Are your MRI contrast agents cost-effective?
Learn more about generic Gadolinium-Based Contrast Agents.
FRESENIUS KABI
caring for life

AJNR

Resting-State Functional MRI: Everything That Nonexperts Have Always Wanted to Know

H. Lv, Z. Wang, E. Tong, L.M. Williams, G. Zaharchuk, M. Zeineh, A.N. Goldstein-Piekarski, T.M. Ball, C. Liao and M. Wintermark

This information is current as of April 19, 2024.

AJNR Am J Neuroradiol published online 18 January 2018
http://www.ajnr.org/content/early/2018/01/18/ajnr.A5527

Published January 18, 2018 as 10.3174/ajnr.A5527

Resting-State Functional MRI: Everything That Nonexperts Have Always Wanted to Know

H. Lv, Z. Wang, E. Tong, L.M. Williams, G. Zaharchuk, M. Zeineh, A.N. Goldstein-Piekarski, T.M. Ball, C. Liao, and M. Wintermark

ABSTRACT

SUMMARY: Resting-state fMRI was first described by Biswal et al in 1995 and has since then been widely used in both healthy subjects and patients with various neurologic, neurosurgical, and psychiatric disorders. As opposed to paradigm- or task-based functional MR imaging, resting-state fMRI does not require subjects to perform any specific task. The low-frequency oscillations of the resting-state fMRI signal have been shown to relate to the spontaneous neural activity. There are many ways to analyze resting-state fMRI data. In this review article, we will briefly describe a few of these and highlight the advantages and limitations of each. This description is to facilitate the adoption and use of resting-state fMRI in the clinical setting, helping neuroradiologists become familiar with these techniques and applying them for the care of patients with neurologic and psychiatric diseases.

ABBREVIATIONS: ALFF = Amplitude of Low Frequency Fluctuations; BOLD = blood oxygen level–dependent; FCD = functional connectivity density; ICA = independent component analysis; ReHo = regional homogeneity; rs-fMRI = resting-state fMRI

The brain controls all the complex functions in the human body. Structurally, the brain is organized grossly into different regions specialized for processing and relaying neural signals; functionally, the brain is subspecialized for perceptual and cognitive processes. Working in concert, these subspecialized areas orchestrate complex bodily functions and allow human behavior.

Neurons do not contain any internal reserves of energy, either in the form of glucose or oxygen. When activated, they are provided with more energy by the adjacent capillaries through a process called the hemodynamic response, which supplies them with increased regional cerebral blood flow and an increase in oxygen supply, usually even greater than their needs.[1,2] This process results in a change in terms of the relative levels of oxyhemoglobin and deoxyhemoglobin that can be detected by MR imaging on the basis of their differential magnetic susceptibilities. This imaging approach is called blood oxygen level–dependent (BOLD) contrast imaging. Conventionally, BOLD signal change has been known to be modulated by the arterial partial pressure of CO_2 level. More recent research suggests that BOLD signal is determined by both the arterial partial pressure of O_2 and CO_2, rather than CO_2 alone.[3] The change in the BOLD signal is the cornerstone of functional MR imaging,[4,5] which is traditionally used to construct maps indicating subspecialized brain regions that are activated by certain tasks or reacting to a stimulus at a low frequency (0.01–0.1Hz). The frequencies of neural activity fluctuations measured by fMRI (which are low-frequency and indirectly measured using BOLD signal) and of neural firing measured in neurophysiologic studies (which are high-frequency and are directly measured) are different.[6,7]

The biologic significance of the neural activity fluctuations was first described by Biswal et al in 1995.[8] When the subjects were asked to perform bilateral finger tapping in that experiment, researchers identified a highly correlated BOLD time course between the left somatosensory cortex and the homologous areas in the contralateral hemisphere.[8] Since then, fMRI has been widely used in both healthy subjects and patients with neurologic and psychiatric disorders to analyze synchronous, spontaneous fluctuations of various resting-state networks.[9] Because of the neurovascular coupling, the BOLD signal, while vascular in nature, is strongly related to neuronal activity.[10] However, the delay of the hemodynamic response following neural activation is responsible

From the Department of Radiology (H.L., Z.W.), Beijing Friendship Hospital, Capital Medical University, Beijing, China; Department of Radiology (H.L., G.Z., M.Z., M.W.), Neuroradiology Division, and Department of Psychiatry and Behavioral Sciences (L.M.W., A.N.G.-P., T.M.B.), Stanford University, Stanford, California; Department of Radiology (E.T.), Neuroradiology Section, University of California, San Francisco, San Francisco, California; and Department of Radiology (C.L.), Yunnan Tumor Hospital (The Third Affiliated Hospital of Kunming Medical University), Kunming, Yunnan Province, China.

Dr Ball is supported by grant T32MH019938 from the National Institute of Mental Health.

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Please address correspondence to Max Wintermark, MD, MAS, MBA, Stanford University, Department of Radiology, Neuroradiology Division, 300 Pasteur Dr, Room S047, Stanford, CA 94305-5105; e-mail: Max.Wintermark@gmail.com; @StanfordNRAD

Indicates open access to non-subscribers at www.ajnr.org

http://dx.doi.org/10.3174/ajnr.A5527

Copyright 2018 by American Society of Neuroradiology.

for the relatively poor temporal resolution of fMRI,[11] and the BOLD signal can be altered in brain regions where the blood circulation is altered.[12-14] For example, pathologic conditions such as traumatic brain injury[15-17] or anoxic brain injury[18-21] might affect neurovascular coupling and therefore make fMRI suboptimal to assess neural activity in these pathologic conditions. Therefore, these factors should be taken into consideration when designing calibrated BOLD experiments and interpreting functional connectivity data, especially in patients with vascular pathologies.[3]

As opposed to paradigm- or task-based functional MR imaging, resting-state fMRI (rs-fMRI) is acquired in the absence of a stimulus or a task, in other words at rest. The principle of rs-fMRI is also based on the BOLD signal fluctuation, which is the same as for active-task fMRI. rs-fMRI focuses on spontaneous BOLD signal alterations. Data can be acquired with a dedicated scan, in which individuals are instructed to simply rest, or by inferring resting-state data from periods of rest embedded within a series of tasks.[22] The lack of a task makes rs-fMRI particularly attractive for patients who may have difficulty with task instructions, such as those with neurologic, neurosurgical, and psychiatric conditions, as well as for pediatric patients. Thus, the application of rs-fMRI in the research and clinical setting has been growing for the past 2 decades.[9,23]

There are multiple ways to analyze rs-fMRI data, and each approach has implications in terms of what information can be extracted from the data. This article attempts to provide a broad overview of major analysis methods that are used in rs-fMRI. We will systematically describe these approaches, their advantages, and limitations. This work will help nonexperts become familiar with rs-fMRI techniques and how to apply them to the benefit of patients with neurologic, neurosurgical, and psychiatric disorders.[24,25]

Analytic Methods

rs-fMRI analysis is challenging due to the massive amount of data and the need for sophisticated analysis. Before one applies any of the analytic methods, realignment and removal of confounding artifacts (eg, head motion, CSF signal) are important preprocessing steps. Other main preprocessing steps are required on rs-fMRI data, including removing the first 10~20 time points, slice timing, data normalization, and band-pass filtering. Other possible procedures, including smoothing, may be performed in different sequences according to the analytic method applied. Several software packages, including but not limited to statistical parametric mapping, Analysis of Functional Neuro Images (AFNI; http://afni.nimh.nih.gov/afni), the CONN toolbox (https://www.nitrc.org/projects/conn/), MELODIC (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC), and Group ICA of fMRI Toolbox Software (GIFT; http://mialab.mrn.org/software/gift/), are commonly used to analyze rs-fMRI data. Pipelines[26,27] have also been developed to analyze data almost automatically, which make the data analysis much easier for nonexperts.

