], as well as easy to use software [146].

In brief, application of the technique entails the following basic steps:

1. Choosing the **features** that are descriptive of the objects and a way to represent them.
2. **Selecting** a subset of these **features** to be used for classification.
3. Selecting the **pattern classification algorithm**.
4. Dividing of the data in two parts: a **“training set”** and a **“testing set”**.
5. Utilizing the training set to train the **classifier** with the features and the prespecified classes of objects. The classifier thus “learns” a functional relationship between the features and the classes.
6. **Testing** of the classification algorithm for its generalization capabilities with the testing set, and measuring the percentage of correct classifications.

Effective feature selection is necessary to prevent the classifier from overfitting the data or reducing complexity. This can be done automatically by using mathematical methods that select relevant discriminative features [147]. Another possibility is **manual feature selection** (e.g., the limitation to certain ROIs). This manual method is of course application specific.

When choosing the proper classifier, certain issues should be considered. In MVPA, a supervised machine learning algorithm is usually used for pattern classification. Examples of such algorithms are support vector machines (SVM), neural networks, or linear discriminant analysis (LDA). They can be used to learn a functional relationship between the features and the classes. Rarely unsupervised machine learners (e.g., clustering) are utilized. Unsupervised algorithms find structure in data without prior knowledge about classes, but one cannot be sure whether it is the desired structure that is found, so supervised learners are normally applied. It is important to state that there is no single algorithm that works best on all problems. There are some classifiers like SVMs that achieve good results for a wide range of problems, but caution is required when relying on this. One thing that can be incorporated when choosing a classifier is knowledge about the functional relationship between the features and the classes. If this relation is assumed to be linear a linear classifier should be used (e.g., LDA, linear SVM). In the non-linear case a technique that can account for non-linearity (e.g., non-linear SVM, neural networks) is advised, although this does not always lead to better results [139]. Finally there are different ways to divide the data into “training set” and “testing set” for testing the generalization capabilities of the classifier. One often-used possibility is cross-validation (see [144] for advantages of this technique).

Applications

Multivariate pattern classification as applied to resting-state fMRI data is still a young field of research. Similar to its application in task-based studies, it has primarily been used for **disease-state prediction** to discriminate between patients and healthy control groups on the basis of resting-state functional networks.

In a study of attention-deficit / hyperactivity disorder (ADHD), Zhu et al. used **principal component analysis-based Fisher discriminative analysis (FDA)** [117] and **pseudo-FDA** [148] for classification. On the basis of **regional homogeneity** as features, they were able to discriminate between patients with ADHD and healthy subjects. The results were also used to identify discriminative regions. They achieved a high generalization rate when comparing results to **linear support vector machines** and **batch perceptrons**.

Wang et al. examined patients with an early stage of Alzheimer's disease using a linear classifier based on ICA and FDA [149]. They put particular emphasis on the choice of features for classification. Correlation coefficients of two intrinsically anti-correlated networks were utilized as features to distinguish patients with Alzheimer's disease from healthy controls. When comparing their classification results to features based on whole-brain functional connectivity, their approach outperformed the latter. They thus concluded that the two anti-correlated networks play an important role in early stages of Alzheimer's disease.

Schizophrenia was investigated by Jafri et al. who used a **three-layer feed-forward neural network** approach to analyze ICA components [150]. Shen et al. utilized a **nonlinear unsupervised-learning classifier** for discrimination and to map statistically relevant regions [118]. They used a **nonlinear learning technique (locally linear embedding)** to reduce dimensionality of the resting-state data. Then **C-means clustering** was applied to discriminate between schizophrenia patients and healthy controls. Classification error rate was very low and it performed better than the linear classifiers it was evaluated against.

Major depressive disorder was also the subject of investigation. Craddock et al. used a **support vector machine classifier** to distinguish healthy persons from depressed ones [116]. Their focus was on testing different feature selection methods. They incorporated **filter** and **wrapper feature selection** and also reliability information. This reliability measure improved the results of classification significantly.

