Chapter

Resting-State fMRI Advances for Functional Brain Dynamics

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Abstract

The development of functional magnetic resonance imaging (fMRI) in quiescent brain imaging has revealed that even at rest, brain activity is highly structured, with voxel-to-voxel comparisons consistently demonstrating a suite of resting-state networks (RSNs). Since its initial use, resting-state fMRI (RS-fMRI) has undergone a renaissance in methodological and interpretive advances that have expanded this functional connectivity understanding of brain RSNs. RS-fMRI has benefitted from the technical developments in MRI such as parallel imaging, high-strength magnetic fields, and big data handling capacity, which have enhanced data acquisition speed, spatial resolution, and whole-brain data retrieval, respectively. It has also benefitted from analytical approaches that have yielded insight into RSN causal connectivity and topological features, now being applied to normal and disease states. Increasingly, these new interpretive methods seek to advance understanding of dynamic network changes that give rise to whole brain states and behavior. This review explores the technical outgrowth of RS-fMRI from fMRI and the use of these technical advances to underwrite the current analytical evolution directed toward understanding the role of RSN dynamics in brain functioning.

Keywords: resting-state networks, resting-state fMRI, big data analysis, high strength magnetic imaging, effective connectivity, parallel imaging, independent components analysis

1. Introduction

Resting-state, functional, magnetic resonance imaging (RS-fMRI) focuses on spontaneous low-frequency fluctuations (< 0.1 Hz) in the BOLD signal that occur in the absence of task-related activities. The functional significance of these fluctuations was first recognized by Biswal et al. [1] in a study in which subjects were told not to perform any cognitive, language, or motor tasks. After determining the correlation between the BOLD time course of a seed region identified by bilateral finger tapping and that of all other areas in the brain, the authors found that fluctuations in the left somatosensory cortex were highly correlated with homologous areas in the contralateral hemisphere. This observed correlation led to their conclusion that such "resting networks" manifested the functional connectivity of the brain.

The observation of spontaneous, synchronous fluctuations occurring between brain regions has since stimulated studies that have identified as many as 7 to 17 other stable networks [2–5], although seven are consistently agreed upon. The visual network, for example, is highly consistent across various studies and spans much of the occipital cortex. The importance of this network structure is reflected in the amount of bodily energy devoted toward brain and, presumably, network maintenance. On a relative basis, the energy consumed by the brain is approximately 20% of the total bodily energy consumption, despite a relative mass of only 2%. Of the brain's consumption, some 60 to 80% of the energy is used while "resting," which is for internal communication and support alone. By contrast, elicited activity consumes less than 1% of the brain's energy resources. Resting networks thus appear to constitute a fundamental organizational architecture for the functional properties of the brain [5].

Because characterization of resting-state networks (RSNs) in the human brain relies on the analysis of temporal fluctuations in the blood oxygenation level-dependent (BOLD) signal, the delineation of RSNs has been directly linked to the ability of fMRI to detect neural activity [6]. Using T2-weighted signal intensity and blood oxygenation as the contrast agent [7], fMRI imaging offers a relatively facile procedure for the acquisition of brain activity data [8, 9], one that has been exploited in numerous studies.

Early investigations [10] confirmed fMRI suitability for RSN determinations. The advantages of RS-fMRI in its own right have since become apparent [8], including ease of signal acquisition, minimal requisite effort from the patients, and proficiency for identifying functional areas in different patient populations. Recent studies have demonstrated that imaging of difficult-to-monitor patients, such as pediatric subjects and patients with disorders of consciousness, that is, coma, vegetative, and minimally conscious states, are able to undergo RS-fMRI. The procedure also offers the capability for functional differentiation, when patients perform specific tasks that are designed to target a single network such as motor, language, memory, vision, attention, and sensory networks.

Despite limitations in use of the BOLD signal, especially the dichotomy between the temporal resolution and the temporal scale of the neural activity measured, RS-fMRI studies have continued to expand, propelled not only by technical improvements at the level of signal acquisition—e.g., parallel MRI imaging, data acquisition [11], and computational advances for preprocessing and feature extraction [12]—but also by theoretical and mathematical tools that have amplified the functional interpretations of quiescent and task-based brain activity [13, 14]. One outcome of these developments has been a more precise view of how RSNs are functionally organized and how this in turn modulates communication within the brain, that is, a more dynamic view of information exchange and regulation [15].

