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Abstract

Imaging studies suggest that individual differences in cognition and behavior might relate to differences in brain connectivity, particularly in the higher order association regions. Understanding the extent to which two brains can differ is crucial in clinical and basic neuroscience research. Here we highlight two major sources of variance that contribute to intersubject variability in connectivity measurements but are often mixed: the spatial distribution variability and the connection strength variability. We then offer a hypothesis about how the cortical surface expansion during human evolution may have led to remarkable intersubject variability in brain connectivity. We propose that a series of changes in connectivity architecture occurred in response to the pressure for processing efficiency in the enlarged brain. These changes not only distinguish us from our evolutionary ancestors, but also enable each individual to develop more uniquely. This hypothesis may gain support from the significant spatial correlations among evolutionary cortical expansion, the density of long-range connections, hemispheric functional specialization, and intersubject variability in connectivity.

Keywords

individual differences, functional connectivity, association cortex, lateralization, evolution, fMRI

Introduction

Why people behave and think differently from one another is one of the most fascinating and long-standing questions in neuroscience. Neuroscientists have tried to find answers in genetics, neuroanatomy, neurophysiology, and more recently in functional connectivity. Emerging evidence from neuroimaging studies suggests that individual differences might be partly explained by the unique configuration of functional connectivity architecture in each person's brain (Smith and others 2013).

Our ability to characterize complex neural connections has advanced rapidly in the past several decades, particularly since the emergence of noninvasive brain imaging techniques such as fMRI. However, imaging functional networks at the single-subject level remains a daunting challenge due to technical limitations such as low signal-to-noise ratio (SNR). Consequently, neuroimaging studies have traditionally focused on identifying global properties of network architecture by taking advantage of the SNR increases gained by group-averaging, while the intersubject variability is averaged out along with noise (Zilles and Amunts 2013). Although these group-based imaging studies have led to remarkable progress in understanding brain organization, the findings may not be able to be directly translated to all individual subjects, especially to patients with neurological and psychiatric disorders.

Human brains differ, but the variation is not chaotic: connectivity is more likely to vary in a set of predetermined regions. Based on a group of subjects who were scanned five times within six months, Mueller and others (2013) recently conducted a systematic quantification of connectivity variability and found that intersubject variability in functional connectivity demonstrated a unique distribution across the cortex: while the association regions including the language, executive control, and attention networks demonstrate high variability, unimodal regions such as the primary visual and sensorimotor cortices are relatively consistent between subjects. A meta-analysis further revealed that loci of functional connectivity predicting individual differences in cognitive and behavioral domains are predominantly located in regions of high functional variability. These observations have raised a fundamental question: How did the association regions become so variable in humans? Mueller and colleagues reported that the spatial distribution of

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connectivity variability is correlated with a map of the estimated evolutionary cortical expansion, implying that individual differences in brain connectivity might be an outcome of brain size expansion. However, a specific theory explaining how brain enlargement can possibly lead to connectivity variability is lacking.

This article offers a hypothesis on the possible origins of the prominent variability in the human brain. Before laying out the hypothesis, we will first provide some background information on the scientific and clinical relevance of functional network variability and highlight two sources of variance that are often mixed in studies of individual differences.

The Individual Brain Is Characterized by Its Unique Connectivity Architecture

The advancement in noninvasive neuroimaging technologies, especially resting-state functional connectivity MRI (rs-fcMRI), has greatly contributed to the emerging field of brain connectomics that aims to characterize connectivity architecture in the individual subject's brain. Rs-fcMRI technology takes advantage of spontaneous brain activity events that cascade through all brain systems (Wisner and others 2013) and thus provides insight into the normally functioning brain, as well as functional abnormalities in brain disease (for reviews, see Fox and Greicius 2010; Fox and Raichle 2007). Variability observed in resting-state functional connectivity has been related to individual differences in human behavior and cognition (see Stevens and Spreng 2014 for a recent review). For example, the characteristics of functional networks can predict the five-factor personality traits (Adelstein and others 2011), intellectual capacity (Cole and others 2012; van den Heuvel and others 2009), reading ability (Koyama and others 2011), musical skill (Jancke 2012), and even impulsivity (Davis and others 2013). Brain changes associated with neurological and psychiatric disorders are also reflected by variations in functional connectivity (Fox and Greicius 2010).