Proper interpretation of rs-fMRI data results requires an understanding of anatomy, pathophysiology, and neuroscience, to make logical inferences. For easy understanding, the large amount of information contained in the rs-fMRI data can be compared with a map.[28] When one looks at a map, one can focus on finding cities or highways linking cities with each other. Similarly, when one analyzes rs-fMRI data, one can extract information on the function of specific brain regions or the functional connectivity between different brain regions. Analytic approaches can be broadly divided into 2 types: functional segregation and functional integration.[29,30] Functional segregation focuses on the local function of specific brain regions and is mainly used for brain mapping. Functional integration focuses on the functional relationships or connectivity between different brain areas and assesses the brain as an integrated network. Functional segregation techniques rely on the analysis of rs-fMRI activity, while functional integration techniques rely on the analysis of rs-fMRI connectivity. By comparing the rs-fMRI results with the way we look at a map, one can understand these different methods more intuitively.

Functional Segregation Methods for Identifying Neural Networks

Functional segregation divides the brain into regions according to their specific functions[30]: Amplitude of Low Frequency Fluctuations (ALFF) and regional homogeneity (ReHo) are methods commonly used in functional segregation assessments. Fractional-ALFF and ReHo reflect different aspects of regional neural activity ("cities") but do not provide information on functional connectivity ("highways"). Although they are similar in many ways, they reveal different aspects of brain abnormalities in clinical populations.[31-34] The combined application of these 2 methods provides more information than either method alone. We next discuss each of these methods and their advantages and disadvantages and how they complement each other.

ALFF Analysis

The ALFF method measures the total power of the BOLD signal within the low-frequency range between 0.01 and 0.1 Hz (Fig 1*A*[35]; the results are visualized with the REST Slice Viewer; http://www.restfmri.net[36]). ALFF is proportional to regional neural activity.[35] Fractional-ALFF is a variant that measures the power within the low-frequency range (0.01–0.1 Hz) divided by the total power in the entire detectable frequency range and represents the relative contribution of the low-frequency oscillations.[37] ALFF and fractional-ALFF measure regional brain activity only (like traffic in cities on a map, ALFF reveals the density of "traffic" as an absolute value, while fractional-ALFF looks at the density of traffic as a proportion in cities). Thus, they do not provide information on functional connectivity between brain regions.

Subsets of frequency bands have been reported as follows: 1) Frequencies between 0.010 and 0.027 Hz may reflect cortical neuronal activity, 2) frequencies between 0.027 and 0.073 Hz may reflect basal ganglia activity, and 3) frequencies between 0.073 and 0.198 Hz and 0.198 and 0.250 Hz have been associated with physiologic noise and white matter signal, respectively.[38-42] However, there is an active ongoing debate about whether rs-fMRI can actually detect white matter activity. Reasons for white matter fMRI activation remain controversial and require further investigation.[13] Mounting evidence supports the spatial properties of the white matter being assessed using functional correlation tensor

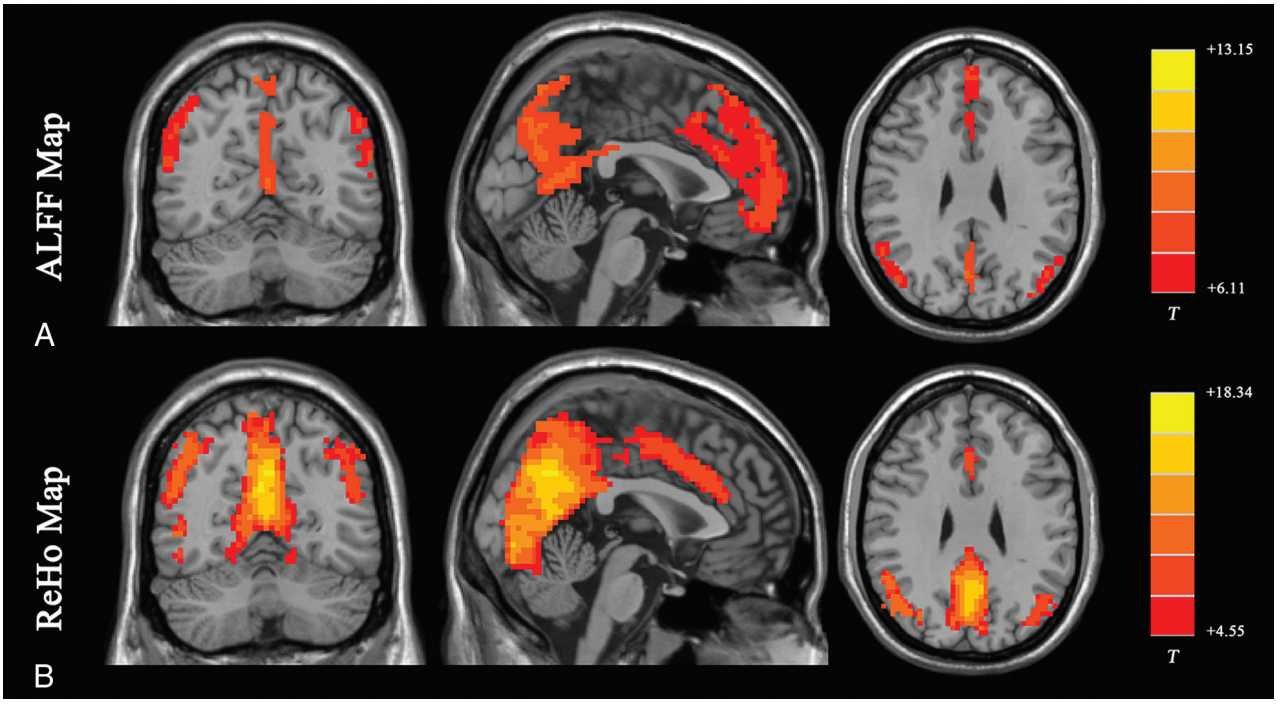

FIG 1. Results of ALFF and ReHo studies (1-sample *t* test results of 200 healthy volunteers [M.W., unpublished data, February 6, 2017]). *A*, ALFF results. *B*, ReHo results. Results of increased ALFF and ReHo are mostly overlapped with the default mode network, which is activated at resting-state in healthy volunteers. (For different kinds of patients, abnormal ALFF or ReHo findings may be detected in other brain areas in the resting-state.) Both ALFF and ReHo results reflect regional neural activities. ALFF is focused on measuring the strength of the activity, while ReHo is more specific for coherence and centrality of regional activity. T indicates peak intensity.

analysis based on rs-fMRI data.[43,44] Functional correlation tensor results showed similarities to those of diffusion tensor imaging but represent a separate entity. Future studies involving functional correlation tensor analysis of rs-fMRI data may provide insight into the network interaction features of the brain within the white matter.

The advantage of the ALFF and fractional-ALFF methods lies in the simplicity of the analysis without any underlying hypothesis. Both ALFF and fractional-ALFF show remarkably high temporal stability[45] and long-term (about 6 months) test-retest reliability.[46] Fractional-ALFF is reportedly more specific to gray matter[37]; however, it has slightly lower test-retest reliability.[46] Therefore, both measurements are commonly reported together to maximize the reliability across subjects, with sufficient specificity to examine individual differences.

Regional Homogeneity Analysis

ReHo analysis is a voxel-based measure of the similarity between the time-series of a given voxel and its nearest neighbors, as calculated by the Kendall coefficient of concordance of the BOLD time-series. It measures the synchrony of adjacent regions (equivalent to the concordance of traffic between "downtown" and the "suburbs" in a city) (Fig 1*B*).[47] A higher ReHo value represents higher coherence and centrality of regional brain activity. Higher coherence and centrality are usually associated with, but not necessarily, equal-to-high activity. Thus, the results of fractional-ALFF and ReHo should be discussed separately.[48] Areas that overlap in ALFF and ReHo represent regions that are not only active at the same time frequency but are also active in sync with neighboring voxels. This representation means that the regions are not only active but also engaging a relatively large group of neurons.[47]

ReHo is usually calculated within a low-frequency range, typically between 0.01 Hz and 0.1 Hz. It can be subdivided into different frequency bands. Lower frequency (0.01–0.04 Hz) ReHo is more sensitive for cortical activity.[49] The exact biologic meaning of ReHo measurements in different frequency bands still needs further exploration. Several studies demonstrated the frequency dependence of the ReHo changes in different neurologic conditions.[42,50-52] Future rs-fMRI research focusing on the biologic meaning of ReHo should be conducted in both healthy subjects and patients with specific conditions using spectrum-specific analytic strategies.