These approaches demonstrate that disease-related differences in resting-state functional connectivity are feasible for disease state prediction and for the identification of discriminative regions of the brain.

Discussion

In summary, the application of MVPA has been successfully expanded to the field of resting-state fMRI. While MVPA has been primarily used in the small domain of disease state prediction, it also has potential for wider applications in addressing differential functional connectivity across general brain states. MVPA has also proven promising in pharmacological studies where medications and placebos are contrasted.

The small number of studies involving MVPA and resting-state fMRI give rise to many open questions. For instance there are a lack of comparative studies. While a portion of the aforementioned studies do compare different features, feature selection methods or classifiers in a very narrow context, this is far from sufficient to assess various strengths and weaknesses for different applications. For example, it would be valuable to investigate if or how involved features and methods could be applied to diseases other than those included in each respective study.

Another important issue that has not yet been investigated is the influence of spatial resolution. While spatial resolution is a crucial factor for all fMRI approaches, it is of particular interest for pattern classification which aims to detect subtle patterns in the data. Many analyses described here, particularly those involving networks and pattern classification, are conducted at a relatively low-resolution scale (50–100 units). Significant efforts and methodological advances are needed to understand how such findings may generalize to higher resolutions.

Graph theory

The mathematical field of graph theory has developed over centuries to characterize various aspects of network structure. Building on the functional connectivity approaches previously discussed, graph theory can be applied to the brain by positing that ROIs (or single voxels) constitute **vertices**, and the connections between them, **edges**. This insight makes it possible to exploit the already existing graph theory knowledge to analyze functional brain networks. As the techniques thus far presented have predominantly focused on mapping the spatial extent of networks, graph theory, in contrast, provides tools to describe and characterize various intrinsic properties of network configuration (e.g., efficiency and modularity).

Technique

Given a selected set of regions from a resting-state fMRI data set, **each ROI corresponds to a vertex**, the **edges are defined by the functional connectivity between vertices** (see Fig. 2). An edge can be assigned between two vertices if the correlation coefficient exceeds a certain threshold, or each correlation coefficient itself can be used to **weight** each edge. A **path** in a graph is a sequence of vertices in which all succeeding vertices are connected by edges, and the length of a path is the number of edges traversed. The

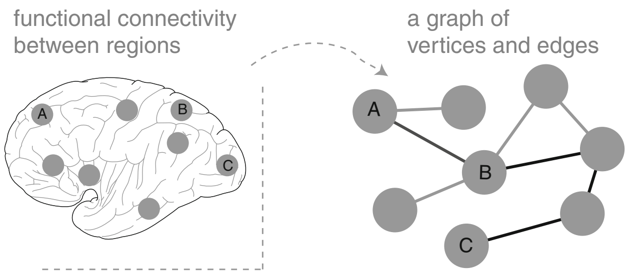

Fig. 2 A schematic illustration depicting the transformation from ROIs to graph representation. The **distance** between vertices *A* and *C* is 4, as marked with the *darkened line*. The **degree** of vertex *B* is 4, *A* is 2, and *C* is 1, as measured by the number of edges connecting to each. Vertex *A* is part of vertex *B*'s neighborhood, but *C* is not, because it is not directly connected to *B* by an edge

distance between two vertices of a graph is the minimum length among all paths connecting them. The **degree** of a vertex is the number of edges connecting to it. The (open) neighborhood of a vertex is all vertices that are connected to it by an edge.

Diestel offers a general introduction to graph theory [151]. For an overview with respect to applications to brain connectivity, see the recent review by Bullmore and Sporns [152]. For implementation, a MATLAB-based "Brain Connectivity Toolbox" is also freely available.[11]

Applications

Numerous measurements have been developed for the characterization of graphs. We will describe **local** measures (assigning values to each vertex individually) and **global** measures (characterizing the graph as a whole).