Nevertheless, the extent to which brain networks can differ between subjects is often underestimated in many basic neuroscience and clinical studies. For example, a common target for the transcranial magnetic stimulation (TMS) treatment of depression is defined by centering the TMS coil at a point 5 cm anterior to the motor cortex, measured along the curvature of the scalp. We recently showed that a target defined in this fashion might fall in substantially different functional networks in different subjects, possibly leading to different therapeutic effects (Fox and others 2012). More broadly, understanding intersubject variability in the disease-related neural circuits is crucial for designing personalized treatment strategies or evaluating longitudinal brain changes for neurological and psychiatric patients. Taking obsessive-compulsive disorder (OCD) as an example, previous studies have repeatedly indicated network abnormalities in a specific neural circuit that involves the orbital frontal cortex (OFC), the dorsal anterior cingulate cortex (dACC), and the striatum (Kwon and others 2009). However, these areas are large and there exist within them discrete nodes that form the OCD-relevant circuit. To illustrate the intersubject variability of this OCD-relevant circuit, we placed a seed in the dorsal striatum and confirmed its strong connectivity to dACC at the group level (Fig. 1). The dorsal striatum seed was defined as the striatal regions connected to the frontoparietal control network based on 1000 subjects (Choi and others 2012). Importantly, the dACC nodes connected to the dorsal striatum demonstrated great intersubject variability, indicating that optimal treatment targets may vary across individuals. Furthermore, to measure the network changes after treatments such as cingulotomy in OCD patients, localizing these functional nodes at the individual level is essential.

Two Major Sources of Variability

Multiple sources can contribute to the observed intersubject variability in brain connectivity. The connectivity profile of a specific functional network is determined by its spatial distribution in the anatomical space, the connectivity patterns among critical nodes within the network, as well as its interactions with other networks. Consequently, intersubject variability can result either from individual differences in connectivity strength between the critical nodes or from differences in the anatomical locations of these nodes. For example, the mixture of variability can significantly confound the findings when studying individual differences in the language network. Spatial distribution variability of the language system has been well recognized: while most people have a left-lateralized language function, some people show bilateral representation and a few people may have completely reversed language dominance. In addition to the spatial distribution variability, connectivity strength between the frontal language area (Broca's area) and the temporal language area (Wernicke's area) can also vary between subjects (Koyama and others 2011), possibly due to size, length, and myelination differences in the fiber tracts connecting these regions.

Because the variability in anatomical location and functional characteristics are intertwined, it is important to properly estimate the potential anatomical confounding factors in functional measurements. Most of the connectivity studies have focused on connectivity strength between specific nodes, after aligning the data of different subjects anatomically. The implicit assumption has been that the anatomical variability is removed or controlled for

