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Regional Homogeneity: A Multimodal, Multiscale Neuroimaging Marker of the Human Connectome

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Abstract

Much effort has been made to understand the organizational principles of human brain function using functional magnetic resonance imaging (fMRI) methods, among which resting-state fMRI (rfMRI) is an increasingly recognized technique for measuring the intrinsic dynamics of the human brain. Functional connectivity (FC) with rfMRI is the most widely used method to describe remote or long-distance relationships in studies of cerebral cortex parcellation, interindividual variability, and brain disorders. In contrast, local or short-distance functional interactions, especially at a scale of millimeters, have rarely been investigated or systematically reviewed like remote FC, although some local FC algorithms have been developed and applied to the discovery of brain-based changes under neuropsychiatric conditions. To fill this gap between remote and local FC studies, this review will (1) briefly survey the history of studies on organizational principles of human brain function; (2) propose local functional homogeneity as a network centrality to characterize multimodal local features of the brain connectome; (3) render a neurobiological perspective on local functional homogeneity by linking its temporal, spatial, and individual variability to information processing, anatomical morphology, and brain development; and (4) discuss its role in performing connectome-wide association studies and identify relevant challenges, and recommend its use in future brain connectomics studies.

Keywords

connectome, centrality, connectomics, regional homogeneity, local connectivity

Introduction

The human brain is one of the most complex systems in nature. An adult human brain is composed of approximately 10^{11} neurons, which are massively interconnected to each other by synapses. Such a vast number of interacting neurons work collectively to execute all types of information processing and mental representations in the brain. It has always been a formidable challenge for neuroscientists and computational biologists to decipher how the brain works and directs behaviors (Pessoa 2014; Tognoli and Kelso 2014). Resting-state functional magnetic resonance imaging (rfMRI) has provided a promising solution for the characterization of human brain dynamics by measuring ongoing brain activity by enabling the recording of the Blood Oxygenation Level Dependent (BOLD) signals, and functional connectivity (FC) is a widely used and reliable method for characterizing functional interactions in the human brain connectome (Biswal and others 2010; Zuo and Xing 2014) (see Box 1).

FC was initially defined as the interregional relationship between remote brain regions and employed Pearson's correlation coefficient between their BOLD time series (Friston and others 1993). Previous studies have illustrated the structural basis (Honey and others 2009), individual variability (Mueller and others 2013), behavioral (Wendelken and others 2015), and neuropsychiatric correlations (Rudorf and Hare 2014) of the remote FC. Recently, with the emergence of the connectome theory of the brain and the increasing popularity of network science approaches,

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some novel features of the human brain such as the existence of hub regions, modules, rich clubs, core networks, and its hierarchical structure have been gradually identified (Bullmore and Sporns 2009, 2012; Sporns 2013; van den Heuvel and Sporns 2013). These findings demonstrated that the brain functions as a whole network system and its different units play distinct roles according to their remote connection profiles. Olaf Sporns and his colleagues conceived of the brain dynamics as an emergent phenomenon from an appropriately structured connectional design (Honey and others 2009). This was one of the answers to how the brain works and guides our behaviors.

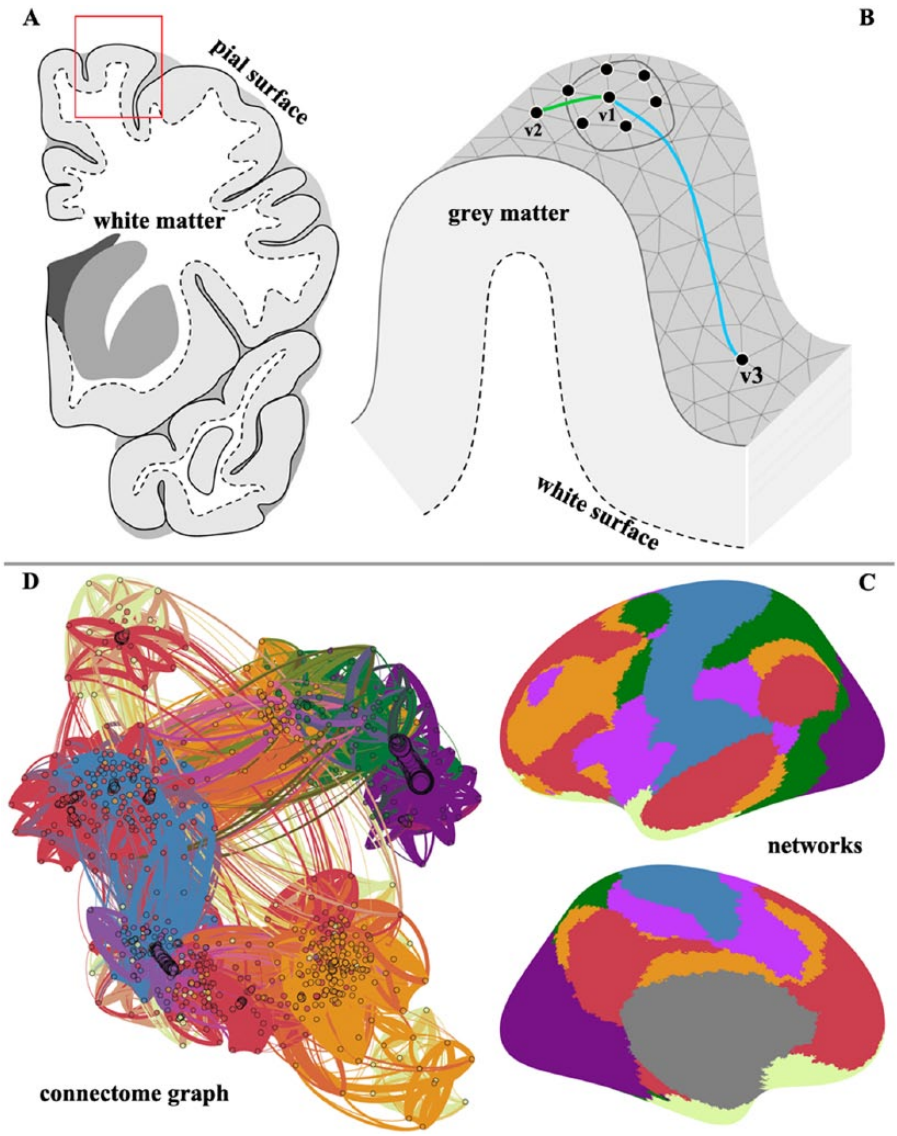
In contrast to the remote FC, local FC is defined as FC at a local spatial scale to measure functional interactions or synchronizations between the neighboring voxels or vertices. The spatial scale for differentiating local FC and remote FC is usually between 10 and 15 mm (e.g., 14 mm used in Sepulcre and others 2010). Deco and others (2014) demonstrated how the local FC profiles affect the whole brain dynamics. More specifically, they described how the local FC could induce alterations in the remote FC. This observation points to the significance of investigating local FC with local functional homogeneity (Zang and others 2004; Zuo and others 2013). Examination of the associations between local and remote FC can thus benefit the modeling of the structure-function relationships in the human brain. The regional variations in local FC suggest that it is problematic to define a node on the basis of a large structurally or anatomically informed region, as well as to construct an edge using an FC matrix. Simply averaging the voxel-wise time series within a large region obviously ignores the variability of the local FC strength across large structural areas, leading to ambiguity in the interpretation of the mean time series and further derived network metrics. This represents the second advantage of investigating the local FC, which indicates the boundaries between functionally heterogeneous regions (Zuo and others 2013) and can measure the nodal degree as a regional boundary point for delineating brain parcellation (Blumensath and others 2013). The final benefit of examining the local FC relates to its multimodal nature for integrating regional homogeneity in both structure and function. This advantage originates from two factors for defining regional homogeneity: (1) the definition of neighbors, which is determined by spatial adjacency reflecting structural or anatomical similarity; and (2) the definition of homogeneity, which is represented by the

Box 1.
Terminology: connectivity, network, connectome, and regional homogeneity.