One simple concept to measure the *global structure* of a graph is the **degree distribution** $P(k)$. This function gives the likelihood that a randomly chosen vertex from a graph has degree k. fMRI data have been found to have various degree distributions: power law [153], exponential [154] and exponentially truncated power law [155,156]. These three different findings could be related to the different spatial scales employed by the studies (ROIs *vs.* voxels).

Degree distribution offers information about the number of vertices which have a very high degree, termed: "**hubs**". Such hubs have been the topic of a recent study by Buckner et al. [157], who found that regions of high "hubness," or **centrality**, were most prone to deterioration in individuals with Alzheimer's disease. **Eigenvector centrality** has also recently been applied to the analysis of fMRI data using both linear correlation and spectral coherence as distance measures [158]. The computational advantage of eigenvector centrality allows for the inclusion of all voxels in the brain.

Degree distribution can also be used to explore the vulnerability of a graph with **random error** and **target attacks** [159]. In "random error", a random vertex is repeatedly deleted from the graph, while "target attack" repeatedly deletes the vertex with the actual highest degree. After each step, the vulnerability of the graph to the attack is then measured using a variety of tools, among them: *clustering coefficient*, *average path length*, *small-world properties*, and *local* and *global efficiency*, which will be further discussed below.

These concepts can be applied to probing the *resilience* or *vulnerability* of the brain's functional organization. For instance, Achard et al. [155] showed that networks observed in wavelet transformed resting-state fMRI data are more resilient to target attacks than a random scale-free network but equally resilient to random error.

One concept used to measure the *local structure* of a graph is the **local clustering coefficient**, which checks whether the triangle between a vertex and two connected vertices is closed by an existing edge. The measurement counts all existing triangles in the neighborhood and divides them by the number of theoretically possible triangles. The clustering coefficient has been interpreted as a measure of resilience to random error [160], since if a vertex is deleted, its neighbors stay connected. The local clustering coefficient can also be used as a global local measurement by averaging over all vertices of a graph.

Another measurement for the global topology is the **average path length** of a graph, which is the mean of all distances between any pair of vertices. The average path length can be understood as a measurement of how well integrated a graph is.

Measures of **modularity** describe how well a network is divisible into separate components ("*modules*") with high internal connectivity, but sparse inter-module connections. He et al. found that recognizable sensory and cognitive systems a highly interconnected modules with sparser intermodule connections [121]. Shen et al. [161] analyzed the **modularity function** by Newmann [162]—which finds dense substructures in a graph by taking the ratio of the number of *existing* to *theoretically-possible* edges within a community— and two similar approaches called **cut** and **Ncut** on resting-state fMRI data. They concluded that whole-brain parcellation is feasible with the three approaches, and that the **Ncut** algorithm is the appropriate way to do so.

Ferrarini et al. [163] described a different approach. Their technique is based on a **non-degree biased cluster coefficient** [164], and the subsequent application of a hierarchical clustering algorithm [165]. Using this approach they showed modularity between frontal, subcortical, parietal and temporal regions of the brain.

Combining these measurements one can characterize a network as being a **small-world network**. This term was first introduced by Watts and Strogatz in 1998 [166], who

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[11] http://www.brain-connectivity-toolbox.net/.

demonstrated that certain real-world networks have a significantly higher clustering coefficient than their random counterpart, without a significantly higher average path length. They proposed that this could also be the case for many other real-world networks—a hypothesis that was later confirmed by findings ranging from road maps [167], food webs [168], airplane passenger traffic [169], metabolite processing networks [170], mobile call graphs [171], ownership links among German companies [172], and, of course, brain networks [173].

There are certain empirical and theoretical reasons for understanding the brain as a small-world network [119]: the brain supports both modular and distributed processing of information. Considering that network architecture underlies cognitive processing, a network with a small topology is most efficiently configured for various scales of information exchange: high clustering supports modular processing, while short distances support distributed processing. Small-world networks thus maximize efficient parallel processing, minimize wiring costs, and are fault tolerant—all optimal properties of a central nervous system.