The test-retest reliability of the ReHo method is very high, even when subjects are rescanned after a long interval (6 months).[46] Zuo et al[53] developed a ReHo computation method along 2 dimensions (surface) using cortical surface-based fMRI analysis after projecting individual preprocessed data into a cortical surface space. It is more reliable than a method based on conventional 3D (volume) because of the following: 1) It could accurately calculate the ReHo value on the cortical surface by avoiding a mixture of gray and white matter; and 2) by avoiding mixing adjacent brain tissues in 3D space due to the highly folded human cortex, it could more precisely characterize functional homogeneity within a brain region. Like ALFF, ReHo does not require an a priori definition of the ROI and can provide information about regional activity throughout the brain. ALFF and ReHo may also be applied together to reveal

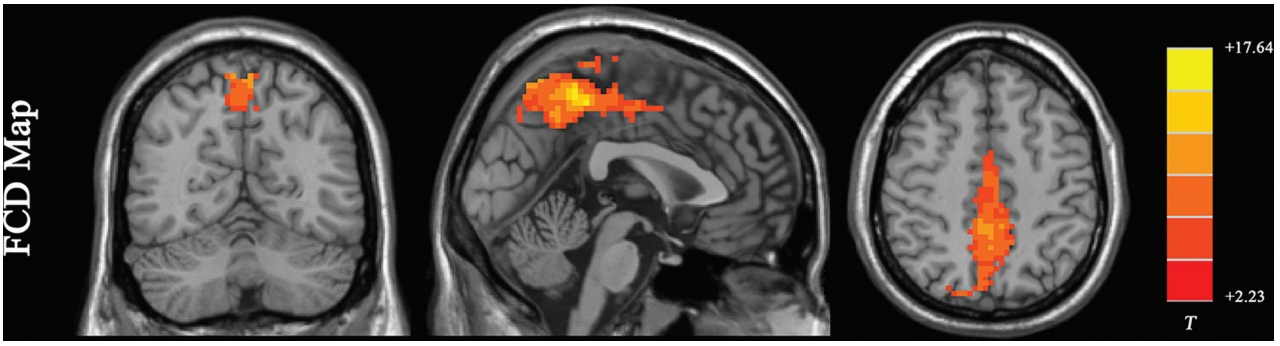

FIG 2. Results of an FCD study (1-sample *t* test results of 200 healthy volunteers [M.W., unpublished data, February 6, 2017]). The FCD reaches its highest value in the posterior cingulate cortex/precuneus, reflecting the highest density of functional connectivity of these voxels in healthy subjects. Results are like those of previous studies reviewed by Tomasi.[58] FCD parameters: $T_{SNR} = 50$ and $T_c = 0.6$.

different aspects of brain regional function and abnormalities arising in clinical populations.[31,33,34,54,55]

Both ALFF and ReHo methods can be used to reveal local neural activity of the brain. Those methods are used to define an ROI for seed-based functional connectivity analysis (further discussed below). However, because the brain is more appropriately studied as an integrated network rather than isolated clusters, the excitement for stand-alone functional segregation methods has gradually receded in favor of functional integration methods. Another limitation of ReHo is the relatively unclear biologic meaning of ReHo in the different frequency bands.

Functional Integration Methods for Identifying Neural Networks

Functional integration focuses on the functional connectivity (highways on the map) between different regions of the brain. Functional connectivity measures the degree of synchrony of the BOLD time-series between different brain regions. The connectivity can be the result of a direct anatomic connection or an indirect path[56] via a mediating region or may have no known anatomic correlate. Functional connectivity can also be due to a common source of input signals. Of note, with rs-fMRI, the highways may not be directly visualized, only the brain regions presumably connected by these paths. Separate research effort focuses on directly visualizing the highways using different MR imaging modalities, including diffusion tensor imaging and tractography. Functional integration is the foundation of information transfer between different brain areas.[30,57]

For assessing functional integration features, commonly used computational methods include functional connectivity density analysis, ROI-based functional connectivity analysis, independent component analysis (ICA), and graph analysis.

Functional Connectivity Density Analysis

Functional connectivity density (FCD) is the most basic measurement of functional connectivity.[58] FCD analysis attempts to identify the highly connected functional hubs (Fig 2). FCD reveals only how connected a voxel is but not the regions with which this voxel is connected. FCD analysis calculates the correlation of the BOLD time-series between each voxel and all the other voxels in the brain. Short-range and long-range FCD maps can be calculated.[59,60] The cutoff distance is typically 75 mm.[59,60] Short-range FCD is measured by the correlation analysis of the BOLD time-series between each voxel and the voxels around it within a distance of 75 mm (and represents some kind of long-range ReHo). The short-range FCD may reflect the regional functional connectivity plasticity around this voxel.[60] The long-range FCD is the result of the global FCD minus the short-range FCD and could reflect long-distance functional connectivity plasticity.

FCD analysis is straightforward. It does not need any model assumptions to be performed. It can reveal the importance of functional hubs of brain connectivity but does not indicate which regions are connected. FCD should be interpreted with caution due to its moderate long-term (about 6 months) test-retest reliability.[46]

Seed-Based Functional Connectivity Analysis

Seed-based functional connectivity, also called ROI-based functional connectivity, finds regions correlated with the activity in a seed region. In seed-based analysis, the cross-correlation is computed between the time-series of the seed and the rest of the brain (telling us where the traffic is communicating between selected cities) (Fig 3, the results are visualized with the BrainNet Viewer; https://www.nitrc.org/projects/bnv/[61]). Several metrics (eg, the cross-correlation coefficient, partial correlations, multiple regressions, and synchronization likelihood) can be used to assess associations between time-series of brain areas. The coupling of activation between different brain areas indicates that they are involved in the same underlying functional process and thus interpreted as functionally connected. These brain regions may not be directly connected by neural fibers. The overall connectivity of the brain with this method can be visualized using a connectivity matrix, showing the strength of all connections between seed regions within the brain (Fig 3). Such a matrix has been commonly used in clinical applications, (eg, presurgical localization, identification of patients with Alzheimer disease, or distinction of different types of dementia).[62] Such clinical applications of rs-fMRI have been extensively described in previous reviews.[63-65]

Seed analysis requires a priori determination of the seeds, which is often based on a hypothesis or prior results. Seeds may also be derived from ALFF or ReHo calculations. Seed time-series may also be performance or physiologic variables (such as breathing or heart rate). The main advantage of seed analysis is that the computation is simple and the interpretation of the results is intuitive. However, when the seed region changes, the results of the