The need to address cognitive dysfunction in the light of these more precise and advanced models of brain operation has also benefitted from this work. The DMN has been an early and continuing focus of study for the exploration of alterations during Alzheimer's and other degenerative diseases, which tend to adapt to the structural profile of the network [16]. There is also increasing interest in examining the neurological changes that occur as a result of traumatic, vascular, or oncological influences, which, because of their focal impact, can affect multiple network domains [17, 18]. Stroke, especially, is a leading cause of disability and dependency in adults—in 2010, there were about 11.6 million incident ischemic stroke events in the United States, and by 2030, an additional 3.4 million adults are predicted to have strokes.

In light of RSN discoveries, the understanding of how these focal effects influence brain functioning has also evolved. Stroke lesions are therefore understood not only to result in focal, location-dependent neurological symptoms but can also induce widespread effects in remote regions in the affected and unaffected hemispheres. Consistent with this, while baseline measures of stroke severity represent the current level of diagnostic and prognostic capability, patients' neurological impairment sometimes exceeds what would be expected from stroke magnitude; that is, growing evidence emphasizes the role of distributed neural networks in the generation of brain states and the control of behavior that could account for stroke outcomes affecting behavior [18, 19]. Such possibilities implicate a need for still more comprehensive RSN tools that can explore the relationship between whole-scale RSN dynamics and behavior in clinical settings.

This review discusses the evolution in the study of brain RSNs as an outgrowth of the methodological principles that have advanced fMRI imaging of neural brain activity. It covers the advances in technical approaches for data retrieval and processing that have provided the basis for improved network analysis and that build on conceptual insights into functional network associations based on connectivity associations. It also considers both the frequently used data-driven approaches and their contribution to larger-scale explorations of brain dynamics based on causal connectivities and topological variation, now being applied in more global models. Improvements in these latter are likely to offer the prospect of clinical insights that can relate network operation to disease states, such as stroke.

2. Modern resting state network methodology

2.1 Resting-state network detection as an outgrowth fMRI

RS-fMRI relies on spontaneous low-frequency fluctuations (< 0.1 Hz) in the BOLD signal, which measures the contrast between the diamagnetic effect of oxy-hemoglobin and the paramagnetic effect of deoxy-hemoglobin [7]. The dependence on the BOLD signal means that RS-fMRI shares advantages that accrue to fMRI—the ability to monitor neural activity, albeit indirectly—but also disadvantages that characterize its use. Chief among these limitations is fMRI's temporal resolution, which is dependent on the hemodynamic response time. Since the hemodynamic response is much slower than the underlying neural processes, temporal information of spiking events is heavily blurred and typically requires the use of mathematical processing, like that of the general linear model [9], or experimental block protocols, to infer event-related, signal activity. With processing, temporal resolution in the 100 ms range can be achieved, which is roughly tenfold slower than the neural events being monitored. By contrast, the spatial resolution of fMRI is considerably better, as well as much superior to electrical and magnetic recording techniques, though slightly reduced from that of MRI. Due to the need for fast acquisition of time series information, the spatial resolution in the case of fMRI is limited somewhat by the signal-to-noise ratio (SNR). With single-shot imaging, for example, the acquisition time for fMRI is reduced and the pixel size must be increased to obtain a satisfactory SNR. With a suitable increase in magnetic strength [20], however, SNR is sufficiently enhanced to yield a pixel size slightly under 1 mm.

A key factor in the use of RS-fMRI is the measurement of neural activity fluctuations rather than spiking events per se. Neural activity fluctuations (low-frequency

and indirectly measured using the BOLD signal) exhibit substantially different time courses from those of neural firing (high-frequency and direct). Accordingly, while the representation of individual, high-frequency spiking events is itself heavily blurred, the slow neural activity fluctuations detected by the BOLD signal display a well-resolved temporal pattern. Measurements of these fluctuations thus provide for accurate functional inferences obtained from voxel-to-voxel comparisons. Together with the high spatial resolution that is an inherent feature of fMRI, RS-fMRI currently constitutes the most powerful tool available for assessing the functional connectivity properties of brain networks.

2.2 Technical advances in RS-fMRI

2.2.1 General acquisition

The early detection of RSNs by Biswal et al. [10] used a standard 1.5 T clinical scanner equipped with a three-axis head gradient coil and a shielded birdcage radio frequency coil. A time course of 512 echo-planar images (EPI) from a 10 mm axial slice (flip angle 34^{O}) was obtained every 250 ms and the respective data sets were band pass filtered at <0.08 Hz. Using these moderate parameters, the study demonstrated a high degree of temporal correlation in the sensorimotor cortex and in several other regions associated with motor function. Departing from this early protocol, most RS-fMRI scanning now employs 3 Tesla (3 T) field strength to obtain clinically reliable data and gradient-echo echo-planar imaging (GE-EPI) sequences [21, 22]. Because RSN acquisition is T2* weighted, GE sequencing is typically used in preference to T2 weighted spin echo sequences [23]. Whole-brain coverage is required, with high in-plane resolution (about 2 to 3 mm) and a repeat time (TR) of 2 to 3 s [24] to capture the distributed configuration of RSNs.