Functional magnetic resonance imaging (fMRI) is a common method for assessing the temporal dynamic relationship between a pair of brain areas. fMRI signals are the recordings of the Blood Oxygenation Level Dependent (BOLD) signals in brain gray matter tissue (panel A). Such functional interaction is usually modeled with statistical dependency (e.g., correlation as in Biswal and others 1995) between BOLD time series of two areas; this interaction is termed as functional connectivity (FC). Currently, the highest resolution for imaging the human brain function with fMRI is 2 to 4 mm in space with a temporal sampling rate (TR) of 0.5 to 3 seconds. Ideally, FC measures would be assessed on the cortical surface to reflect the intrinsically layered organization of the human brain as a two-dimensional manifold. In practice, however, the accurate reconstruction of cortical surfaces has been a challenging topic in the field of computational geometry. Most frequently used, the mesh grid model for surface-based neuroimaging data analysis is a tessellation using finite elements of mesh with triangles (panel B). Both pial and white surfaces can be reconstructed by extracting boundaries between gray matter and cerebrospinal fluid (solid line in panel A) as well as boundaries between white matter and gray matter (dashed line in panel B). On the surfaces, local FC (green line in panel B) is defined as the FC between two nearby vertices (v1 and v2 as in panel B), whereas remote FC (blue line in panel B) refers to the FC between two distant vertices (v1 and v3 in panel B). The geodesic distance for differentiating local FC and remote FC is usually between 10 and 15 mm (Sepulcre and others 2010). FC profiles have segregated the human brain into different networks of connectivity between pairs of vertices. Panel C renders a network parcellation based on resting-state fMRI (rfMRI) data sets from 1,000 healthy adults, unfolding a total of seven networks in the human brain cortex (Yeo and others 2011). From the perspective of a whole brain system, the entirety of FC (functional connectome) is functional outcomes given by the underlying structural connectivity as a whole network (Biswal and others 2010; Sporns and others 2005; Zuo and others 2012). Panel D depicts a connectome graph (14,299 surface vertices as nodes) derived from 1,003 participants (same as in Zuo and others 2012) from the 1000 Functional Connectomes Project (Biswal and others 2010). In this brain graph, a node's contribution (how central it is) to the graph connection is quantified by the centrality metric of the network modeled by the graph. Therefore, theoretically, any index measuring the connectional contribution of a network can be termed as a network centrality metric. Regional homogeneity (ReHo) describes the summarized local FC between a given node and its nearest neighboring nodes (v1 and surrounding six vertices in panel B) and thus can be understood as an index of network centrality for characterizing the importance of the node in the human functional connectome. This metric has been widely applied to study the association between healthy or disease conditions and the local FC network centrality, namely, human connectome association studies (HCAS).

(continued)

Box 1. (continued)



functional homogeneity of the time series from these neighbors. These two features make regional homogeneity a network centrality metric with both structural and functional connectomics characterization.

This review has the following four aims: (1) briefly survey the history of studies on the organizational principles of human brain function; (2) propose local functional homogeneity as a network centrality to characterize the multimodal local features of the brain connectome; (3) render a neurobiological perspective on local functional homogeneity by linking its temporal, spatial, and individual variability to information processing, anatomical morphology, and brain development; and (4) discuss its role and recommend its use in performing connectome-wide association studies as well as identify the relevant challenges for future brain connectomics studies.

Principles of Human Brain Function

Explorations into uncovering the organizational principles of human brain function can be dated to as far back as one hundred years ago, when the dominant theories of functional interactions focused on either segregation or integration of human brain function (Tononi and others 1994). The functional segregation model posited that different brain regions were partitioned and specialized for the control of specific brain functions. This conceptual framework of brain function led directly to the discovery of the famous

Broca and Wernicke areas. Researchers typically targeted only one functional region at a time, and this method was proven to be one of the most efficient approaches for detecting specific cognitive functions within the entire brain, as well as to reveal hub regions for a given brain network. An alternative conceptual framework was proposed that suggested that neural pathways and circuits involving multiple brain regions supported the information processing hierarchies in the visual and auditory systems (Mesulam 1998). This concept of segregated brain functions has been developed further using task-based fMRI, where each segregated unit was conceived to respond selectively to an aspect of brain function.

The brain works as a whole network, and different regions play different roles according to their connectional patterns. Such an integration of segregated brain modules has been increasingly recognized in both empirical and computational neuroscience studies employing the tools of graph theory (Sporns 2013). Recently, neuroscientists have begun to extend our understanding of the brain functional organization of the brain by applying network science tools to the analysis of rfMRI data. This updated approach to the study of the human brain has enriched our knowledge through the discovery of various network properties, including the existence of hubs and their "rich clubs," hierarchically organized modules, and small world networks in the brain (Bullmore and Sporns 2009, 2012). Conversely, many computational biophysical models based on the fMRI technique were derived according to the classical Hodgkin-Huxley model (Börgers and others 2010), which used the electrochemical properties of neurons to calculate the membrane potential. It is a relatively complicated model containing many parameters and thus has not been widely applied in later studies aiming to generate high-resolution brain connectomes. Simplified versions of this model, such as the FitzHugh-Nagumo model (Ratas and Pyragas 2011), the Ghosh model (Ghosh and others 2008), and the Breakspear model (Breakspear and others 2003), have emerged to study human brain connectomes at a macro-scale (Honey and others 2009).

In summary, studying both functional segregation and integration in the brain is a promising method for understanding the functional organization of the brain and how it guides our behaviors. Whereas most studies, especially those focused on computational modeling, have focused on large-scale brain connectomics defined by whole brain system dynamics across 100 to 1,000 units, higher resolution connectomics composed of several 50,000 units of millimeters (commonly a resolution of imaging volumetric elements or voxel) has been very challenging for neuroscientists (e.g., Buckner and others 2009; Zuo and others 2012). These challenges originated from several issues related to examinations of both functional segregation and integration: (1) the difficulty in explicitly reconstructing such a large connectivity matrix, due to its computation and storage; (2) the need to generalize the network metrics at a large scale to those equally applicable at this high resolution; and (3) the requirements of integrated connectome algorithms across imaging modalities and temporal/spatial scales. Regional homogeneity (ReHo) was developed to address these issues.

A Multimodal and Multiscale Network Centrality

fMRI measures human brain function in vivo and in real time, which has greatly facilitated the discovery of the organizational principles of human brain function and has enriched our understanding of mind-brain-behavior relationships (Buckner and others 2013; Cole and others 2013; Cole and others 2014; Sporns 2014). Although the exact physiological meaning of the BOLD signal is currently a topic of intense research, fMRI is the most efficient tool for studying human brain function at a timescale of seconds and a spatial scale of millimeters. The BOLD-derived local functional homogeneity or connectivity (local FC) has been examined with the use of many different metrics (for a methodology review, see Zuo and others 2013); however, it has rarely been linked to brain connectomics (for a highlight of this idea, see Zuo and Xing 2014).

Characterizing Local Connectivity with ReHo

Local FC is defined by the temporal coherence or synchronization of the BOLD time series within a set of a given voxel's nearest neighbors. There are three factors relevant to quantifying the local FC: (1) the definition of nearest neighbors, (2) the computation of coherence or synchronization, and (3) the suppression of noise. Beyond other FC metrics, ReHo represents the most efficient, reliable, and widely used index (Zuo and others 2013; Zuo and Xing 2014). Specifically, for a given node (voxel or vertex of high-resolution connectomes) of a graph, we identify its K nearest neighbors (including this node) and denote $v_i(t)$ as their BOLD time series. The ReHo index of this node is computed as Kendall's coefficient of concordance (KCC) (Zang and others 2004) among these time series. The mathematical formula on KCC is detailed as the following equation (Kendall and Gibbons 1990):

$$\mathrm{KCC}=\frac{\sum_{i=1}^{n} R_i^2 - n(\bar{R})^2}{\frac{1}{12}K^2(n^3-n)} = 12\frac{\sum_{i=1}^{n}(\bar{R}_i)^2}{(n^3-n)} - 3\frac{(n+1)}{(n-1)},$$

where $R_{i=1,\ldots,n}$ represents the ranks of $v_i(t)$ and n is the number of temporal observations in the time series, $\bar{R}_i$ is

the mean rank across the K neighbors at the ith temporal observation, and $\overline{R}$ is the overall mean rank across all the K neighbors and all temporal observations. According to the equation, this index has obvious advantages in all three aspects of local FC: (1) the nearest neighboring nodes can be defined spatially, which is highly flexible for changing the neighboring size and usually reflects anatomical, morphological, and intrinsically geometric features in a local brain structure; (2) the rank-based computation is highly efficient in the time domain; and (3) this index is very robust against noise by integrating noise-filtering operations across both the spatial domain (the mean-rank filter) and the temporal domain (the order-rank filter).

Zang and others (2004) proposed the original ReHo in 3D volume imaging space. The neighbor relationship of a given voxel was determined by the adjacency of the voxel in either native or standard template 3D spaces (Fig. 1C). For example, two common neighbor sizes are 1 or 2, corresponding to the cubic box sizes of 3 or 5, which contain 9 or 27 neighbor voxels. We refer to these two ReHo metrics as 3dReHo-1 and 3dReHo-2. A highly efficient computation can be implemented by using commands in AFNI and FSL. This script has been released as part of the Connectome Computation System (CCS; Xu and others 2015). However, one issue with 3dReHo is that the partial volume effects are particularly salient for voxels close to the boundaries between different tissues (e.g., the boundary between gray matter and white matter, the yellow curve in Fig. 1A). To address this issue, Zuo and others (2013) developed a two-dimensional (2D) version of this metric by extending the computation onto the cortical mantle, namely 2D ReHo.

In nature, the cerebral cortex is organized into a sheet-like 2D surface (Fig. 1B), which is embedded into 3D space, and distributes its function according to both the topological and geometrical properties of this surface. Therefore, a surface-based analysis of functional data is particularly useful for integrating the intrinsic geometry (e.g., curvature, geodesic distance, and shape) of the cortical mantle into functional data analyses. While surface-based approaches have been developed for long-distance FC metrics, local FC is rarely examined on the surface model of the human cerebral cortex. Beyond the set of general benefits discussed above, an additional advantage of the surface-based ReHo is that neighboring relationships are both functionally and geographically meaningful. Figure 1D depicts two different neighbor sizes of 2D ReHo computation for a given vertex (orange color): (1) step-one 2D ReHo (6 blue neighbor vertices) and (2) step-two 2D ReHo (6 blue plus 12 pink, for a total of 18 neighbor vertices). The fast computation of surface-based ReHo as well as other functional metrics has also been released as part of the CCS.