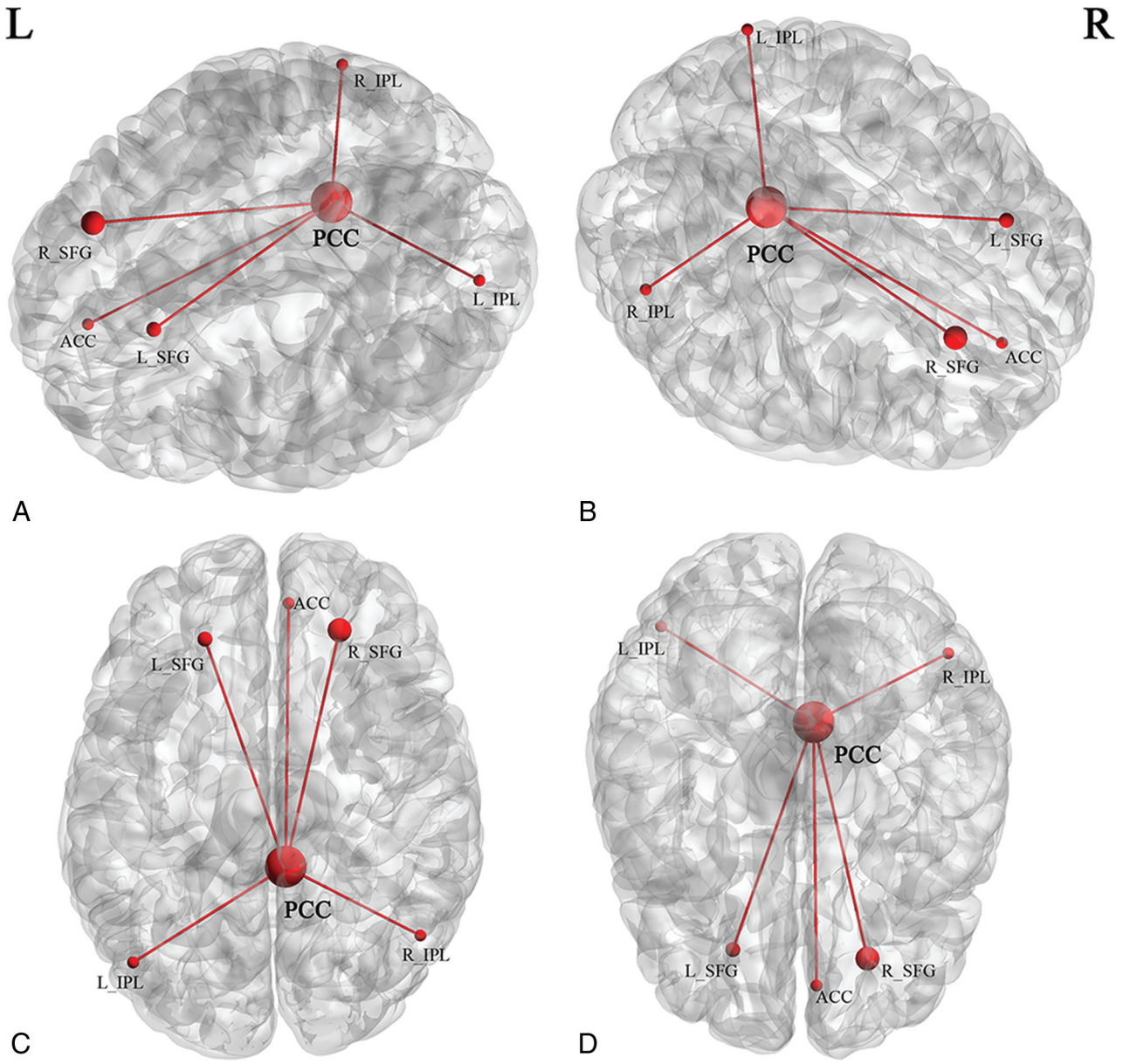

FIG 3. Brain maps show the group average spatial representation of the results of a seed-based functional connectivity study (results of 200 healthy volunteers [M.W., unpublished data, October 6, 2017]). The posterior cingulate cortex was set as a seed. *Nodes* represent brain area; *lines* represent functional connectivity between *nodes*. *A*, Left view. *B*, Right view. *C*, Upper view. *D*, Lower view. R indicates right; L, left; PCC, posterior cingulate cortex; ACC, anterior cingulate cortex; SFG, superior frontal gyrus; IPL, inferior parietal lobule.

functional connectivity analysis will also change, and sometimes obviously. Thus, the disadvantage of seed analysis is its dependence on the selection of seeds, which makes it vulnerable to bias.

Independent Component Analysis

Independent component analysis uses multivariate decomposition to separate the BOLD signal into several independent functional networks in the form of spatial maps, which are temporally correlated.[66-68] Each functional network (component) embodies an independent network of neurons with synchronized BOLD activity (network of cities with high traffic between them). Each functional network is reported as a spatial map of the *z* scores derived from the correlation between the time-series of each voxel and the mean time-series of that brain network. The average *z* score for each network indicates the magnitude of functional connectivity within the network.

There are several resting-state networks that commonly emerge from ICA analysis in rs-fMRI studies, including but not limited to the default mode network, auditory network, salience network, executive control network, medial visual network, lateral visual network, sensorimotor cortex, dorsal visual stream (frontoparietal attention network), basal ganglia network, limbic network, and precuneus network.[68-70] These networks show resting-state connectivities, some of which are observed to be up- or down-regulated during specific cognitive tasks.

ICA is data-driven as opposed to seed-based analysis, which is ROI-driven. ICA can be performed without any a priori assump-

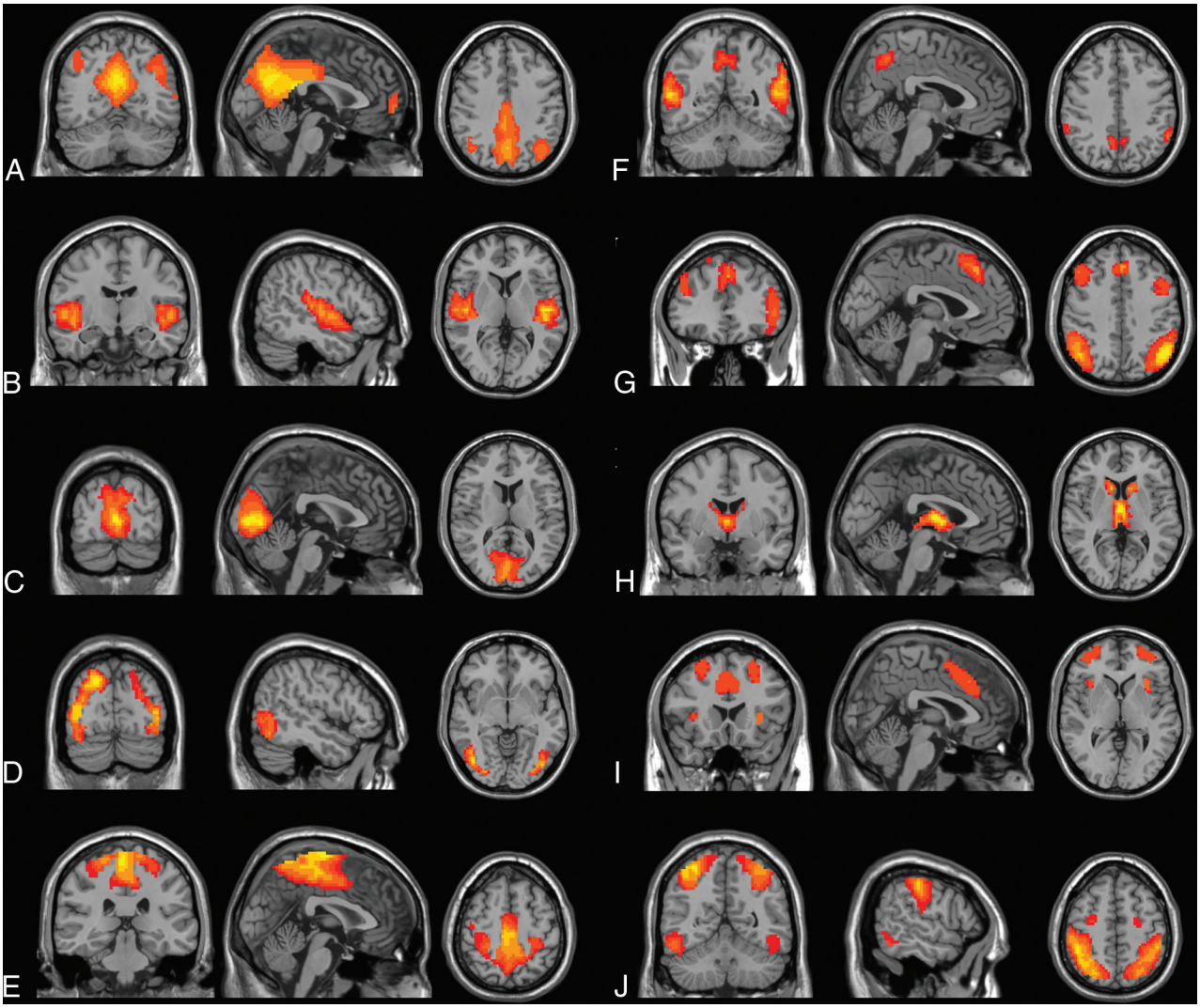

FIG 4. Typical reported networks (results of 200 healthy volunteers [M.W., unpublished data, February 6, 2017]). *A*, Default mode network. *B*, Auditory network. *C*, Medial visual network. *D*, Lateral visual network. *E*, Sensorimotor network. *F*, Precuneus network. *G*, Dorsal visual stream (frontoparietal attention network). *H*, Basal ganglia network. *I*, Executive control network. *J*, Visuospatial network.

tions, except the selection of the number of independent components to identify. While seed analysis extracts only the regions functionally connected to the ROI, ICA extracts all detectable networks within the subject (Fig 4). ICA analysis shows relatively high test-retest reliability for both the short term (<45 minutes) and the long term (5~16 months).[71] However, the underlying cause of the perceived synchrony within the functional networks may be nonneural in origin (such as breathing or pulsation). This inherent property of ICA complicates the interpretation of ICA results. ICA only presents brain networks one by one. It does not show between-module connections or communications between different brain networks.[72] Additional issues are that a single network could be broken into subnetworks, depending on the number of independent components specified, and that using ICA requires either manual or computer-driven identification of specific networks.