While most RS-fMRI imaging studies rely on these or comparable protocols, current resting-state procedures also have available an arsenal of advances that can supplement the current standard conditions. Among other developments, these include procedures for increasing data acquisition speed [22], enhancing spatial resolution by improving SNR capabilities with high-strength magnetic fields [20], preprocessing corrections for motion artifacts [25], and big data acquisition capability [26].

2.2.2 Rapid data acquisition

The advent of parallel imaging has stimulated an increasing number of studies that have sought to harness the speed of data acquisition made possible by its development [11]. Fast RS-fMRI has been motivated by various objectives. Firstly, increasing data acquisition speed can assist multivariate approaches while also retaining a comparable level of sensitivity. For clinical groups for whom RS-fMRI is an increasingly used diagnostic approach, this affords greater interpretive power [27]. The use of rapid data approaches also enables better discretization of dynamical changes associated with connectivity changes, which are posited to reflect distinct brain states [28–30]. Additionally, rapid RS-fMRI data acquisition can help to identify artifactual contributions, such as cardiac and respiratory rhythms [31, 32]. With low sampling rates, these sources of physiological noise often alias to lower, functionally associated, frequency bands [33] making them difficult to resolve since task time series are unavailable in the resting state [34].

Parallel MRI imaging employs multiple receiver coils for fast data acquisition. These capture spatially distinct data sets due to the differential spatial profiles of the receivers. The most widely used configurations are Multiband (MB) and 3D echo planar imaging (EPI) [35]. Multiband pulses excite a set number of slices simultaneously, ranging from MB2–4 up to MB8, which are then unfolded. Faster sampling rates can be achieved by reducing the overlap between slices with techniques like GRAPPA or CAIPIRINHA [36–39]. Both of these techniques operate in the frequency domain and are based on the principle that k space information within a given point is partially retained in neighboring points of the k domain, which can be retrieved during scanning. The CAIPIRINHA technique is an evolution of the GRAPPA technique, in which there is an applied acceleration along the K_y and K_z directions and an additional phase offset (slice-shift) along the K_z direction. These modifications yield unique frequency patterns and therefore simpler aliasing to solve. In 3D EPI, the slice direction is embedded with a phase encoding gradient. Each repetition excites the whole imaging volume, requiring a smaller flip angle. The use of the encoding gradient also accelerates data acquisition, which when used in conjunction with the CAIPIRINHA approach, can still achieve faster retrieval [40].

Another approach used for rapid data retrieval is that of Magnetic Resonance Electroencephalography (MREG). This approach derives its speed from the ability to traverse the k-space with a stack of spiral trajectories [41], which significantly reduces sampling recovery, enabling whole data scans in less than 100 ms. A drawback is the relatively low spatial resolution of about 3 mm. However, the method offers the significant advantage of greatly facilitating dynamic functional connectivity analyses [42] that require large data sets.

2.2.3 High strength fields in RS-fMRI

Although most RS-fMRI studies are conducted at 3 T, higher field strengths offer advantages not provided by standard 3 T field strength. Higher field strengths yield correlation coefficients that are consistently higher for resting networks, due to the linear dependency of the SNR on the magnetic field [43, 44]. The higher correlation and enhanced signal combine to improve signal detection and lessen the amount of mathematical processing needed for signal resolution, which means that the spatial characteristics of resting networks can be measured with greater precision than at lower field strengths. The chief advantage of higher fields thus is an improved spatial resolution, which enables a better spatial delineation of network maps.

Additionally, due to the higher SNR, the temporal reliability of mapping is also improved, lending the technique a broader clinical range. For example, RS-fMRI at 7 T has been shown to enhance the temporal reliability of sensorimotor and language network detection in preoperative planning [45] and for mapping habenula resting-state networks involved in anxiety and addiction disorders [46].

On the other hand, use of higher field strengths has several drawbacks, including longer sampling intervals, inhomogenous magnetic field properties, and the logarithmic growth in specific absorption rate (SAR) with increasing field strength [22]. In particular, the higher spatial resolution requires long repetition times, due to the need to include data acquisition from the whole brain to accommodate the brain-wide distribution of major RSNs. Additionally, inhomogeneities in magnetic field affect receive and transmit RF coil sensitivity [47], which requires correction for accurate connective mapping, while SAR constraints on echo planar imaging affect multiband pulses [22].