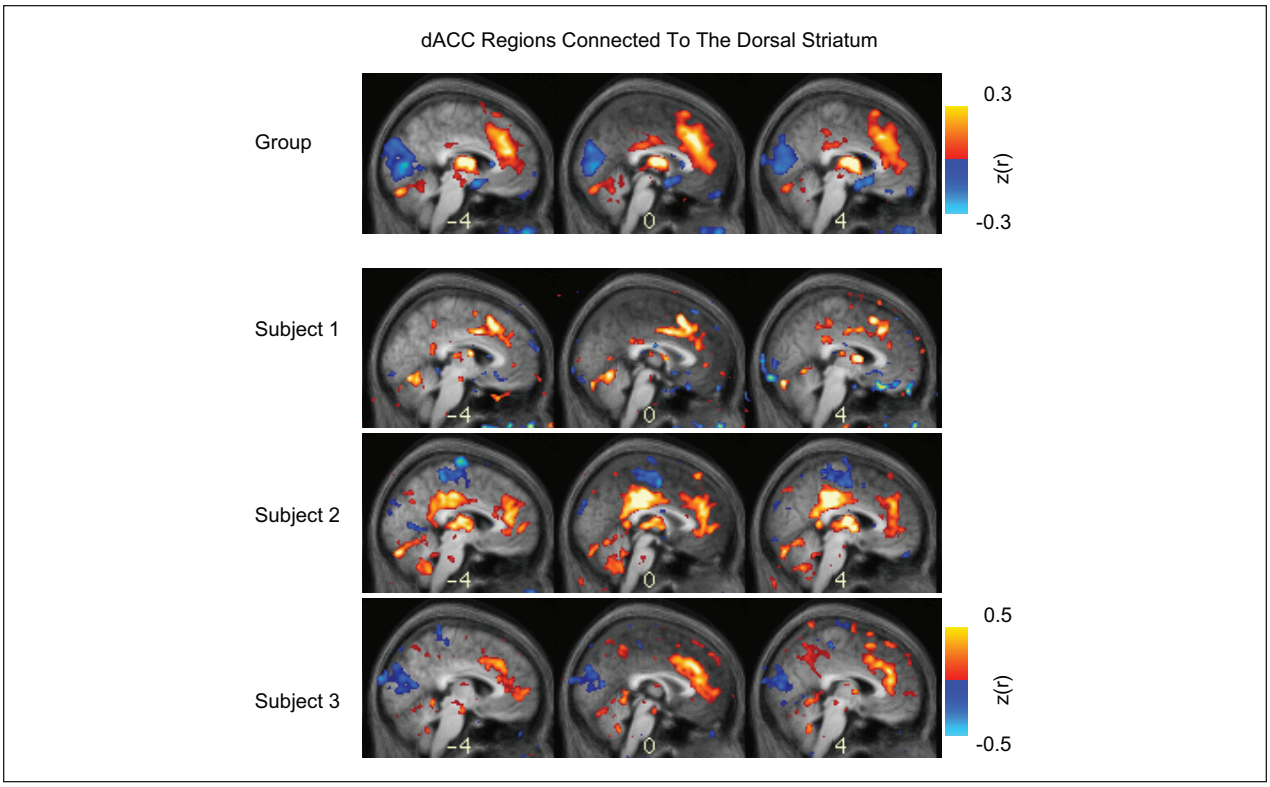

Figure 1. Resting-state functional connectivity suggests that great individual variability exists in a circuit related to obsessive-compulsive disorder (OCD). Previous studies on OCD have indicated connectivity abnormalities in a specific neural circuit that involves the orbital frontal cortex, the dorsal anterior cingulate cortex (dACC), and the striatum. We computed resting-state functional connectivity maps in 50 healthy subjects based on a dorsal striatum seed. The group-averaged connectivity maps (*Z*-transformed) are shown in the top row. The connectivity maps of three individual subjects are shown in the bottom rows. The maps demonstrate that the dorsal striatum seed can connect to different subregions in the dACC area in different subjects.

by intersubject alignment. Unfortunately, this assumption is not always true. Cross-subject alignment is usually based on the global morphology of two subjects' brains, or is based on the cytoarchitectural segmentation of a template (Fischl and others 1999). It is conceivable that these strategies cannot guarantee the alignment of functional networks if the intersubject variability in spatial distribution is high. Alignment error is particularly large for those lateralized functions because they can be localized to different hemispheres in different subjects.

The mixture of variability calls for special attention when one relates connectivity strength between anatomically defined or population-based regions of interest (ROIs) to cognitive capability (Hampson and others 2006), brain disorders (Fox and Greicius 2010), or genetic underpinnings (Thompson and others 2013), because the targeted networks in these studies are often those most variable, both anatomically and functionally (Fox and others 2012; Mueller and others 2013). The mismatch between the anatomical reference system and the functional layout makes the observed intersubject variability less specific to functional differences or sometimes completely irrelevant. In addition, due to great intersubject variability in cortical folding patterns, even anatomically aligning subjects is an exceedingly challenging task (Smith and others 2013).

Various methods have been proposed to factorize the spatial and functional variability of functional networks. For example, to study the connectivity strength between two functional regions, instead of using ROIs defined by anatomy or by population-averaged fMRI activation, some researchers have proposed defining individual-based ROIs using a functional localizer (Fedorenko and others 2010). Recently, more efforts have been devoted to parcellating the functional networks of the brain at the individual level based on resting-state connectivity (Cohen and others 2008; Hacker and others 2013; Nelson and others 2010; Wig and others 2013). Individualized functional atlases will enable the future development of new cross-subject normalization techniques for group-based analyses by aligning subjects functionally instead of anatomically.

A Hypothesis about the Origins of Connectivity Variability

A fundamental question regarding individual variability is how the connectivity architecture became particularly variable in the association regions. Here we hypothesize that the dramatic size expansion of the brain over the course of human evolution may have led to a series of changes that not only distinguish modern humans from our ancestors but that these same changes also make us different from one another. These changes include abundant long-distance connections that link the association regions that are widely distributed across the brain, as well as critical changes in organizational properties such as hemispheric specialization.