Independent vector analysis[73-75] is a recent extension of ICA. Like ICA, independent vector analysis maximizes the dependence between associated components from different datasets. These components are conceptually regrouped into so-called source component vectors. The ability of independent vector analysis to capture variability in spatial components across individuals and groups may be superior to that of ICA.[76-78] Independent vector analysis can also be applied in the analysis of spatiotemporal dynamic features of brain networks.

Graph Analysis

Graph theory has been extensively used to examine the properties of complex networks. A small-world network (or "clique"), which was first described in social networks, is characterized as graphs with attenuated local connections and few long connections.[79] A small-world network is one in which most nodes (ie, regions) are not connected to one another, but nodes can be reached from every other node through a small number of connections. In other words, there are small networks of highly connected nodes in clusters (cities in 1 "state") working together ("brain moduli"[72] or states) to carry out a specific task or perform a specific cognitive function, with a few connections (limited number of highways between states) between these networks exhibiting prominent small-world organization and facilitating efficient information delivery at low wiring and energy costs.[80]

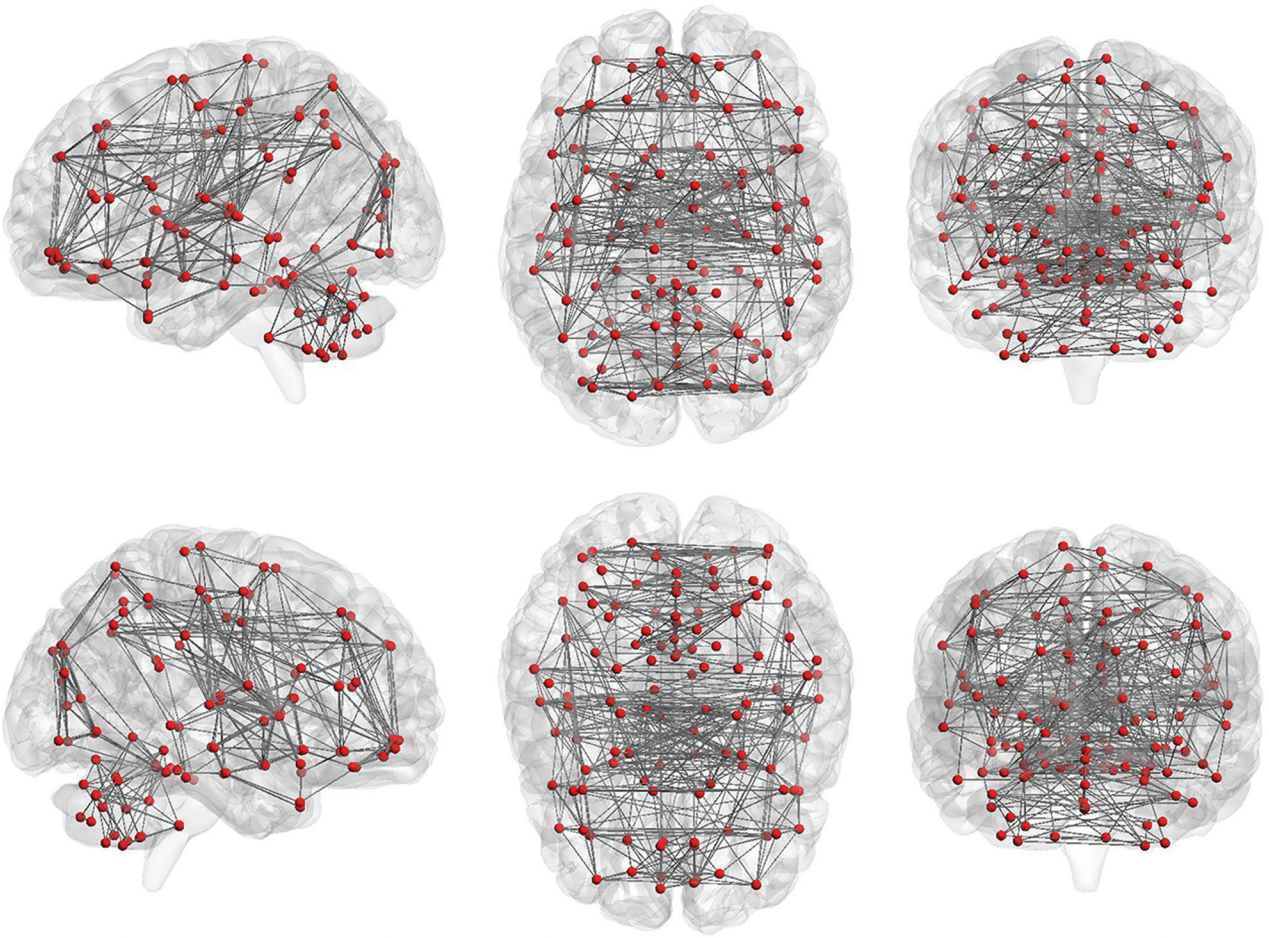

FIG 5. Nodes and functional connections are the basis of graph analysis. The whole brain includes 116 seeds (*red dots*; 45 nodes in each hemisphere of the cerebrum and 26 nodes in cerebellum) set on the basis of the anatomic parcellation defined by the Automated Anatomical Labeling atlas. *Lines* represent possible functional connections between those seeds.

Graph theory provides a theoretic framework for analyzing the topology of brain networks by examining both the local and global organization of neural networks.[80-82] In graph theory, functional brain networks can be defined as a graph (G) as a function of nodes (V) and functional connections (E), represented by $G = f(V,E)$.[59,83,84] Nodes (V) may represent voxels or ROIs. The Automated Anatomical Labeling atlas, which contains 116 regions (90 nodes in the cerebrum and 26 nodes in the cerebellum, Fig 5), can be used to define the nodes for this analysis, but there are also many other parcellation schemes available for general use.[69,85-87] The level of functional connectivity (E) between 2 nodes is computed by the correlation between the time-series of the 2 nodes. First, the functional connectivity between all possible node-pairs is computed. A graph representation of the functional brain network is then constructed using a predefined cutoff threshold of E. The following are some of the key graph analysis parameters:

1) "Clustering coefficient" describes the level of local neighborhood clustering. It reflects the level of local connectedness of a network.

2) "Characteristic path length" describes the average number of connections between all pairs of nodes. It reflects the global connectivity of the network, which reflects the efficiency of the network.

3) "Node degree" describes the number of connections of a node. It helps identify the highly connected nodes within the network.

4) "Centrality" describes the number of short-range connections for each node. Nodes with higher centrality contribute more to the overall efficiency of the network.

5) "Modularity" describes the extent to which groups of nodes are connected to the members of their own group. It reflects the existence of subnetworks within the full network.

Graph analysis of rs-fMRI reveals a highly efficient organization of the brain network optimized toward a high level of local and global efficiency,[81,82] often referred to as small-world topology. The small-world topology could characterize the whole-brain map as well as different brain networks. Graph analysis can be automatically performed using published software,[88] without any a priori assumptions and with minimal bias. However, the results are often not intuitive and may be difficult to interpret.