2.2.4 Big data

Current increases in study size are generating exceptional amounts of data in their attempts to explore ever-larger studies of RSNs in brain operation. The Human Connectome Project [48] and the 1000 Functional Connectomes Project [49] have released in excess of 1000 RS-fMRI data sets, for example. Traditional data-driven methods for handling RS-fMRI data, such as independent components analysis and graph theoretic approaches, become unwieldy and lose descriptive power at elevated data levels. The need for suitable techniques to address big data handling is thus currently stimulating the development of new preprocessing methods and analytical adaptions that can accurately reflect network structure and dynamics [50].

Large data sets are typically characterized in three ways, the amount of data, termed Big Volume, the diversity of information, termed Big Variety, and the reliability of the data as a representation of brain functional architecture, termed Big Veracity. Big-volume RSN data sets are characterized by an informational mass exceeding that of a single very large computer processing capacity [50], though not so large as whole genome data sets. Big variety reflects the diversity of information within a single data set but can also extend to comparisons between two data sets, such as occurs with two or more imaging data sets or with other information modes like behavior, for example, the Open Access Series of Imaging Studies (OASIS) project with more than 500 subjects worth of data [51]. Big Veracity considers the various data sources that can lessen the ability to extract meaningful network data, including noise, resolution artifacts, data inconsistencies, and acquisition errors.

Initial steps involved in big data handling entail preprocessing to remove the effects of sources that diminish the ability to assess meaningful data. Several preprocessing steps are becoming more accepted, but these can also greatly increase computational load. The most widely used is the minimal preprocessing pipeline [50]. Its goal is to provide RS-fMRI data for analysis with a minimum level of quality, which also minimizes the loss of meaningful data. This can be of substantial benefit to researchers lacking access to high-powered preprocessing of Big Volume data sets. Currently, preprocessing software tools tend to adopt a parallelization approach with functions running in parallel for tools such as statistical parametric mapping (SPM) [50].

Analytical procedures have tended to emphasize graph-theoretic tools that are amenable to statistical mechanical methods. One of the most used topological tools is Mapper, developed by Singh et al. [52], which adopts a persistent homology approach. Mapper lends itself to big data analysis because the global organizational structure is divided into a series of overlapping slices. These are reconstructed *via* the use of common points located in the overlapping zones, which serve as a vehicle to orient topology.

3. Assessing functional connectivity in RSN data

Several approaches have been developed to analyze imaging data after preprocessing and band-pass filtering. These include approaches driven by research focus as well as those dictated by the data itself, the so-called data-driven and model-free approaches. Each can be used to delineate the distribution of functional connections that characterize major networks of the brain.

3.1 Regions of interest seed-based analyses

Functional connectivity determinations extend fMRI measurements of brain activity by providing likelihood estimates of functional associations between neural activity zones [1]. In practice, seed-based analyses identify deviations from independence between distributed and often distant sources of neural activity and a region of interest; that is, statistically significant deviations from independence reveal dependent relationships that functionally connect activity zones. Extending these relationships to multiple zones enables the construction of connectivity maps that become identified with unique networks. Exploiting a seed-based ROI strategy, for instance, one comprehensive study of resting-state fMRI sequences from 1000 healthy adults [53] revealed seven functionally connected networks at coarse resolution and 17 at fine resolution. The simplicity and interpretability of the ROI technique make it procedurally facile and a frequently adopted approach. However, the method relies entirely on user-defined ROIs and so is limited for network discovery by its a priori, selected criteria.

3.2 Independent components analysis (ICA)

In light of this caveat, coupled with the evolution of mathematical models and improved computational capabilities, there has been a paradigm shift from that of imposing initial conditions, that is, seed-based ROIs, on the data to that of extracting patterns of brain activity directly from the raw time series. The main example of this approach is independent components analysis. In this approach, the time series signal is assumed to be due to multiple spatio-temporal processes that are statistically independent of each other. By extracting the independent signals, various time courses of specific brain regions can be constructed and grouped into maps representative of their spatial distribution.