Group-level analysis is an important step in studies using ReHo. Due to ReHo being a regional property, one key confounding factor would be the regional differences in image registration. As a result, we recommend including Jacobian values from the white surface transformation in general linear models as nuisance variables to control for the regional variability of registration. For multiple comparison correction, we recommend the cluster-wise method based on random field theory (cluster-defining $P = 0.01$, cluster-level corrected $P = 0.05$), which requests a Gaussian field. This requirement can be fulfilled by the spatial smoothness intrinsically included in ReHo computation.

Thinking about ReHo as a Network Centrality

In a graph, a node's contribution (or, how central a node is) to the connection flow is quantified by the centrality metric of the network modeled by the graph (Borgatti 2005) and serves an important analytic tool in social sciences (Borgatti and others 2009). Therefore, theoretically, any index measuring the connectional contribution of a network can be termed as a network centrality metric. Different network centrality maps can be used to characterize different network connectivity by constructing a functional brain graph explicitly (e.g., Zuo and others 2012). In contrast, it is not obvious that ReHo can be treated as a network centrality metric because the brain graph it depends on is not explicitly modeled. In fact, the graph behind the ReHo computation is the whole cortical network with its vertices as nodes, and temporal synchronizations between pairs of nodes as edges. This implicit graphical methodology offers several advantages in preserving weak connectivity in functional connectomics (Jiang and others 2015b; Pessoa 2014). From its definition, ReHo describes the functional connectivity relationships between a given node and its nearest neighboring nodes and thus quantifies the degree of connections with the nearest neighbors of a node in the brain graph. It can be understood as an index of network centrality to characterize the importance of the node in the human brain connectome regarding its local functional interactions.

To demonstrate the centrality property of ReHo, we calculated individual ReHo maps in both native 3D volume space (1.5 mm isotropic voxel) and 2D surface space (2 mm between-vertex distance) of a participant (sub001) from a publicly shared 7-T rfMRI data set, which is a part of the Consortium for Reliability and Reproducibility (CoRR; Zuo and others 2014). The details of the MRI scanning can be found in the data descriptor of this particular data set (Gorgolewski and others 2015). All image preprocessing was implemented in CCS and described comprehensively in the CCS pipeline paper. To achieve a ReHo computation without the confounding factors that

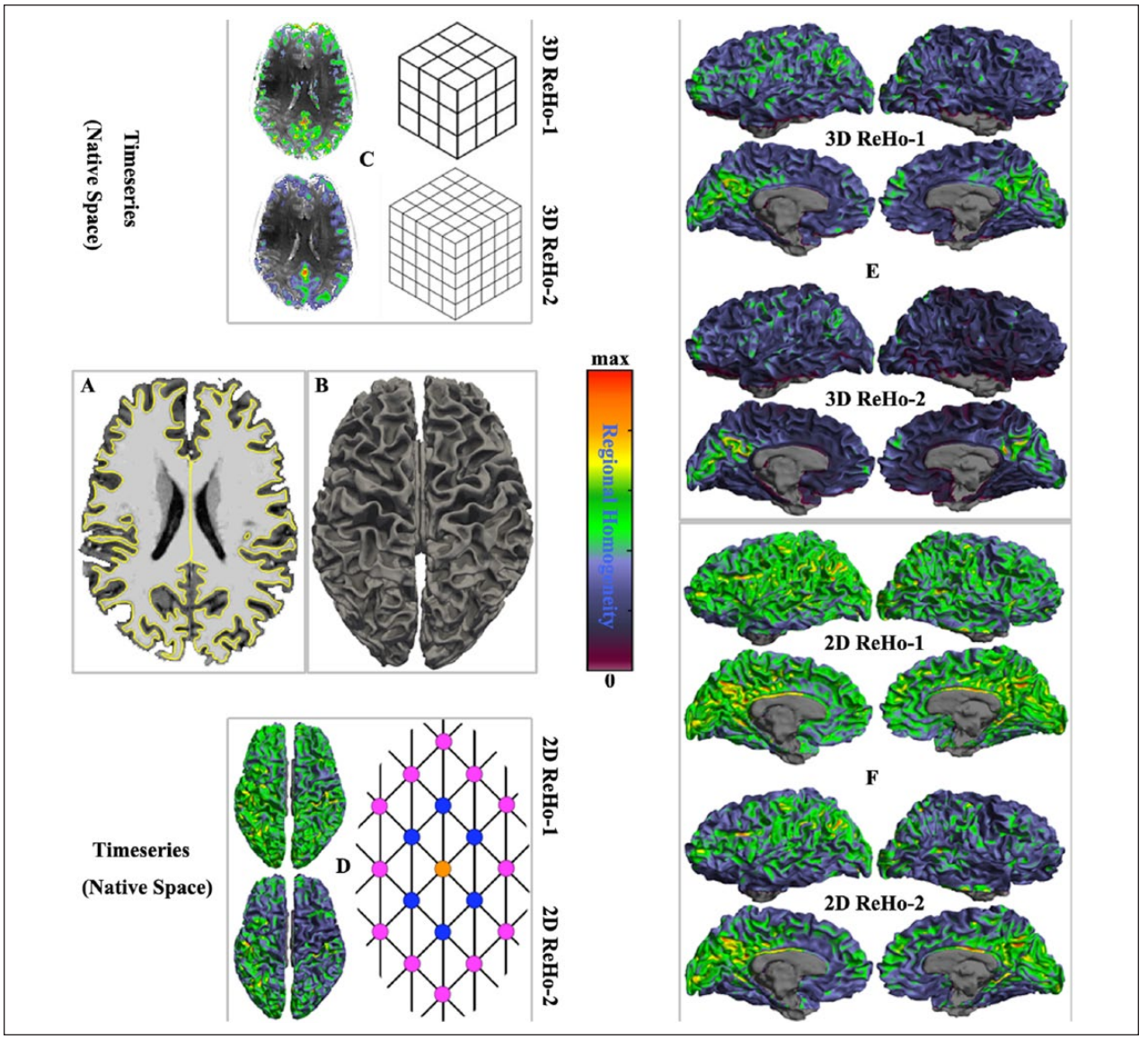


Figure 1. Computation procedures for ReHo in individual native spaces. (A) The brain tissue segmentation generated the boundary curve between gray matter (GM) and white matter (WM) tissues (yellow curve). (B) Cortical white surface was reconstructed from the GM/WM boundary by FreeSurfer in native space. (C) ReHo was calculated with the time series in native 3D volume space for two common neighbor sizes of 1 and 2 (namely 3D ReHo-1 and 3D ReHo-2), corresponding to the cubic box sizes of 3 or 5, which contain 27 or 125 neighbor voxels. (D) The time series in 3D space were projected onto the native 2D surface space. ReHo was then calculated with the time series in native 2D surface space for two common neighbor sizes of 1 and 2 (namely 2D ReHo-1 and 2D ReHo-2), which contain 7 or 19 neighbor vertices. (E) Map of 3D ReHo was projected onto the native 2D surface space. (F) Map of 2D ReHo was visualized on the native 2D surface space.

may be introduced by spatial normalization and interpolation, we implemented the computation in the individual native (both 3D volume and 2D surface) spaces. Specifically, in the 3D native volume space, the preprocessed rfMRI time series were used to estimate the 3D ReHo computation for both 9 and 27 neighbors (Fig. 1C). To make 3D and 2D ReHo comparable, these 3D ReHo maps were projected onto a native surface (2 mm between-vertex distance) as in Figure 1E by using boundary-based registration. For 2D ReHo, the time series were first projected onto the native surface space, and then the KCC values were estimated across all the vertices for both 7 and 19 neighbors (Fig. 1D). Both 2D ReHo-1 and 2D ReHo-2 were visualized vertex-wise as in Figure 1F.

The assessment of a network centrality metric is essential for understanding a series of topological properties of the network (Zuo and others 2012). ReHo exhibited the

highest values in the default network regions, the precuneus and medial visual cortex, revealing highly connected cortical hubs (Buckner and others 2009; Tomasi and Volkow 2011). Previous studies have demonstrated power-law and truncated exponent distributions of degree centrality for both structurally and functionally sparse large-scale networks (Bassett and Bullmore 2006). The edge densities of these large-scale networks are commonly smaller than 10% and thus named "sparsity." However, recent studies have demonstrated very dense (edge density >60%) networks in the monkey brain (Markov and others 2014), questioning the suitability of the use of the term "sparsity" in connectomics. In humans, the true edge density of the brain connectome at voxel or vertex level is unknown, and the distribution of its centrality can serve as an indirect measure of understanding the network organization in such meso-scale human connectomes. In Figure 2, we plotted the distribution functions or probability densities of 3D ReHo and 2D ReHo for two different neighbor sizes (both step-one and step-two neighbors) across the entire cortical mantle (Fig. 1E and F). This plot indicates three features of ReHo: (1) the distribution of ReHo is approximately Gaussian or normal across both 3D volume and 2D surface space; (2) the mean and range of ReHo are largely improved by 2D surface-based computation; and (3) the increase in neighbor size reduces the mean ReHo but does not change the shape of its distribution. These observations raise real challenges for investigating these meso-scale functional interactions as outputs from the underlying structural connectome.