Combined Study Recommendations

rs-fMRI has been widely used to characterize neuropsychiatric disorders using many of the methods described above.[89] There are multiple methods available to identify networks within rs-fMRI data on the basis of the connectivity using data-driven parcellation and on anatomic priors. Each method emphasizes different

approaches to defining brain connectivity. There is no single method currently considered a criterion standard on its own. Thus, these different methods are complementary to each other. The application of rs-fMRI is facilitated by methods that use a priori definitions of brain regions and brain networks. Combining different methods is one opportunity for yielding a more complete data-driven characterization of whole-brain resting connectivity than may be possible using one of the currently available single methods. An example of such a combination is the use of FCD, fractional-ALFF, or ReHo analysis, based on a graph theory framework, to identify ROIs for the functional connectivity analysis, as described above.

New Horizons

rs-fMRI is a rapidly evolving field with new analytic techniques introduced on a very regular basis. One such new methodology currently being proposed is the "chronnectome."[90] So far, researchers mainly focused on the temporal properties of functional connectivity between different brain regions, implicitly assuming that functional connectivity (or traffic between cities) during the scanning time is relatively static. The chronnectome approach is based on a different assumption, that of temporal evolution of spatial properties of functional connectivity (dynamic, nonstationary patterns of traffic between cities) during the scanning time. Chronnectome approaches have shown promising results for studying the spatiotemporal dynamic features of brain networks in healthy subjects[91-95] and patients.[43,96-101]

CONCLUSIONS

rs-fMRI is an imaging technique that plays a growing role in characterizing normal and abnormal functional brain connectivity in a variety of clinical conditions. To date, there are several different approaches and techniques to analyze rs-fMRI data, and the number of available methods is continually expanding. The different analysis methods are complementary, and applying several methods to the same dataset may yield better results compared with applying 1 method alone. A better understanding of each processing method is helpful in interpreting the common/divergent findings reported in the rs-fMRI literature.

Disclosures: Leanne M. Williams—*UNRELATED*: *Board Membership*: PsyberGuide, *Comments*: member of the Scientific Advisory Board; *Grants/Grants Pending*: National Institutes of Health*; *Payment for Lectures Including Service on Speakers Bureaus*: University of Minnesota, *Comments*: Grand Rounds. Greg Zaharchuk—*UNRELATED*: *Grants/Grants Pending*: National Institutes of Health, GE Healthcare. Michael Zeineh—*UNRELATED*: *Grants/Grants Pending*: National Institutes of Health, Doris Duke Charitable Foundation, Dana Foundation, Foundation of the ASNR, GE Healthcare*. Tali M. Ball—*RELATED*: *Grant*: National Institute of Mental Health, *Comments*: Salary support was provided by National Institute of Mental Health training grant T32MH019938; *UNRELATED*: *Other*: PsyberGuide, *Comments*: one-time payment to provide content for their Web site. Max Wintermark—*UNRELATED*: *Board Membership:* GE NFL Advisory Board. *Money paid to the institution.

REFERENCES

1. Handwerker DA, Bandettini PA. **Hemodynamic signals not predicted? Not so: a comment on Sirotin and Das (2009).** *Neuroimage* 2011;55:1409–12 CrossRef Medline
2. Sirotin YB, Das A. **Anticipatory haemodynamic signals in sensory cortex not predicted by local neuronal activity.** *Nature* 2009;457:475–79 CrossRef Medline
3. Nasrallah FA, Yeow LY, Biswal B, et al. **Dependence of BOLD signal fluctuation on arterial blood CO2 and O2: implication for resting-state functional connectivity.** *Neuroimage* 2015;117:29–39 CrossRef Medline
4. Ogawa S, Lee TM, Kay AR, et al. **Brain magnetic resonance imaging with contrast dependent on blood oxygenation.** *Proc Natl Acad Sci U S A* 1990;87:9868–72 CrossRef Medline
5. Kwong KK, Belliveau JW, Chesler DA, et al. **Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation.** *Proc Natl Acad Sci U S A* 1992;89:5675–79 CrossRef Medline
6. Hyder F, Rothman DL. **Neuronal correlate of BOLD signal fluctuations at rest: err on the side of the baseline.** *Proc Natl Acad Sci U S A* 2010;107:10773–74 CrossRef Medline
7. Schölvinck ML, Maier A, Ye FQ, et al. **Neural basis of global resting-state fMRI activity.** *Proc Natl Acad Sci U S A* 2010;107:10238–43 CrossRef Medline
8. Biswal B, Yetkin FZ, Haughton VM, et al. **Functional connectivity in the motor cortex of resting human brain using echo-planar MRI.** *Magn Reson Med* 1995;34:537–41 CrossRef Medline
9. Smith K. **Brain imaging: fMRI 2.0.** *Nature* 2012;484:24–26 CrossRef Medline
10. Hermes D, Nguyen M, Winawer J. **Neuronal synchrony and the relation between the blood-oxygen-level dependent response and the local field potential.** *PLoS Biol* 2017;15:e2001461 CrossRef Medline
11. Koch C, Reid RC. **Neuroscience: observatories of the mind.** *Nature* 2012;483:397–98 CrossRef Medline
12. Christen T, Jahanian H, Ni WW, et al. **Noncontrast mapping of arterial delay and functional connectivity using resting-state functional MRI: a study in Moyamoya patients.** *J Magn Reson Imaging* 2015;41:424–30 CrossRef Medline
13. Gawryluk JR, Mazerolle EL, D'Arcy RC. **Does functional MRI detect activation in white matter? A review of emerging evidence, issues, and future directions.** *Front Neurosci* 2014;8:239 CrossRef Medline
14. Beissner F. **Functional MRI of the brainstem: common problems and their solutions.** *Clin Neuroradiol* 2015;25(Suppl 2):251–57 CrossRef Medline
15. Wintermark M, Sanelli PC, Anzai Y, et al; American College of Radiology Head Injury Institute. **Imaging evidence and recommendations for traumatic brain injury: advanced neuro- and neurovascular imaging techniques.** *AJNR Am J Neuroradiol* 2015;36:E1–E11 CrossRef Medline
16. Mayer AR, Bellgowan PS, Hanlon FM. **Functional magnetic resonance imaging of mild traumatic brain injury.** *Neurosci Biobehav Rev* 2014;49:8–18 CrossRef Medline
17. Stevens MC, Lovejoy D, Kim J, et al. **Multiple resting state network functional connectivity abnormalities in mild traumatic brain injury.** *Brain Imaging Behav* 2012;6:293–318 CrossRef Medline
18. Ishaque M, Manning JH, Woolsey MD, et al. **Functional integrity in children with anoxic brain injury from drowning.** *Hum Brain Mapp* 2017;38:4813–31 CrossRef Medline
19. Arngrim N, Hougaard A, Schytz HW, et al. **Effect of hypoxia on BOLD fMRI response and total cerebral blood flow in migraine with aura patients**. *J Cereb Blood Flow Metab* 2017 Jan 1. [Epub ahead of print] CrossRef Medline
20. Lv Y, Margulies DS, Cameron CR, et al. **Identifying the perfusion deficit in acute stroke with resting-state functional magnetic resonance imaging.** *Ann Neurol* 2013;73:136–40 CrossRef Medline
21. Amemiya S, Kunimatsu A, Saito N, et al. **Cerebral hemodynamic impairment: assessment with resting-state functional MR imaging.** *Radiology* 2014;270:548–55 CrossRef Medline
22. Korgaonkar MS, Ram K, Williams LM, et al. **Establishing the resting state default mode network derived from functional magnetic resonance imaging tasks as an endophenotype: a twins study.** *Hum Brain Mapp* 2014;35:3893–902 CrossRef Medline
23. Smith K. **Brain decoding: reading minds.** *Nature* 2013;502:428–30 CrossRef Medline