Independent components analysis (ICA) aims at overcoming the selective bias toward priors contained in seed-based approaches by relying on direct data-driven interrogation for assessment of functional connectivity [54]. To do so, ICA posits an inherent representation of independent factors in the captured time series data. Its goal is to decompose the vector representation of these factors, Z, as a product of a combinatorial matrix and the spatially independent components where:

$$Z = NC + E = \sum_{j=1}^{J} n_j c_j + E,$$

Here, N is a $T \times J$ combinatorial matrix with columns n_j, and C is the $J \times Nv$ matrix of independent components with rows c_j, where each c_j corresponds to component j for a cumulative total of J independent components. These components represent the networks of various functions. The elements of the matrix E are independent, normally distributed noise contributions. It is presumed that the component maps, c_j, $j = 1,\ldots, J$ contain overlapping and statistically dependent signals, but that the individual component map distributions are independent. Each independent component c_j is a vector of size Nv and represents the relative amount of a given voxel that is modulated by the activation of that component. Due to the retrieval of large data during the acquisition stage, various algorithms have been developed to estimate the components, for example, the independent components analysis with a reconstruction cost (RICA) algorithm [55].

3.3 Graph theory analysis

Another approach to the interpretation of RS-fMRI datasets employs graph theory, where activity sources comprise nodes and connectivity defines the edges that link these nodes [56]. Unlike ICA, which focuses chiefly on the strength of correlation between different domains, graph theory characterizes the features of network topology. The graph theory approach describes the interaction between nodes by means of such graph parameters as average path length, clustering coefficients, node degree, centrality measures, and level of modularity. Graph theory is thus a promising technique for exploring the integration and segregation of networks in the brain. Graph metrics like average path length, for example, reveal the extent of integration of brain networks. Centrality, on the other hand, examines whether a particular node has a central or leading role in information segregation *via* its propagation to other nodes in a network.

Increasingly, modularity assessments have been used to characterize functional adjustments occurring during behavior, network perturbations, or pathologies that affect network function and the observed values have been shown to undergo significant alteration in such pathologies as stroke [57] and psychiatric disease [58–60]. Modularity assesses the presence of functionally independent units or modules that compose resting-state networks. These are defined as clusters of nodes displaying greater functional connectivity within the group than with the rest of the brain. During task-specific activity, such clusters are reallocated, implying that the networks themselves are reorganized topologically [61, 62]. Their flexibility suggests that they operate as independent functional entities inducing [63–65] specific behaviors *via* their reallocation [66, 67].

In practice, modularity analysis [63] describes the difference between the network configuration at rest and the network reconfiguration during behaviorally altered conditions by means of a quality function (Q) [68] that maximizes the optimal modular decomposition. As expressed by Q, the modularity index provides a measure of the degree of modular segregation [69], where Q is close to one when there are few edges between modules and high density inside modules—that is, module segregation is present—and Q is close to zero when the number of connections between modules is comparable to that of random—indicating an absence of segregation.

3.4 RSN functional connectivity maps

The first demonstration of correlated spontaneous fluctuations explored somatosensory areas. Since this initial demonstration, multiple other resting networks have been discovered. Functional connectivity determinations have shown that these networks can be reliably reproduced [53], although much variation in the identification of networks is dependent on the degree of resolution achieved during scanning. Major resting networks, according to Yeo's seven network parcellation atlas [4, 53], are listed in **Table 1** and classed broadly as belonging to either sensorimotor or association groups. While numerically greater numbers of networks can be detected at finer resolution, e.g., 17 network estimate of Yeo et al. [53], generally, the 17-network determination fractionates the lesser member set into smaller network components of the seven major networks.

Network	Type	Description
Default Mode Network a	Association	Contains the dorsal prefrontal cortex, posterior cingulate cortex, precuneus, and angular gyrus
Dorsal Attention Network. n s	Association	Includes gyri adjacent to the intraparietal sulcus, cortex near the MT + complex, and both the frontal and secondary eye-fields
Ventral Attention Network r	Association	Includes the temporo-parietal junction and ventral frontal cortex
Fronto-Parietal Network p	Association	Includes the dorsolateral prefrontal cortex, the inferior parietal lobule, and the middle temporal gyrus,
Limbic Network m	Association	Contains subcortical areas including amygdala, thalamus, basal ganglia, and cortical cingulate gyrus
Visual Network	Sensory-motor	Includes the striate and extrastriate cortical regions
Somato-Motor Network	Sensory-motor	Contains the primary motor and somato-sensory cortex

Table 1.
Major resting state networks of the human brain classified according to association or sensory-motor functions. Network identification follows that of Yeo et al., [53].

4. RSN dynamics and brain states

4.1 Assessing sources of connectivity modulation

While methodological advances in RS-fMRI have made significant strides in unveiling a macro-scale, network-based architecture for the brain, how brain functions emerge from network connectivity remains uncertain. Brain states like those of sleep or altered states of consciousness undergo continually changing dynamics involving whole brain networks. These dynamics are regularly modulated by internal fluctuations in activity that can affect sensory efferent or motor afferent activity [70, 71] and alter spatiotemporal patterning [72]. The ubiquity of these influences reveals that brain dynamics involve causal influences affecting network connectivity, which can be detected with BOLD fMRI [73]. Accordingly, recent developments in RS-fMRI seek to build on functional connectivity determinations by relating causal sources of connectivity changes to brain states and behavior. Network descriptions of these have been termed effective connectivity.