Revealing ReHo's Multimodal and Multiscale Nature

Theoretically, the core aspect of ReHo depends on the structural definition of nearest neighbors across the cortical mantle, and such neighboring node information usually reflects anatomical, morphological, and intrinsically geometric features in local brain structure, with contributions to the determinant of local connectivity measured by ReHo. The computational implementation of ReHo is primarily constrained within a 2D mesh grid of the cortical surfaces, which is reconstructed from high-resolution individual anatomical data. This not only establishes a highly reliable index for measuring ReHo's multimodal nature (Zuo and Xing 2014) but also provides a highly feasible solution for common multimodal imaging studies by simultaneously integrating structural, functional, morphological, geometrical, and geographical features for a node or vertex on the surfaces (e.g., Jiang and others 2014). In addition, this method can also be employed to analyze regional homogeneity of data obtained by other imaging modalities across individuals. This has been demonstrated for studying the locally spatial covariance of the cortical thickness in the following section. Equally, such an index can be used to examine the local covariance of other morphological (thickness and area), geometric (curvature and local gyri index), and metabolic properties.

Another powerful feature of ReHo metrics is its multiscale nature because the neighbor size can be freely adjusted to capture the local connectivity across different spatial scales (Fig. 1). Regarding the sampling scale space, the common ReHo method was developed in the temporal domain, and its KCC values (KCC-ReHo) would be reduced if there were time lags among the time series of neighbors, despite sharing similar shapes. Accordingly, switching to the frequency domain, Liu and colleagues proposed coherence to measure regional homogeneity (Cohe-ReHo) (Liu and others 2010a) and found Cohe-ReHo was more sensitive than KCC-ReHo in detecting the differences in rfMRI activities.

The theory of neuronal oscillations in the mammalian brain proposed a spectrum of oscillatory bands for the implementation of functioning in human cognition. The whole frequency band could be categorized into 10 subbands: slow5 (0.01–0.027 Hz), slow4 (0.027–0.073 Hz), slow3 (0.073–0.198 Hz), slow2 (0.198–0.25 Hz), slow1 (0.25–1.5 Hz), delta (1.5–4 Hz), theta (4–10 Hz), beta (10–30 Hz), gamma (30–80 Hz), fast (80–200 Hz), and ultrafast (200–600 Hz) (Buzsaki and Draguhn, 2004). They revealed a $1/f$ power-law relationship between the power density of EEG and the frequency (f), as well as the possible function of the neuronal oscillation synchrony for input selection, binding cell assemblies, consolidation, and the combination of information. With rfMRI, Zuo and others (2013) investigated frequency-dependent properties of ReHo measures across different scales of the aforementioned slow subbands. Using a series of data-driven frequency bands, Song and colleagues generated ReHo maps within different frequency intervals and found that ReHo in cortical areas were higher and more frequency-dependent or richer in scales than those in the subcortical areas (Song and others 2014). The frequency-specific ReHo properties of different brain regions may arise from the varied cytoarchitecture or synaptic types in these areas and may underlie the neural-physiological basis of the local BOLD activities and the functional specificity of different brain regions.

Linking ReHo to Remote Functional Connectivity

The human brain functions as a whole network and a highly efficient, complex physical system. It is intuitive that neighbor-to-neighbor transmission or connection would bridge local connectivity and remote connectivity.

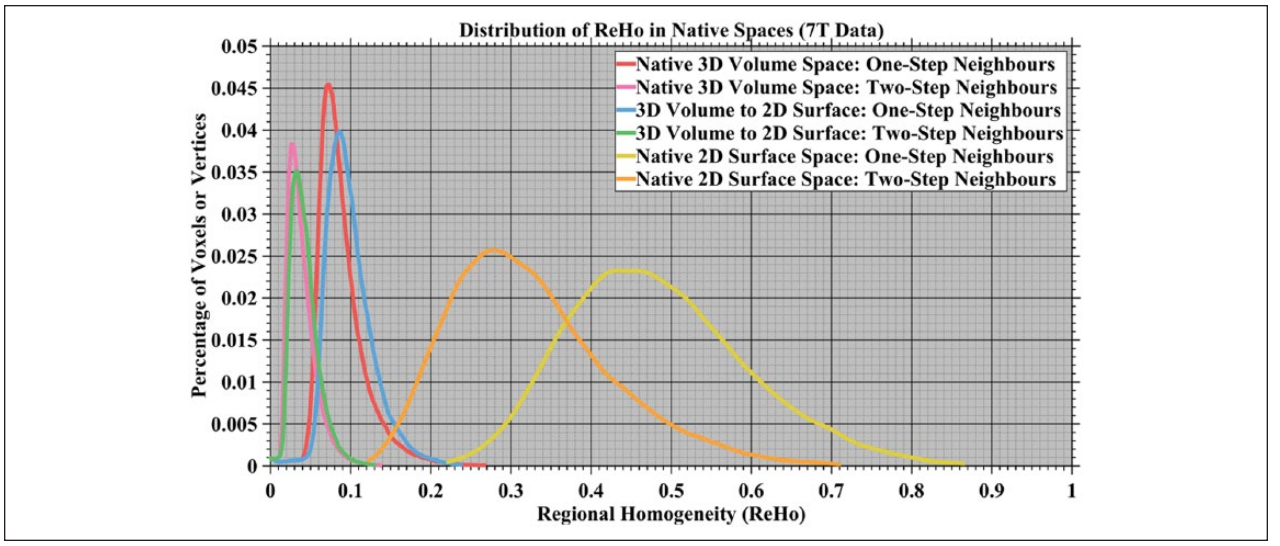


Figure 2. Distribution functions of 3D ReHo and 2D ReHo for two different neighbor sizes (both one-step and two-step neighbors) across the entire cortical mantle.

From a quantitative standpoint, Deco and others (2014) employed biophysical models to illustrate the effects of local feedback inhibition on the global dynamics of the large-scale brain network. They constructed a large-scale brain network model with 66 areas, wherein a cortical area was defined as a canonical local circuit composed of interconnected excitatory and inhibitory neurons coupled through NMDA, AMPA, and GABA synapses (Breakspear and others 2003), and inter-area couplings were constrained by the white matter fiber density connecting the two given brain areas (Honey and others 2009). They transformed the simulated excitatory synaptic activity to BOLD signals using the Ballon-Windkessel hemodynamic model (Buxton and others 1998). Their theoretical simulations demonstrated that the local feedback inhibition control model largely improved the prediction of remote functional connectivity and enhanced the dynamical repertoire of evoking the network and the accuracy of encoding the external stimulus. All these quantitatively validated findings highlighted the idea that the local connectivity profile within a network can essentially influence the global network dynamics. A very recent study made such efforts by fully decoding the links between local FC and remote FC from the perspective of the human brain being a complex system to generate synchronization, nonlinear dynamics, and low-frequency fluctuations (Minati and others 2015).

Besides the fact that computational neurosciences have revealed the importance of local connectivity in generating the global dynamics of the brain connectome, there is also increasing evidence that a similar mechanism for local-to-remote connectivity has existed for human brain development across much longer time scales, such as neurodevelopment (Fair and others 2009) or lifespan developmental changes (Betzel and others 2014; Cao and others 2014; Chan and others 2014; Zuo and others 2010a, 2010b). The changes of ReHo as a measure of local FC thus most likely induce the alterations of remote FC across the cortical mantle. In one recent study, with the use of 2dReHo, we demonstrated a local-to-remote FC miswiring profile of connectomes in schizophrenia (Jiang and others 2015b). The importance of physical distance between nodes in human brain network architecture has been validated (Ercsey-Ravasz and others 2013; Markov and others 2014). Interregional covariance of anatomical properties has been related to genetic factors, behavioral and cognitive abilities, as well as systematic lifespan changes (for a comprehensive review, see Alexander-Bloch and others 2013). The biological meaning of these structural covariance profiles may reflect regional homogeneity of developmental coordination or synchronized maturation. Future studies of the covariance network constructed from the correlations between local functional homogeneity (ReHo) and remote FC would help increase our understanding of the organizational principles underlying human brain function.

A Neurobiological Perspective for ReHo

A controversy surrounding ReHo concerns its utility as a biologically meaningful measure of human brain function, although previous studies have made some speculations based on its applications in brain diseases (Liu and others 2008). This difficulty of interpretation is partly caused by the nonlinearity of the rank-based operation in

ReHo computation and the indirect measure of neuronal activity using BOLD signals. Beyond that, ReHo is believed to reflect the local synchronization of spontaneous neural activity. However, strong evidence supporting this local synchronization hypothesis was missing. Recently, we systematically examined regional differences in ReHo and its morphological relevance, leading to a set of neurobiological evidence supporting the position that ReHo reflects the hierarchical organization of the brain and neurodevelopmental factors (Jiang and others 2014). The main findings in that study are briefly reviewed and highlighted as follows.