24. Williams LM. **Defining biotypes for depression and anxiety based on large-scale circuit dysfunction: a theoretical review of the evidence and future directions for clinical translation.** *Depress Anxiety* 2017;34:9–24 CrossRef Medline
25. Khazaee A, Ebrahimzadeh A, Babajani-Feremi A. **Classification of patients with MCI and AD from healthy controls using directed graph measures of resting-state fMRI.** *Brain Behav Res* 2017;322:339–50 CrossRef Medline
26. Schirner M, Rothmeier S, Jirsa VK, et al. **An automated pipeline for constructing personalized virtual brains from multimodal neuroimaging data.** *Neuroimage* 2015;117:343–57 CrossRef Medline
27. Chao-Gan Y, Yu-Feng Z. **DPARSF: a MATLAB toolbox for "Pipeline" data analysis of resting-state fMRI.** *Front Syst Neurosci* 2010;4:13 CrossRef Medline
28. Dance A. **Neuroscience: connectomes make the map.** *Nature* 2015;526:147–49 CrossRef Medline
29. Liu Y, Gao JH, Liotti M, et al. **Temporal dissociation of parallel processing in the human subcortical outputs.** *Nature* 1999;400:364–67 CrossRef Medline
30. Tononi G, Sporns O, Edelman GM. **A measure for brain complexity: relating functional segregation and integration in the nervous system.** *Proc Natl Acad Sci U S A* 1994;91:5033–37 CrossRef Medline
31. Han L, Zhaohui L, Fei Y, et al. **Disrupted neural activity in unilateral vascular pulsatile tinnitus patients in the early stage of disease: evidence from resting-state fMRI.** *Prog Neuropsychopharmacol Biol Psychiatry* 2015;59:91–99 CrossRef Medline
32. Premi E, Cauda F, Gasparotti R, et al. **Multimodal FMRI resting-state functional connectivity in granulin mutations: the case of fronto-parietal dementia.** *PLoS One* 2014;9:e106500 CrossRef Medline
33. An L, Cao QJ, Sui MQ, et al. **Local synchronization and amplitude of the fluctuation of spontaneous brain activity in attention-deficit/hyperactivity disorder: a resting-state fMRI study.** *Neurosci Bull* 2013;29:603–13 CrossRef Medline
34. Lei D, Ma J, Du X, et al. **Spontaneous brain activity changes in children with primary monosymptomatic nocturnal enuresis: a resting-state fMRI study.** *Neurourol Urodyn* 2012;31:99–104 CrossRef Medline
35. Zang YF, He Y, Zhu CZ, et al. **Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI.** *Brain Dev* 2007;29:83–91 CrossRef Medline
36. Song XW, Dong ZY, Long XY, et al. **REST: a toolkit for resting-state functional magnetic resonance imaging data processing.** *PLoS One* 2011;6:e25031 CrossRef Medline
37. Zou QH, Zhu CZ, Yang Y, et al. **An improved approach to detection of Amplitude of Low-Frequency Fluctuation (ALFF) for resting-state fMRI: fractional ALFF.** *J Neurosci Methods* 2008;172:137–41 CrossRef Medline
38. Buzsáki G, Draguhn A. **Neuronal oscillations in cortical networks.** *Science* 2004;304:1926–29 CrossRef Medline
39. Zuo XN, Di Martino A, Kelly C, et al. **The oscillating brain: complex and reliable.** *Neuroimage* 2010;49:1432–45 CrossRef Medline
40. Xue SW, Li D, Weng XC, et al. **Different neural manifestations of two slow frequency bands in resting functional magnetic resonance imaging: a systemic survey at regional, interregional, and network levels.** *Brain Connect* 2014;4:242–55 CrossRef Medline
41. Liu X, Wang S, Zhang X, et al. **Abnormal amplitude of low-frequency fluctuations of intrinsic brain activity in Alzheimer's disease.** *J Alzheimers Dis* 2014;40:387–97 CrossRef Medline
42. Xue S, Wang X, Wang W, et al. **Frequency-dependent alterations in regional homogeneity in major depression.** *Brain Behav Res* 2016;306:13–19 CrossRef Medline
43. Chen X, Zhang H, Zhang L, et al. **Extraction of dynamic functional connectivity from brain grey matter and white matter for MCI classification.** *Hum Brain Mapp* 2017;38:5019–34 CrossRef Medline
44. Zhang L, Zhang H, Chen X, et al. **Learning-based structurally-guided construction of resting-state functional correlation tensors.** *Magn Reson Imaging* 2017;43:110–21 CrossRef Medline
45. Küblböck M, Woletz M, Höflich A, et al. **Stability of low-frequency fluctuation amplitudes in prolonged resting-state fMRI.** *Neuroimage* 2014;103:249–57 CrossRef Medline
46. Zuo XN, Xing XX. **Test-retest reliabilities of resting-state FMRI measurements in human brain functional connectomics: a systems neuroscience perspective.** *Neurosci Biobehav Rev* 2014;45:100–18 CrossRef Medline
47. Zang Y, Jiang T, Lu Y, et al. **Regional homogeneity approach to fMRI data analysis.** *Neuroimage* 2004;22:394–400 CrossRef Medline
48. Zang YF, Zuo XN, Milham M, et al. **Toward a meta-analytic synthesis of the resting-state fMRI literature for clinical populations.** *Biomed Res Int* 2015;2015:435265 CrossRef Medline
49. Song X, Zhang Y, Liu Y. **Frequency specificity of regional homogeneity in the resting-state human brain.** *PLoS One* 2014;9:e86818 CrossRef Medline
50. Liu ZR, Miao HH, Yu Y, et al. **Frequency-specific local synchronization changes in paroxysmal kinesigenic dyskinesia.** *Medicine (Baltimore)* 2016;95:e3293 CrossRef Medline
51. Huang Z, Wang Z, Zhang J, et al. **Altered temporal variance and neural synchronization of spontaneous brain activity in anesthesia.** *Hum Brain Mapp* 2014;35:5368–78 CrossRef Medline
52. Yu R, Hsieh MH, Wang HL, et al. **Frequency dependent alterations in regional homogeneity of baseline brain activity in schizophrenia.** *PLoS One* 2013;8:e57516 CrossRef Medline
53. Zuo XN, Xu T, Jiang L, et al. **Toward reliable characterization of functional homogeneity in the human brain: preprocessing, scan duration, imaging resolution and computational space.** *Neuroimage* 2013;65:374–86 CrossRef Medline
54. Cui Y, Jiao Y, Chen YC, et al. **Altered spontaneous brain activity in type 2 diabetes: a resting-state functional MRI study.** *Diabetes* 2014;63:749–60 CrossRef Medline
55. Premi E, Cauda F, Gasparotti R, et al. **Multimodal fMRI resting-state functional connectivity in granulin mutations: the case of fronto-parietal dementia.** *PLoS One* 2014;9:e106500 CrossRef Medline
56. Lanting CP, de Kleine E, Langers DR, et al. **Unilateral tinnitus: changes in connectivity and response lateralization measured with fMRI.** *PLoS One* 2014;9:e110704 CrossRef Medline
57. Friston KJ. **Modalities, modes, and models in functional neuroimaging.** *Science* 2009;326:399–403 CrossRef Medline
58. Tomasi D, Volkow ND. **Functional connectivity density mapping.** *Proc Natl Acad Sci U S A* 2010;107:9885–90 CrossRef Medline
59. Achard S, Salvador R, Whitcher B, et al. **A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs.** *J Neurosci* 2006;26:63–72 CrossRef Medline
60. He Y, Chen ZJ, Evans AC. **Small-world anatomical networks in the human brain revealed by cortical thickness from MRI.** *Cereb Cortex* 2007;17:2407–19 CrossRef Medline
61. Xia M, Wang J, He Y. **BrainNet Viewer: a network visualization tool for human brain connectomics.** *PLoS One* 2013;8:e68910 CrossRef Medline
62. Lee MH, Smyser CD, Shimony JS. **Resting-state fMRI: a review of methods and clinical applications.** *AJNR Am J Neuroradiol* 2013;34:1866–72 CrossRef Medline
63. Wilson PH, Smits-Engelsman B, Caeyenberghs K, et al. **Cognitive and neuroimaging findings in developmental coordination disorder: new insights from a systematic review of recent research.** *Dev Med Child Neurol* 2017;59:1117–29 CrossRef Medline
64. Koyama MS, Parvaz MA, Goldstein RZ. **The adolescent brain at risk for substance use disorders: a review of functional MRI research on motor response inhibition.** *Curr Opin Behav Sci* 2017;13:186–95 CrossRef Medline
65. Gravel N, Harvey BM, Renken RJ, et al. **Phase-synchronization-based parcellation of resting state fMRI signals reveals topograph-**