4.1.1 Effective connectivity

Effective connectivity presumes that efficient causes precede their effects and that these are revealed in the time domain. Because the functional coupling among neuronal populations changes as a function of processing demands [74] it is inherently context-dependent and dynamic. Accordingly, effective connectivity has been used

to clarify sources of brain activity and the directionality of their influence. Inferences of causality are used to interpret the mechanisms that underlie neuronal dynamics and assist studies of how neuronal populations are functionally integrated [75]. In practice, models of effective connectivity seek to assess whether functional coupling is modulated under task-based manipulations and rely on fMRI data. The most common analytical methods include structural equation modeling (SEM), multivariate autoregressive models (MAR), GRANGER, and dynamic causal modeling (DCM).

DCM is perhaps the most widely employed approach for assessing effective connectivity and is based on an input-output model for a system of n interacting brain regions [76]. In this method, the activity of a neuronal population from each region is represented by a single state variable, which is perturbed by controlled inputs. DCM models report the series activity changes vis a vis the system's resting state represented by the system state vector (mathematical approximations of the system typically employ a Taylor series approximation that describes non-linear functions). Using these models it is possible to explore the dynamic character of brain activity under normal and pathological conditions. Unlike other approaches, DCM does not utilize time series data directly but combines a proposed model of the unknown neuronal dynamics with a forward model that translates neuronal states into output measurements. The description of the neuronal population activity employs a bilinear differential equation process, which is combined with the forward model.

Since the inception of the DCM, various methodological changes have extended the DCM approach [77, 78]. Recent, and more complex, models have included simulations from various prominent neuron classes, such as deep pyramidal cells, and spin stellate excitatory interneurons that contribute to the neuronal state [79]. Because of the complexity of these neuronal models, more general models have attempted to overcome their perceived difficulties in data fitting. One approach premises neural activity on generalized spiking described by Wilson Cowan spiking equations to satisfy a wider range of applications. In this adaptation, the Wilson Cowan equations are used to describe the evolution of excitatory and inhibitory activity in a population of neurons, instead of the bilinear equations used for both single and two- state DCM [80].

In a novel variant of DCM, effective connectivity analyses are conducted for large-scale or even whole-brain networks [81, 82]. This approach modifies the original DCM procedure in several ways: (i) translation of equations of state from the time to frequency domain using Fourier transformation, (ii) application of a mean field approximation across regions, and (iii) specification of conjugate priors on neuronal input. Choosing appropriate priors yield a generative model that can be used for making inferences about changes in directed connection strengths and inputs.

4.1.2 Granger causal analysis

Like DCM, Granger causal analysis provides a statistical tool for assessing directed functional connections from time series data, based on the concept that causes precede and induce their outcomes [13]. The method includes linear vector autoregressive models obtained from time series neural data, where a variable at a specific time point is modeled as a linearly weighted sum of its own past and that of a set of other variables, each represented by a vector. Minimizing estimation errors yields the set of optimal connection weights. Variable Y is said to be caused by variable X if the time series of X provides unique information not present in the prior Y series [83] that helps to predict the future Y series.

4.2 Macroscale brain organization and RSN dynamics

In principle, inferences of causality from directional connectivity determinations can be extended to brain-wide neuronal dynamics. Empirical studies from RS-fMRI, for example, show that RSNs are differentiated on the basis of their metastability and synchrony [84]. These and similar observations have stimulated models of brain function and behavior that predict that the human brain at rest operates at maximum metastability, that is, in a state of maximal network switching. Under such conditions, information flow can be said to be guided by temporally ordered sequences of metastable states [85, 86]. The existence of RSN properties like metastability thus implicates directed connectivity changes in the construction of brain states, which emerges from the dynamics of RSNs in whole brain, effective connectivity [87] in health, disease, or trauma. The methodological question that arises is that of generating a descriptive approach relating functional neuroimaging data to whole brain dynamics. Recent attempts to address this question have adopted two approaches.

4.2.1 Recurrence structure analysis

The first employs a BOLD, data-driven, computational method that leverages the method of *recurrence structure analysis* (RSA), a mathematical procedure derived from Poincare's recurrence theorem [15]. The Poincaré theorem states that trajectories of a complex dynamical system visit certain regions of their available state space more frequently over the course of time than other regions of the state space. This "recurrent" behavior can be described by a *recurrence plot method* (RP), which allows a matrix-based visualization of recurrent states. These latter are mapped into state space trajectories described by symbolic sequences [88]. Combining the structure-function modules of a brain hierarchical atlas with the optimized recurrent structures yields resting-state networks presumed to reflect time-dependent, recurrent cognitive states.