Hierarchies and Interindividual Variances

The existence of signaling pathways across multiple brain regions is the most important organization principle of human brain function. The signaling hierarchy usually comprises the primary sensory, upstream unimodal, downstream unimodal, heteromodal, paralimbic, and limbic zones of the cerebral cortex (Mesulam 1998). Gradients of ReHo characterize the degree of local functional integration and segregation of the human brain. The regional variation of local functional homogeneity within a pathway of brain regions can help clarify our understanding of the organizational principles of human brain function.

The visual system occupies the largest area of the human cerebral cortex and gives organisms the ability to process visual details, as well as enables the formation of several non-image photo response functions. This system detects and interprets information from visible light to build a representation of the surrounding environment. The division of cortical visual processing into distinct ventral and dorsal streams is a key framework that guides visual neuroscience. The ventral visual stream (VVS) is a more widely accepted and influential model in both non-human primates and humans, compared to the dorsal visual stream. The VVS has been clearly demonstrated to have a hierarchical organization. The information processing hierarchy in this stream can be used to detect the hierarchical variation of ReHo and begin unraveling the organizational principles of human vision within the brain. In the VVS, the primary visual cortex is also known as V1, striate cortex, calcarine cortex or Brodmann area (BA) 17 and covers the banks of the calcarine fissure. The unimodal visual association cortex can be divided into an upstream peri-striate component (BA 18, 19) and a downstream temporal component including the fusiform (BA 37), inferior temporal cortex (BA 20), and perhaps parts of the middle temporal gyrus (BA 21).

The mean 2D ReHo across the six VVS areas were ordered regarding their hierarchies of information processing, indicating a correlation between decreases in 2D ReHo and increases in complexity of information processing across the stream. This order of regional changes in 2D ReHo is highly reproducible across the two hemispheres and three large samples of neuroimaging data (Fig. 3A). Similarly, regional variation in high-order pathways such as posterior medial cortex (Fig. 3B) and prefrontal cortex (Fig. 3C) demonstrated more complex but reproducible hierarchical profiles of information processing. Such exciting illustrations proved that 2D ReHo has clearly neurobiological significance for measuring human brain function in terms of potential signaling pathways.

In general group analysis, we always need to calculate mean responses of brain function from a group of participants, and interindividual variability is often treated as noise and is ignored, being irrelevant to our research interests. However, covariance network studies of brain structure (Mechelli and others 2005) and function (Zhang and others 2011) have gradually elucidated the significance of interindividual variability or covariance. A recent study demonstrated that the interindividual variability of remote functional connectivity is heterogeneous across the human cortex, displaying significantly higher variability in the multimodal association cortex (Mueller and others 2013). Rather than being noise, interindividual variability is invaluable for understanding the principles of brain organization, evolution, and development.

To characterize the regional homogeneity of interindividual variability for local FC, we proposed the spatial covariance of ReHo (scovReHo) as KCC by iteratively applying the ReHo method on the cortical surfaces. More specifically, for each vertex, this algorithm replaced the number of time points in Equation (1) with the number of participants and the time series in Equation (1) with the ReHo values of all individual participants. A total of 627 participants from three large samples were selected to calculate the scovReHo: (1) 126 participants from the Nathan Kline Institute-Rockland Sample (NKI-RS; mean age: 36.84 ± 21.20 years; 68 males) (Nooner and others 2012), (2) 316 participants from the Enhanced NKI-RS sample (mean age: 44.38 ± 19.72 years; 112 males), and (3) 185 participants from the Chinese Color Nest Program (CCNP; mean age: 11.91 ± 3.14; 86 males) as part of the Consortium for Reliability and Reproducibility (CoRR; Zuo and others 2014). As control analyses, we also calculated coefficient of variation (CV) of ReHo (cvReHo) as an IIV metric of ReHo as well as similar computation for cortical thickness (CT), that is, scovCT and cvCT. Effects of site, gender, brain size, head motion, and registration error have been controlled during the analyses.

As shown in Figure 4, across the human lifespan of a temporal scale of years, the four high-order networks (frontoparietal control, dorsal attention, default mode, and ventral attention) exhibited low interindividual variability

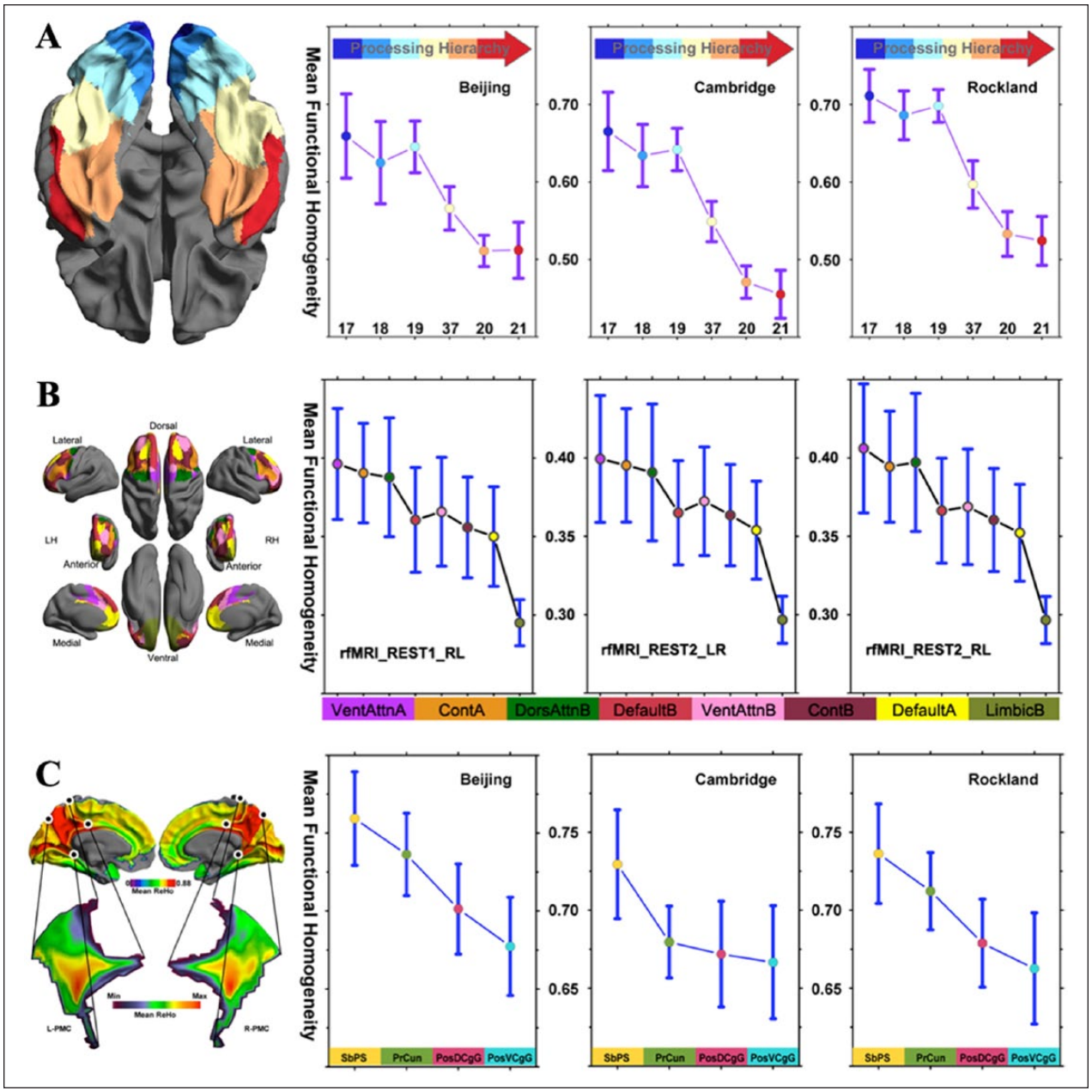


Figure 3. Regional hierarchies of ReHo and their reproducibility. Panel A illustrates regional variation of local functional homogeneity in the ventral visual system. Panel B illustrates functional network hierarchy of local functional homogeneity of the prefrontal cortex. Panel C illustrates regional variation of local functional homogeneity in the posterior medial cortex. Figures are reproduced and modified from Jiang and others (2014).

of ReHo, whereas the other three primary networks (visual, somatomotor, and limbic) demonstrated high IIV of ReHo (Fig. 4A). In contrast, the spatial covariance profiles of this interindividual variability demonstrated a considerably different distribution (Fig. 4C): (1) the visual and somatomotor networks are highly homogeneous in their lifespan changes of the local functional homogeneity and (2) the default mode, limbic, and control networks showed lower regional covariance of their local connectivity. These two findings, together, reveal a systematic and dynamic picture of the local functional homogeneity in the common neural networks across the human lifespan (Collin and van den Heuvel 2013). The high-resolution maps also serve as evidence for the local boundaries across cortical mantle and indicate a highly stable multimodal neuroimaging marker of local FC across the lifespan. In the posterior medial cortex (PMC), the gradient of ReHo covariance transformed into a distinct profile across the dorsal PMC and ventral