Many studies have examined the small-world characteristics of brain networks, and they will not all be reviewed in detail here. For a comprehensive review of this particular topic, please see the superlative article by Bassett and Bullmore [119]. Small-world analyses seem to have particular relevance for the study of disease states. For example, Supekar et al. [174] performed a study on wavelet transformed resting-state fMRI data acquired from patients with Alzheimer's disease. They observed a significantly reduced clustering coefficient in patients with Alzheimer's disease. Furthermore, the clustering coefficient distinguishes participants with Alzheimer's from controls with high sensitivity and specificity, suggesting the decreased small-world property may be a viable diagnostic marker.

Nakamura et al. [154] used resting-state fMRI data acquired at different time-points during recovery from traumatic brain injury. They showed an increasing "small-worldness" during the recovery process. Hayasaka and Laurienti [175] made a comparison of small-world characteristics between region-based and voxel-based brain networks. They showed that voxel-based networks have a higher clustering coefficient ratio than region-based networks, suggesting that voxel-based networks are more "small-world–like".

In addition to the "classical" small-world parameters, **local** and **global efficiency** can be used to measure the network's ability for information transmission [176]. Although these measurements are very similar, they have the conceptual advantage that they can deal with disconnected graphs. Achard and Bullmore [177] showed lower efficiency in frontal and temporal cortical and subcortical regions in an elderly group of participants. From a more methodological perspective, Wang et al. [178] found different network efficiencies depending on which atlas was used to determine ROIs.

Discussion

Graph theory offers a host of tools for characterizing brain organization that extend beyond the network itself. While graph theory is effective at analyzing topology, such as small-world or modularity and even changing topology (by deleting hubs), it is not appropriate for the analysis of real-time dynamics. In a sense one also has to pay for the generality of the various graph theory metrics with a loss of specialization. Due to the computational complexity of many of the described approaches, their application to the whole-brain set of voxels is not feasible, and they are in practice applied to groups of voxels of a set of ROIs. Since these regions of interest have to be defined *a priori*, the same problems of ROI selection outlined earlier apply. Undeniably, graph approaches require assumption in order to reduce the complexity of the network. Analytic approaches are computationally difficult, and one must often work with heuristics.

"Local" methods

Although the majority of analytic techniques for resting-state fMRI data address functional connectivity, approaches that address local activity are also possible.

Two such "local" measures are: the **amplitude of low frequency fluctuations (ALFF)**, which calculates the voxel-wise magnitude of specific frequency bands in the frequency domain, and **regional homogeneity (ReHo)**, which is computed only from the direct neighborhood of single voxels. The measures are conceptually and practically straightforward, and are complementary to the other resting-state post-processing tools.[12]

Amplitude of low frequency fluctuations

ALFF is defined as the total power within a defined low-frequency range (for example: 0.01–0.1 Hz) [25,179]. Fractional ALFF (fALFF), a measure with reduced sensitivity to physiological noise, can be obtained by taking the ratio of the low-frequency power to the sum across the whole frequency range [123].

It should be noted that several physiological and neural factors can impact low frequency fluctuations; for example, Biswal et al. observed that low frequency fluctuations were suppressed by hypercapnea [180], and that ALFF was higher

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[12] Both techniques can be implemented using the MATLAB toolbox REST: http://groups.google.com/group/fc-toolbox.

in gray matter than in white matter [16]. Some studies showed that ALFF measures are susceptible to possible artifactual findings in the vicinity of blood vessels and cerebral ventricles [25,123]. Special care has to be taken when reporting results of ALFF calculation near these brain areas.