4.2.2 Landscape of informational structures

The second approach posits the governance of RSN dynamics by a ground-state global attractor. This global ground state is mathematically described as a stable stationary solution representing a point of maximal stability in a landscape of stationary points (nodes) that information flows toward or away from [89]. Similar to whole-brain models, the description of this landscape consists of coupling local dynamics with anatomical brain connectivity. The stability and instability directions of each stationary point are characterized by non-stationary solutions entering or leaving these points, respectively. This provides a framework in which coupled systems of differential equations describe individual brain regions (nodes) in terms of other brain regions and with respect to the global ground state; hence, there exists a global structure linking all stationary points. Accordingly, such points can be ordered by their level of attraction or stability and characterized by various topological measures, for example, number of energy levels (NoEL) or sensitivity to perturbations (criticality) [90], based on connectivity data. This theoretical framework has been shown to successfully account for the highly structured dynamics arising from spontaneous brain activity in RSNs [91].

5. Resting state networks in disease

5.1 RS-fMRI studies in clinical diagnosis

Given the utility of RSNs for understanding the brain's functional organization in healthy individuals, RS-fMRI has also been exploited for determining how the brain's organization is modified as the result of trauma, degeneration, or disease [92]. A majority of RS-fMRI studies have consisted of comparisons of resting-state functional connectivity patterns between groups of normal subjects and those with neurological or psychiatric impairments [93], in part due to the relative ease with which these studies can be conducted. While changes in the correlation patterns of spontaneous activity have been reported in many cases, the consistency of the correlations has varied significantly with the disease type. Studies of the default mode network in AD, for example, generally yield consistent patterning whereas network patterns in other types of diseases, for example, schizophrenia, exhibit wide variation.

Underlying mechanisms and even diagnostic markers of these dysfunctions are in many cases unknown, moreover, a hindrance to assessing how functional network changes modify behavior. This obstacle could be partially surmounted by knowing how focal perturbations impact functional and task-based connectivity. Supporting this, neuroimaging studies show that localized changes in neural activity result in distinct activity and functional connectivity changes within and between networks [93, 94]. Mapping of whole-brain effects on RSNs due to local trauma may therefore reveal how RSNs are globally reorganized following these insults. For example, the characterization of large-scale deregulations in functional connectivity may emerge from studies of selective trauma in highly interconnected core regions [95].

5.2 RS-fMRI tools for stroke-induced changes in brain organization

With this as an objective, RS-fMRI technical and analytical procedures have been exploited to interrogate RSN-based changes that occur in stroke. By definition, stroke is a clinical syndrome characterized as an acute, focal neurological deficit that is the result of vascular injury (e.g., infarction, hemorrhage) within the central nervous system [96]. It is itself a major cause of death and disability across the globe. In adults worldwide, stroke is the chief cause of acquired physical disability, and the second leading cause of mortality in middle-to high-income countries. Because the disruption is usually sudden, stroke's effects on neural networks can be directly attributed to the focal impairment, rather than to more widely extended and long-term processes, such as degeneration. Stroke frequently results from ischemia, for instance, which deprives the supply of blood to adjacent cerebral tissue [17].

Assessing the spatial locus of a stroke-based lesion requires knowledge of the brain vasculature, which assists in co-localizing fiber pathways and structural connectivity. Anterior circulation, for example, includes regions supplied by the anterior and middle cerebral arteries, which contain the ophthalmic artery. Strokes occurring within the opthalmic artery lead to monocular loss of vision. Proximal occlusion of the middle cerebral artery, on the other hand, can cause contralateral hemiparesis and hemi-sensory loss, visual field defect, and/or hemineglect [96].

5.3 Connectivity determinations in stroke diagnosis

As mentioned, stroke outcomes involve not only focal disturbances at affected sites, that is, the set of regions directly damaged or indirectly affected by the stroke, but also those more distally located that are embedded within the larger functional network that is in dynamic balance with other networks of the brain. Hence, resting-state measures of connectivity can be expected to reflect a more distributed network organization than the lesion site alone and to be correspondingly seen in spatially extended, connectivity changes.