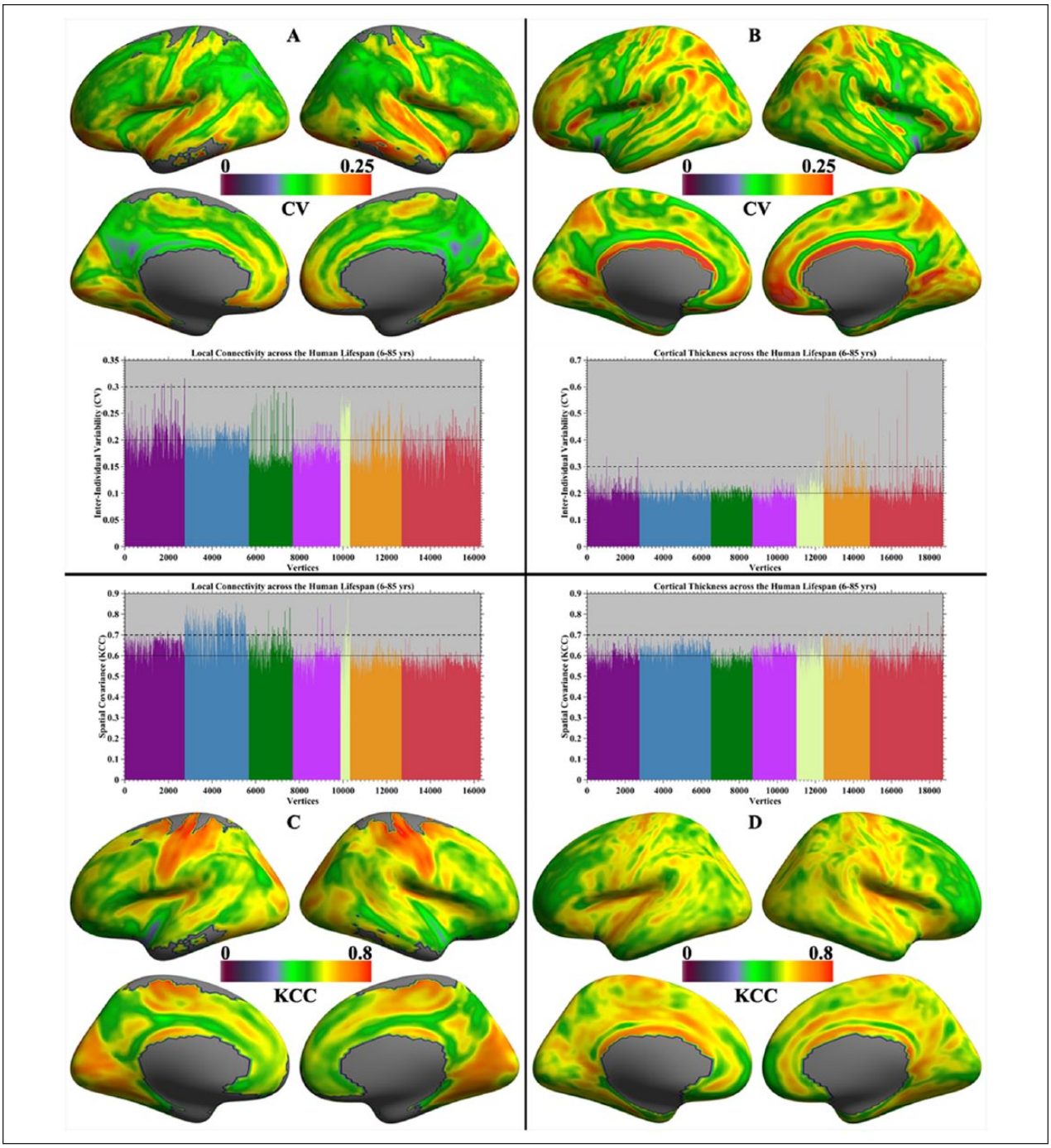


Figure 4. Interindividual variability and its regional covariance for local connectivity and cortical thickness across the human lifespan. Interindividual variability is measured with coefficient of variation (CV), and the relevant regional covariance is quantified by Kendall's coefficient of concordance (KCC). Panel A depicts the CV map of local connectivity and its Manhattan plot clustered according the seven common neural networks. Panel C renders KCC surface of local connectivity and its Manhattan plot. Panels B and D illustrates the same plots of cortical thickness regarding CV and KCC, respectively.

PMC (for a similar finding, see Jiang and others 2014). This echoes that the precuneus had different lifespan trajectories in relation to that of the default mode network (Yang and others 2014), which was recently highlighted in Power and others (2014). As for the control analyses, the cortical thickness exhibited different profiles for both interindividual variability (Fig. 4B) and spatial local covariance (Fig. 4D), indicating the distinct lifespan changes of

the neural networks as related to their function and morphology.

Brain Structure, Morphology, and Metabolism

Deciphering the structure-function relationship of the human brain has been a persistent challenge for scientists. In the field of single-cell biology, computational biologists have constructed multiple biophysical models of signaling pathways to explore how the signaling network topology supports its function (Jiang and others 2010). In the field of human brain connectomics, Olaf Sporns and colleagues conceived of brain dynamics as a phenomenon emerging from the appropriate connectional network structure of the brain to explain how the structural connectivity matrix shapes the functional connectivity matrix (Honey and others 2009). An exponential distance distribution that features stronger local connectivity than remote connectivity has also been characterized as a key property in human brain networks (Ercsey-Ravasz and others 2013), and a simple model derived from this exponential distance rule reproduced many properties of human brain networks (Markov and others 2014). From the single-cell level, Brodmann areas were constructed based on localized cytoarchitecture of neurons and remained the most widely known and frequently cited cerebral cortex parcellation of human brain function for over 100 years. These validate the dependence of human brain function on the structure or structural associations of function.

The homogeneity of cell number/type and neuron density can contribute to the functional homogeneity within a small region. However, at the time of this writing, these cell-level measurements are unavailable because of the constraints of the technique. From a morphological perspective, at the spatial scale of millimeters, cell properties determine the general morphology of cortex. Morphological MRI can safely measure cortical thickness, surface area, mean curvature, sulcal depth, and the gyrification index across the entire cortical mantle. We recently employed these metrics to estimate the structural contribution to 2D ReHo (Jiang and others 2014) and found widely distributed negative correlations between surface area and ReHo across the cortex, where the posterior dorsal part of the cingulate gyrus exhibited the highest area-homogeneity association. The functional homogeneity of the parieto-occipital sulcus, the marginalis cingulate sulcus, and the cingulate cortex exhibited significant positive correlations with their cortical thicknesses. Geometrically, the mean curvature of the cortical surface exhibited a high positive correlation with ReHo in a variety of sulcal clusters distributed into the frontal, temporal, parietal, and occipital cortices. This association was particularly salient along the cingulate sulcus. In several clusters of both temporal and parietal cortex as well as the anterior medial prefrontal cortex, the ReHo was significantly negatively correlated with the sulcal depth. Regarding folding pattern of the cortex, significant positive correlations between the local gyrus index and ReHo were observed in the dorsolateral prefrontal cortex and the middle temporal gyrus. These findings support the assertion that ReHo not only shares the individual variability with a wide range of cortical morphologies but also holds its own unique functional variability, which warrants comprehensive investigation in future studies.

From a metabolic perspective, the intercell or interneuron variability in the biochemistry of the relevant signaling pathways influences the variability of brain activity measured by fMRI. The magnitude of the BOLD signal and the connectivity across subjects within the default mode and the dorsal attention networks have been found to be associated with glucose metabolism (Nugent and others 2015). Significant positive correlations were observed across the whole brain between the regional metabolic rate of glucose and ReHo. Another important metabolic variable is cerebral blood flow (CBF), which can be examined with arterial spin labeling (ASL) imaging technology. Interestingly, the spatial distribution profiles were highly similar across CBF and ReHo metrics, particularly within the default network (Zou and others 2009). Li and others (2012) directly examined the relationship between rfMRI-derived ReHo and CBF regarding their interindividual variability and found ReHo was reliably correlated with CBF in most brain regions. Highly connected hub regions in functional connectomes have their physiological basis of blood flow (Liang and others 2013). These results demonstrated that the variability of CBF could, at least in part, explain ReHo-based variability, assigning a metabolic role to this local connectivity metric.