Areas within the default mode network have been observed to exhibit higher ALFF during resting-state than other areas [25,123,179,181]. ALFF of visual cortices in eyes-open condition was reported to be significantly higher than in eyes-closed condition [181]. Zuo et al. revealed significant and highly reliable ranking orders of ALFF among anatomical parcellation units [25]. The method has also been applied in studies which compared clinical populations to healthy controls. Children with ADHD showed decreased ALFF in inferior frontal cortex and increased ALFF in anterior cingulate and left sensorimotor cortex [182]. Patients with schizophrenia showed reduced ALFF in lingual gyrus, cuneus and precuneus and increased ALFF in left parahippocampal gyrus [183].

Regional homogeneity

Zang et al. [122] initially proposed ReHo to measure the functional coherence of a given voxel with its nearest neighbors based on the hypothesis that abutting voxels within a functional brain area synchronize their metabolic activity under certain conditions. Homogeneity is measured using **Kendall's coefficient of concordance (KCC)**, a calculation of similarity which uses ranking—a more stable measure—rather than a linear statistical measure.

ReHo analysis is highly affected by the magnitude of spatial smoothing and the size of the "neighborhood" (7, 19, or 27 voxels, respectively) included in the analysis [122]. The pattern of resting-state brain activities obtained using ReHo has been shown to be consistent with the default mode network [122,184]. In a study of cerebellar seed-based functional connectivity, He et al. integrated ReHo into the seed-selection process by using the areas of high ReHo to derive coordinates for masks regions [185].

ReHo analysis has been widely applied to the study of brain diseases. For instance, in a group of patients with schizophrenia ReHo values are decreased in bilateral frontal, temporal, occipital, cerebellar posterior, right parietal and left limbic lobes [186]. Boys with attention deficit hyperactivity disorder showed decreased ReHo in frontal-striatal-cerebellar circuits and increased ReHo in occipital cortex [187]. A study also found significant decreases of ReHo in the posteromedial cortex of patients with Alzheimer's disease [188]. Decreased ReHo in frontal, temporal, parietal lobes and increased ReHo in putamen, frontal, parietal lobes were found in remitted geriatric depression patients [189]. Parkinson's disease (PD) patients showed decreased ReHo in putamen, thalamus and supplementary motor areas and increased ReHo in cerebellum, primary sensorimotor cortex and premotor areas [190]. Paakki et al. have demonstrated decreased ReHo in right temporal, frontal and bilateral cerebellar crus 1 areas and increased ReHo in right thalamus, left frontal areas in patients with autism spectrum disorders [191].

Another variation on the ReHo approach was implemented by Uddin et al. to measure the **network homogeneity (NetHo)**, which is the KCC for each voxel within a pre-defined network mask [192].

Discussion

In summary, ReHo and ALFF methods are both easily implemented, straightforward techniques which can be used to characterize spontaneous local brain activity. While initial innovations have made use of such voxelwise techniques for subsequent functional connectivity analysis, much room remains for exploration.

Conclusions

We hope that the above review has provided a flavor of each of the many options for interrogating brain organization with resting-state fMRI data, the assumptions and advantages of each, and the kinds of questions and hypotheses that they can be employed to evaluate. The release of the *1,000 Functional Connectomes* resting-state data consortium[13] leaves little want for analytic fodder [193]. Thus, the challenge in study design may rather shift to cross-polinating methodologies. An exciting area of research has recently blossomed which explores the effects of task and mental state on spontaneous "resting" brain activity [29,194–197].

Looking forward, the most promising resting-state approaches will successfully integrate multiple sources of information concerning the connectivity of the brain, for example: task-based functional localization providing information about co-activation, diffusion measures of structural connectivity and known anatomical connectivity, as well as data obtained with EEG or MEG, and the simultaneous combination of EEG or optical imaging with fMRI. Several studies have already made considerable strides in these directions (e.g., [62,111,198–204]), suggesting that researchers will soon witness further exciting methodological advancements that will elevate the field of resting-state functional connectivity to the next level of excellence.

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[13] http://www.nitrc.org/projects/fcon_1,000/.

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