Consistent with this, global studies of focal infarcts affecting motor behaviors characteristically display a decrease in functional connectivity involving interhemispheric homologous sensory and motor areas, which is correlated with the degree of behavioral impairment. Reduced functional connectivity between hemispheres is also seen in rodent models of stroke [97], corresponding with decreases in motor proficiency [98]. In the first few days after stroke, this involves the connectivity between the ipsilesional primary sensorimotor cortex and its contralateral homologs [99]. Similarly, RS-fMRI of the sensorimotor network in humans, including the M1, SMA, secondary somatosensory cortex, cerebellum, putamen, and thalamus regions, reveals a direct correlation between motor performance and the degree of M1 interhemispheric connectivity [100]. Structural observations are consistent with this and show that the integrity of corticospinal fibers correlates with the reduction in interhemispheric M1 resting-state connectivity [99, 101]; RSN studies of effective connectivity with DCM further show that post-stroke excitatory, ipsilesional influences from premotor areas to M1 are also reduced, decreasing M1 output for paretic hand movements [17]. Ipsilesional inhibitory influences from M1 to the contralesional M1 are also attenuated. Together, these results implicate a reduction in inhibitory interhemispheric control of M1 homologs in paretic motor movements and excitatory intrahemispheric effects from premotor areas to M1. Importantly, they also reveal the interpretive utility of combining RS-fMRI effective and functional connectivity determinations in network assessments.

5.4 Assessing topological changes in stroke

Functional determinations assist in the identification of resting networks based on characterization of connectivity number, direction, and weight. Changes in such parameters help to assess the degree to which the network has retained its functional association; that is, the degree to which it is intact. On the other hand, they do not assess connectivity topography, which reflects how the organization of the network influences information flow, which needs to be assessed with graph theoretical parameters like centrality or modularity. Recent evidence in animal models notably indicates that network topology is likely to change following stroke [98]. In a mice model, total functional connectivity increases in comparison with normal controls. Since interhemispheric connectivity is reduced in most stroke subtypes, this suggests that intrahemispheric functional connectivity is cumulatively increased, generating a new organizational network structure within the affected hemisphere; that is, a transference of interhemispheric callosal connections to intrahemispheric targets.

Diagnostic assessments of network reorganization in stroke patients, accordingly, have been required, typically employing graph theoretic modular analysis. Modular analysis of task-based studies in normal subjects, for example, shows a high level of reorganization of nodes in the frontal and temporal cortices from the resting state.

Moreover, as mentioned, complex dynamics occur between networks during task performance, which involves the reallocation of network modules. Graph theoretic analysis shows that this entails the switching of network topologies between the frontoparietal, ventral attention, and the dorsal attention areas [63–65]. In like manner, modularity determinations can be expected to show stroke-induced reorganization.

Existing studies reveal, in fact, a low-dimensional architecture following stroke [57]. The significance of this network reorganization is as yet undetermined. One possibility is that decreased modularity reflects a default strategy for efficient behavioral responses in a complex environment, which is needed to reduce the degrees of freedom in movement [102]. In healthy individuals, a higher modularity provides for exploration of varied trajectories, that is, there is a maximizing of degrees of freedom, which needs to be reduced to provide stability for tasking. In stroke, this exploratory ability is lost, together with a corresponding loss in modularity. The reduction in modularity would thus imply a reduced ability to process information effectively [57].

Methodologically, assessing this possibility would require RS-fMRI procedures capable of whole-brain modeling to determine whether and which topographical adjustments occur on a global scale [90]. This is likely to require a synergy of ongoing developments that merge enhanced signal recognition and data acquisition, big data processing pipelines, and whole brain reconstruction [22, 50, 90], suggesting that advanced clinical analysis with RS-fMRI remains at an early, but promising stage.

6. Conclusion

Resting-state fMRI has enabled the identification of brain networks critical to affecting how humans interact, perceive, and process environmental and internal stimuli. Much of the success of this discovery can be attributed to the synergy between the technical capabilities of fMRI and the low-frequency activity characterizing RSNs. RS-fMRI has benefitted from a spectrum of technical advances in fMRI that have occurred since the initial discovery of RSNs, including improved data-gathering capacity, processing, and handling. The enhanced reliability of RSN detection made possible by these advances has underwritten increasingly powerful interpretive tools that are clarifying the role and structure of brain networks in organizing and executing global brain function. These insights into global brain events have in turn revealed areas where new technical advances, like big data processing and whole brain modeling, are needed, which can interrogate not only resting-state connectivity associations but also the dynamic variations in these associations that occur during brain behavior. While the use of these tools is currently limited to the research laboratory, their future potential for clinical use warrants the current expansion in technical development that will make possible the diagnosis of brain states.

Resting-State fMRI Advances for Functional Brain Dynamics
DOI: http://dx.doi.org/10.5772/intechopen.113802

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