Developmental Underpinnings

The development of human brain function is a highly complex process involving both genetic and environmental variables. The application of in vivo rfMRI has greatly supported the elucidation of core principles during the human lifespan. Neuroimaging evidence consistently suggests that short-range connections evolve into long-range connections during human brain development, representing a transition from local to distributed organization during development (Lopez-Larson and others 2011). Specifically, this normal distance-dependent organization represents dynamic changes from short or homologous interhemispheric circuits to long-range and more efficient networks. Consistently, Uddin and others (2010) observed the pruning of local network connectivity and strengthening of long-range network connectivity with increasing age. It is thus not surprising that weakened short-range

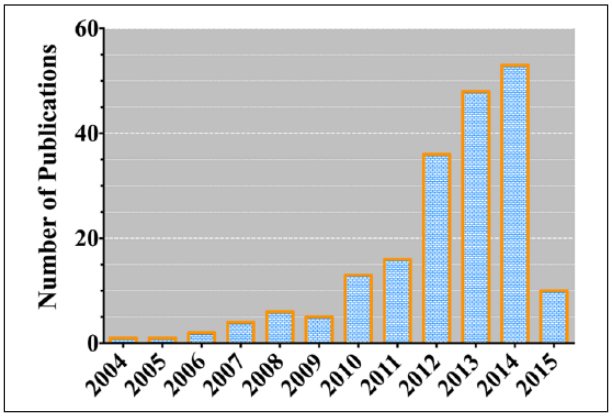


Figure 5. The number of published research papers using ReHo since 2004. These data were obtained by searching the PubMed database using the terms "regional homogeneity" followed by the manual exclusion of irrelevant references at 8:00 p.m. on February 17, 2015.

functional connections can serve as a good predictor of brain maturity as indexed by chronological age (Dosenbach and others 2010). ReHo as an index of local FC is associated with age in healthy brains, reflecting this local-to-remote developmental pattern. A general decrease in ReHo with age (11–35 years) was observed across the whole brain, of which the anterior cingulate and temporal lobe exhibited the greatest reduction (Lopez-Larson and others 2011). This reduction of ReHo with age was also detectable in a normal aging sample (59–73 years; Wu and others 2007) and was recently reproduced in a large lifespan (13–85 years) sample (N = 913; Tomasi and Volkow 2011).

In addition to the age effects of ReHo discussed above, the ReHo-based interindividual covariance network also suggested the developmental neurobiological meanings of this local connectivity metric. The structural covariance in the human cortex has increasingly been recognized as a reflection of the underlying developmental coordination or synchronized maturation between brain areas (Alexander-Bloch and others 2013). This rationale is generalizable to ReHo due to its structural and morphological associations. By analyzing the ReHo covariance network, we revealed a clear hierarchy of five modules in the human brain: the association network, motor network, visual network, auditory network, and transition network. This topology is attributed, at least in part, to interregional relationships in information processing or developing the cognitive capacities during brain development across the human lifespan. Interestingly, the degree centrality map (see Fig. 7 in Jiang and others 2014) of this ReHo covariance network exhibits a highly similar pattern of spatial distribution to that of myelin maps (see Fig. 3 in Glasser and Van Essen 2011). These findings indicate a potential link during neurodevelopment between structure and function regarding the interregional covariation of local functional homogeneity.

Physiological Confounding

Separation of physiological noise from fMRI signals is a major challenge in all the BOLD-based neuroimaging studies. ReHo, as a measure of local connectivity, may be particularly sensitive to cardiac or respiration effects within a local region. While we can take some steps to mitigate physiological noise influences on ReHo by regressing out white matter and cerebrospinal fluid signals and band-pass filtering signals of noninterest, some further processing can improve the accuracy and the specificity of physiological noise correction. One can model the physiological processes by simultaneously recording these noises during the imaging scans and then take out these physiological signals from rfMRI time-series (e.g., RETROICOR in Glover and others 2000). Another set of physiologically de-noising methods is purely data-driven and involves extracting noise-related processes from the rfMRI data (e.g., Falahpour and others 2013; Griffanti and others 2014; Pruim and others 2015a; Pruim and others 2015b; Salimi-Khorshidi and others 2014). A recent study proposed a very promising solution by combining these two strategies: modeling the physiological response functions using participant-specific TR of imaging sequences for the noise suppression (Cordes and others 2014). These methods are highly valuable for ReHo computation and will be implemented in future releases of CCS-based ReHo analysis (Xu and others 2015).

Human Connectome Association Studies

Since Zang's seminal work on the ReHo method published in 2004, the number of published research articles using ReHo is rapidly increasing, especially in recent years, as illustrated in Figure *5*. Beyond a small number of methodology papers, most previous studies employed ReHo to study the association between healthy or disease conditions and the local connectivity of the human brain connectome, termed Human Connectome Association Studies (HCAS). Healthy HCAS mainly targeted behavioral correlations of local connectivity with cognitive control and intelligence, whereas disease HCAS explored changes of local connectivity in a wide range of neuropsychiatric conditions across the lifespan, such as autism spectrum disorders (ASD), attention-deficit/hyperactivity disorder (ADHD), schizophrenia, major depression disorder (MDD), addiction, mild cognitive impairment (MCI), dementia, and Alzheimer's

disease (AD). Here, we systematically review these findings and interpret their explanations under a new perspective of the local functional homogeneity as a multimodal, multiscale marker of the human connectome. For all these papers, please visit the online data at http://www.ncbi.nlm.nih.gov/sites/myncbi/1hwqAdhRyR6/collections/47536879/public, which were obtained by searching the PubMed database using the terms "regional homogeneity" followed by manually excluding irrelevant references (8 p.m., February 17, 2015).

Behavior HCAS: Cognitive Control

Individual variation in the ability to control thoughts and behaviors represents individual differences in cognitive control. The main function of cognitive control is to accomplish goal-directed behaviors by monitoring interference or response conflict and dynamically adjusting performance. Such highly feasible and automatic adaptive adjustments can be studied via the "conflict adaptation effect" in congruency tasks. In the dorsal lateral prefrontal cortex (DLPFC), individual differences in ReHo can reproducibly and robustly predict individual variability in performance on a task of the behavioral conflict adaptation (Wang and others 2014). This finding indicated that higher ReHo values were linked to better performance during conflict adaptation behaviors. The underlying neural mechanism likely involves the variable complexity of information processing in the intrinsic functional architecture across different individuals.

Another feature of the brain's control system is response inhibition, which refers to the ability to suppress responses that are no longer required or appropriate. This ability thus supports flexible behavior in ever-changing environments and is a key component of executive control. The deterioration of response inhibition has been linked to certain disorders such as ADHD, OCD, and substance abuse. It has been demonstrated that ReHo could successfully predict stop signal reaction time (SSRT) in a stop signal task (Tian and others 2012). Specifically, positive correlations were observed in the bilateral inferior frontal cortex and three critical components of the default mode network (DMN), and negative ReHo-SSRT correlations were observed in the rolandic area/posterior insula and the bilateral middle occipital cortex. This may suggest that the degree of local functional integration or specialization was specifically associated with the task performance during response inhibition. More unwanted thoughts have been associated with lower ReHo (over functional specialization) in the right DLPFC and higher ReHo (over functional integration) in the left striatum (Kuhn and others 2014). The failure to suppress unwanted self-related thoughts can lead to extreme forms of negative thoughts that characterize psychiatric illness such as obsessive-compulsive, depression, anxiety, or posttraumatic stress disorders.

Behavior HCAS: Intelligence

Since the historical examination of Albert Einstein's brain, one of the most striking challenges in the field of neuroscience has been to understand the brain mechanism underlying intelligence. The intelligence quotient (IQ) is a standardized measure of human intellectual capacity that takes into account a wide range of cognitive skills and generally involves three measures: verbal, performance, and a synthesized full-scale IQ (FSIQ). With the advancement of image acquisition and analysis methods in recent years, the neural mechanism underlying human intelligence has been studied using rfMRI methods. Among these, ReHo was demonstrated to correlate positively with the FSIQ scores from the Chinese Revised Wechsler Adult Intelligence Scale within the bilateral inferior parietal lobules, the middle frontal, parahippocampal and inferior temporal gyri, the right thalamus, superior frontal and fusiform gyri, and the left superior parietal lobule (Wang and others 2011). The main findings here are consistent with the parieto-frontal integration theory of intelligence. Another study reported that Raven's Standard Progressive Matrices (RSPM) scores were positively correlated with ReHo values in the right fronto-insular cortex of the salience network, the right middle frontal gyrus and temporal pole, and the left fusiform and parahippocampal gyri. In contrast, RSPM scores were negatively correlated with ReHo in the bilateral sensorimotor cortex, the posterior cingulate cortex, the precuneus, and the right inferior parietal lobule of the default mode network (Yuan and others 2012). Although these findings seem to converge onto a macro-scale profile of local functional organization in the intrinsic architecture of human brain function, both the spatial and the statistical distribution of these correlational results are still controversial. This may be an indication that many methodological and neurobiological aspects of ReHo remain challenging and need to be carefully addressed in future studies.