ically organized clusters in early visual cortex. *Neuroimage* 2017 Sep 1. [Epub ahead of print] CrossRef Medline
66. Kiviniemi V, Kantola JH, Jauhiainen J, et al. **Independent component analysis of nondeterministic fMRI signal sources.** *Neuroimage* 2003;19:253–60 CrossRef Medline
67. van de Ven VG, Formisano E, Prvulovic D, et al. **Functional connectivity as revealed by spatial independent component analysis of fMRI measurements during rest.** *Hum Brain Mapp* 2004;22:165–78 CrossRef Medline
68. Beckmann CF, DeLuca M, Devlin JT, et al. **Investigations into resting-state connectivity using independent component analysis.** *Philos Trans R Soc Lond B Biol Sci* 2005;360:1001–13 CrossRef Medline
69. Shirer WR, Ryali S, Rykhlevskaia E, et al. **Decoding subject-driven cognitive states with whole-brain connectivity patterns.** *Cereb Cortex* 2012;22:158–65 CrossRef Medline
70. Seeley WW, Menon V, Schatzberg AF, et al. **Dissociable intrinsic connectivity networks for salience processing and executive control.** *J Neurosci* 2007;27:2349–56 CrossRef Medline
71. Zuo XN, Kelly C, Adelstein JS, et al. **Reliable intrinsic connectivity networks: test-retest evaluation using ICA and dual regression approach.** *Neuroimage* 2010;49:2163–77 CrossRef Medline
72. Bertolero MA, Yeo BT, D'Esposito M. **The modular and integrative functional architecture of the human brain.** *Proc Natl Acad Sci U S A* 2015;112:E6798–807 CrossRef Medline
73. Anderson M, Fu GS, Phlypo R, et al. **Independent vector analysis: identification conditions and performance bounds.** *IEEE Trans Signal Process* 2014;62:4399–410 CrossRef
74. Lee JH, Lee TW, Jolesz FA, et al. **Independent vector analysis (IVA): multivariate approach for fMRI group study.** *Neuroimage* 2008;40:86–109 CrossRef Medline
75. Anderson M, Adali T, Li XL. **Joint blind source separation with multivariate Gaussian model: algorithms and performance analysis.** *IEEE Trans Signal Process* 2012;60:1672–83
76. Laney J, Westlake KP, Ma S, et al. **Capturing subject variability in fMRI data: a graph-theoretical analysis of GICA vs. IVA.** *J Neurosci Methods* 2015;247:32–40 CrossRef Medline
77. Ma S, Phlypo R, Calhoun VD, et al. **Capturing group variability using IVA: a simulation study and graph-theoretical analysis.** *Proc IEEE Int Conf Acoust Speech Signal Process* 2013:3128–32 CrossRef
78. Allen EA, Erhardt EB, Wei Y, et al. **Capturing inter-subject variability with group independent component analysis of fMRI data: a simulation study.** *Neuroimage* 2012;59:4141–59 CrossRef Medline
79. Watts DJ, Strogatz SH. **Collective dynamics of 'small-world' networks.** *Nature* 1998;393:440–42 CrossRef Medline
80. Liao X, Vasilakos AV, He Y. **Small-world human brain networks: perspectives and challenges.** *Neurosci Biobehav Rev* 2017;77:286–300 CrossRef Medline
81. Bullmore E, Sporns O. **Complex brain networks: graph theoretical analysis of structural and functional systems.** *Nat Rev Neurosci* 2009;10:186–98 CrossRef Medline
82. Sporns O, Honey CJ, Kotter R. **Identification and classification of hubs in brain networks.** *PLoS One* 2007;2:e1049 CrossRef Medline
83. van den Heuvel MP, Stam CJ, Boersma M, et al. **Small-world and scale-free organization of voxel-based resting-state functional connectivity in the human brain.** *Neuroimage* 2008;43:528–39 CrossRef Medline
84. Achard S, Bullmore E. **Efficiency and cost of economical brain functional networks.** *PLoS Comput Biol* 2007;3:e17 CrossRef Medline
85. Glasser MF, Coalson TS, Robinson EC, et al. **A multi-modal parcellation of human cerebral cortex.** *Nature* 2016;536:171–78 CrossRef Medline
86. Zalesky A, Fornito A, Harding IH, et al. **Whole-brain anatomical networks: does the choice of nodes matter?** *Neuroimage* 2010;50:970–83 CrossRef Medline
87. Li W, Andreasen NC, Nopoulos P, et al. **Automated parcellation of the brain surface generated from magnetic resonance images.** *Front Neuroinform* 2013;7:23 CrossRef Medline
88. Wang J, Wang X, Xia M, et al. **GRETNA: a graph theoretical network analysis toolbox for imaging connectomics.** *Front Hum Neurosci* 2015;9:386 CrossRef Medline
89. Menon V. **Large-scale brain networks and psychopathology: a unifying triple network model.** *Trends Cogn Sci* 2011;15:483–506 CrossRef Medline
90. Calhoun VD, Miller R, Pearlson G, et al. **The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery.** *Neuron* 2014;84:262–74 CrossRef Medline
91. Griffa A, Ricaud B, Benzi K, et al. **Transient networks of spatio-temporal connectivity map communication pathways in brain functional systems.** *Neuroimage* 2017;155:490–502 CrossRef Medline
92. Abrol A, Damaraju E, Miller RL, et al. **Replicability of time-varying connectivity patterns in large resting state fMRI samples.** *Neuroimage* 2017;163:160–76 CrossRef Medline
93. Abrol A, Chaze C, Damaraju E, et al. **The chronnectome: evaluating replicability of dynamic connectivity patterns in 7500 resting fMRI datasets.** *Conf Proc IEEE Eng Med Biol Soc* 2016;2016:5571–74 CrossRef Medline
94. Thompson WH, Fransson P. **The frequency dimension of fMRI dynamic connectivity: network connectivity, functional hubs and integration in the resting brain.** *Neuroimage* 2015;121:227–42 CrossRef Medline
95. Chen Y, Wang W, Zhao X, et al. **Age-related decline in the variation of dynamic functional connectivity: a resting state analysis.** *Front Aging Neurosci* 2017;9:203 CrossRef Medline
96. Park BY, Moon T, Park H. **Dynamic functional connectivity analysis reveals improved association between brain networks and eating behaviors compared to static analysis.** *Brain Behav Res* 2018;337:114–21 CrossRef Medline
97. Cheng JC, Bosma RL, Hemington KS, et al. **Slow-5 dynamic functional connectivity reflects the capacity to sustain cognitive performance during pain.** *Neuroimage* 2017;157:61–68 CrossRef Medline
98. Damaraju E, Allen EA, Belger A, et al. **Dynamic functional connectivity analysis reveals transient states of dysconnectivity in schizophrenia.** *Neuroimage Clin* 2014;5:298–308 CrossRef Medline
99. Hutchison RM, Womelsdorf T, Allen EA, et al. **Dynamic functional connectivity: promise, issues, and interpretations.** *Neuroimage* 2013;80:360–78 CrossRef Medline
100. Preti MG, Bolton TA, Van De Ville D. **The dynamic functional connectome: state-of-the-art and perspectives.** *Neuroimage* 2017;160:41–54 CrossRef Medline
101. Lindquist MA, Xu Y, Nebel MB, et al. **Evaluating dynamic bivariate correlations in resting-state fMRI: a comparison study and a new approach.** *Neuroimage* 2014;101:531–46 CrossRef Medline