Disease HCAS: ASD, ADHD, and Schizophrenia

ReHo was implicated as a reliable metric of neurodevelopment, which may be altered in various neurodevelopmental disorders such as ASD, ADHD, and early-onset schizophrenia. Previous studies have investigated abnormal changes in ReHo across these disorders. More specifically, when compared with typically developing controls, patients with ASD exhibited decreases in ReHo in the right superior temporal sulcus, inferior and middle frontal gyri, superior parietal and anterior prefrontal

regions, bilateral cerebellar crus I, right insula, and right postcentral gyrus, as well as increases in ReHo in the right thalamus, left inferior frontal and anterior subcallosal gyrus, bilateral cerebellar lobule VIII, and lateral and medial temporal regions (Di Martino and others 2014; Jiang and others 2015a; Paakki and others 2010; Shukla and others 2010). These abnormal organizations of local functional homogeneity are predominantly in the right hemisphere, leading to the conclusion that ASD is characterized by a right-hemisphere-dominant profile of ReHo alterations. Together with the most recent studies of the brain connectomics in autism using graph theory, we suggest that ReHo is a highly sensitive and reliable measure for characterizing local or short-distance connectivity and for detecting their abnormalities in ASD.

There are numerous studies that have examined abnormal brain changes in ADHD children compared to typical developing children. Nearly half of these studies employed ReHo as a feature for classifier methods and revealed some highly discriminative brain regions between ADHD and normal children, such as the prefrontal cortex, anterior cingulate cortex, and the thalamus. The ADHD symptom scores demonstrated positive correlations with the ReHo values in the right cerebellum, dorsal anterior cingulate cortex, and left lingual gyrus. These studies converged on a set of abnormal circuits in ADHD across frontal, parietal, temporal, and cingulo-occipito-cerebellar areas, suggesting the altered local function across these circuits and a link to abnormal behavioral outcomes (An and others 2013).

RfMRI-based ReHo studies on schizophrenia involved multiple perspectives, including discriminative models, different onset ages, first-degree relatives, DAOA gene effects, frequency dependent effects, and MA abuse effects. The brain regions showing abnormal ReHo included the frontal, the temporal, the cingulate gyrus, the cerebellum, the precuneus, the precentral gyrus, the middle occipital gyrus, and the insula. Regarding the neurodevelopmental aspect of this disorder, it is worth noting that consistent increases in local connectivity were observed across both early-onset schizophrenia (EOS) and adulthood-onset schizophrenia (AOS) patients in the right superior frontal gyrus, where the connectivity strength was correlated with the positive syndrome score in AOS patients (Jiang and others 2015b). In contrast, deceases in ReHo were only detectable for EOS patients in the postcentral gyrus, where the connectivity strength was correlated with the negative syndrome score. Diagnosis-age interactions in local FC and long-distance FC were also detectable in EOS patients.

Disease HCAS: MDD and Addiction

RfMRI studies have identified prominent abnormalities in large-scale brain networks of patients with pediatric, geriatric, early onset, late onset, late life, unipolar and bipolar depression, as well as relevant pharmacological and genetic effects. Unfortunately, it is unclear how localized dysfunctions of specific brain regions contribute to network-level abnormalities. We thus summarized studies investigating changes in ReHo using rfMRI depression (Iwabuchi and others 2015) and found that the medial prefrontal cortex (MPFC) showed the most robust, reproducible, and reliable increase in local functional connectivity in depression. This abnormality was greater in medication-free patients with multiple episodes. The brain networks anchoring this region have been identified previously to show aberrant connectivity in depression, and we thus propose that the localized neuronal inefficiency of MPFC (loss of optimal balance between functional integration and specialization) exists alongside network-level disruptions.

Addiction has been thought to be associated with abnormal brain organization for a long time. Moreover, recent addiction studies are increasingly focusing on non-substance addiction disorders, such as Internet addiction disorder (IAD). The pathogenesis of IAD has been explored regarding its underlying neural correlates by using the ReHo method (Kim and others 2015). To analyze encephalic functional characteristic of IAD, researchers recruited college students and examined their ReHo changes under resting state according to their self-reported levels of Internet use. The results showed that there are abnormalities of local functional homogeneity in IAD college students compared with the controls, indicating an enhancement of functional synchronization in most encephalic regions (Liu and others 2010b). Further studies revealed that long-term online game playing enhanced brain synchronization in sensory-motor coordination related brain regions and decreased the excitability in visual and auditory related brain regions (Dong and others 2012). These results show that functional changes of local connectivity were detectable in IAD college students and were related to reward pathways.

Disease HCAS: MCI, Dementia, and AD

Most patients with mild cognitive impairment (MCI) are thought to be in a very early stage of AD. As an index of regional brain activity, ReHo can provide a fast method for mapping local functional connectivity across the whole brain in MCI. Decreased ReHo or increased local functional segregation were found in the bilateral precuneus, left middle occipital gyrus, right inferior parietal lobe, and right angular gyrus of MCI patients, whereas increased ReHo or increased local functional integration were detected mainly in the left medial frontal gyrus, right para-central lobe, and cingulate cortex (Han and others 2011; Zhang and others 2012). Correlational

analyses indicated that decreases in ReHo were associated with the reduction of the memory and other cognitive abilities in MCI.

Monogenic dementias represent a great opportunity to trace disease progression from preclinical to symptomatic stages. Frontotemporal dementia related to Granulin (GRN) mutations presents a specific framework of brain damage, involving frontotemporal regions and long interhemispheric white matter bundles. Multimodal rfMRI is a promising tool for carefully describing the disease signatures in the earliest disease phase. In nature, ReHo is a multimodal neuroimaging metric for defining local connectivity and has been applied to examine alterations in GRN-related pathology moving from the presymptomatic (asymptomatic GRN mutation carriers) to the clinical phase of the disease (GRN-related frontotemporal dementia). Asymptomatic GRN carriers had a selective reduction of ReHo in the left parietal region and increases in ReHo in multiple frontal regions compared to healthy controls. Considering frontotemporal dementia patients (Premi and others 2014), these abnormal changes mainly targeted the inferior parietal lobule (IPL), frontal lobes, and posterior cingulate cortex (PCC), whereas GRN mutation carriers demonstrated a negative correlation with age in PCC, IPL, and orbitofrontal cortex.

Alzheimer's disease, the most prevalent cause of dementia in the elderly, is characterized by progressive cognitive and intellectual deficits. Altered spontaneous brain activations were found in MPFC, PCC/precuneus, and the left IPL in both MCI and AD. A correlation analysis indicated that the lower the memory and other cognitive abilities, the lower the ReHo in both MCI patients and AD patients (Zhang and others 2012). Dai and others (2012) proposed a novel methodological framework, namely, multimodal imaging and multilevel characteristics with multi-classifiers (M3), to discriminate patients with AD from healthy controls. The M3 approach chose ReHo as a favorite functional feature of the brain and contributed greatly to the patient classification predominantly involving several default-mode (MPFC, PCC, hippocampus and parahippocampal gyrus), occipital (fusiform gyrus, inferior and middle occipital gyrus), and subcortical (amygdale and pallidum of lenticular nucleus) regions. This supported the use of ReHo as an intrinsic index of human brain function.

Conclusion, Recommendation, and Challenges

No optimal protocol currently exists for ReHo analysis in the neuroimaging field. Regarding the recent advances in development of ReHo methodology as presented in this review, we would recommend the following considerations in use of ReHo. First, compared to 3dReHo, 2dReHo is more specific to intrinsic functional organization of the cortical mantle and has higher test-retest reliability. It should be recommended for more use in future studies. Second, ReHo represents the temporal synchronization of the nearest neighbors of a given node in a brain graph. The nearest neighbors could be defined as two lengths: one node (ReHo-1) or two nodes (ReHo-2) away from the given node. A large size of neighboring area increases the partial volume effect by mixing signals from different brain tissues. To optimize the trade-off between mitigation of partial volume effects and generation of Gaussian random fields, 3dReHo-1 (27 voxels) should be used as it is more appropriate for covering all directions in 3D space. In contrast, 2dReHo-2 (19 vertices) should be used regarding its comparable number of neighbors to 3dReHo-1.Third, both 3dReHo and 2dReHo computation should be implemented in individual native spaces to avoid multiple confounding sources introduced by head motion, imperfect image registration, and nonneural physiological processes. Finally, ReHo algorithm is purely data-driven and all the advantages discussed in the present work make ReHo highly feasible for analyzing images from brains with lesions. ReHo can be used to detect brain regions with abnormal local FC caused by lesions. Once detected, further analysis using these regions as targets of interests can reveal lesion-related changes of remote FC.

Anatomical distance and connection profiles are two key factors in wiring the human connectome and in generating its functional outcomes. Coming with an adaptive and elegant trade-off between signal and noise, the ReHo method introduced by Zang and colleagues is increasingly recognized as a highly sensitive, reproducible, and reliable neuroimaging marker to characterize the human brain according to its local functional organization as well as its relationships with network-level characteristics. During the last decade, over 100 scientific papers using ReHo have been published in the functional connectomics field. The rapid advancements not only validated ReHo's significance but also raised further challenges for functional connectomics. Recent advances in ReHo methodology validates its use as a network centrality metric with multiscale nature across both space and frequency, its relationship with remote long-distance functional connectivity, its neurobiological meanings related to information processing complexity and brain development, and its contributions to behaviors and neuropsychiatric disorders. As a result, we propose ReHo as a multimodal, multiscale neuroimaging marker of the brain connectome. These advances not only provide a novel perspective on understanding local functional homogeneity but also raise a series of challenges regarding its biological interpretation specific to behavior and disease as well as those specific to structure and function of the human brain connectome.

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