The human cerebral cortex is three times the size of modern great apes and has about 10 times the surface area of the macaque monkey (Preuss 2011; Sherwood and others 2012). Importantly, this evolutionary expansion is not uniform across the entire cortex but exhibits disproportionate enlargement in the association cortex. The expansion of the cortical areas was recently estimated by comparing the size of putative homologous regions in the macaque brain and the human brain (Hill and others 2010; Van Essen and Dierker 2007). Evolutionary expansion was estimated by interspecies surface-based registration according to "regions known or strongly suspected to be homologous as registration constraints" (Hill and others 2010). It should be noted that determining homology across different species is particularly difficult for higher-order cognitive regions (see, e.g., Rizzolatti and others 1996 and Saleem and others 2014 for different propositions of the monkey homology of the inferior frontal gyrus in humans), and some areas in humans may not have apparent homology in nonhuman primates. Therefore, the estimate of evolutionary expansion should be interpreted with appropriate caution. Distributed association regions in the temporal, parietal, and frontal lobes demonstrated disproportionate expansion, whereas the motor and sensory areas showed a lower rate of expansion (Fig. 2A). Importantly, the areas that expanded rapidly during human brain evolution also exhibit greater expansion during postnatal development and mature more slowly. A greatly expanded and slowly maturing association cortex can provide a higher degree of freedom both in physical space and time for environmental factors to act on, potentially giving rise to intersubject variability. The flexibility to change neural wiring under variable environmental influences and the resulting diversity may eventually bring advantages to humans through natural selection.

The evolutionary and developmental cortical expansions may both be accompanied by modification, and possibly optimization, of the connectivity architecture.

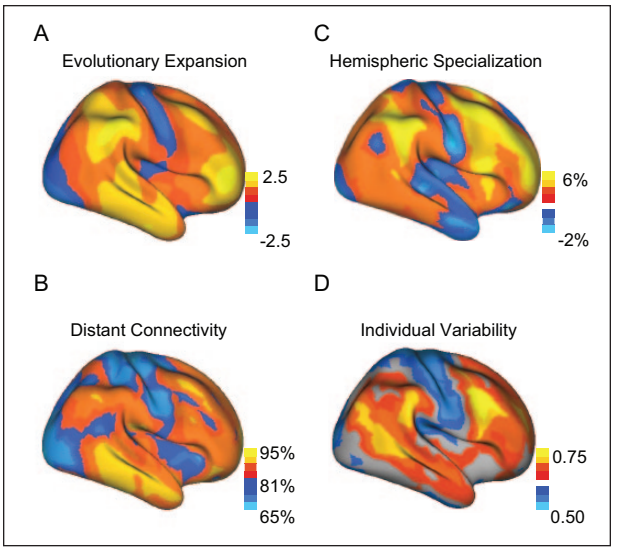

Figure 2. (A) The evolutionary cortical expansion was estimated by interspecies surface-based registration between an adult macaque and the average human adult PALS-B12 atlas, according to regions known or strongly suspected to be homologous as registration constraints. Distributed association regions in the temporal, parietal, and frontal lobes demonstrated disproportionate expansion, whereas the motor and sensory areas showed a lower rate of expansion. Data were provided by Van Essen and colleagues (Van Essen and Dierker 2007). (B) A map of distant connectivity. Distant connectivity was defined as the connection ($r > 0.25$) between two regions with a distance larger than 25 mm. Local connectivity was defined as the connection ($r > 0.25$) within 12 mm. The percentage of distant connectivity was then estimated at each brain voxel and projected to the brain surface (Mueller and others 2013). (C) A map of hemispheric specialization. Hemispheric specialization was calculated at each vertex by subtracting the count of cross-hemispheric connections from the count of within-hemispheric connections based on 1000 healthy subjects (Wang and others 2012). The counts of connections were normalized by the total number of vertices in each hemisphere. The specialization index is denoted as a percentage. Regions with higher within-hemispheric connectivity than cross-hemispheric connectivity are shown in warm colors. Regions with higher cross-hemispheric connectivity are shown in cold colors. (D) Intersubject variability was quantified at each surface vertex across 23 subjects after correction for underlying intrasubject variability (Mueller and others 2013).

The expanded association areas in humans are organized as multiple interdigitated networks; each network involves regions widely distributed in the frontal, parietal, temporal, and cingulate cortices that are linked by parallel, long-range connections (Buckner and Krienen 2013; Goldman-Rakic 1988; Mesulam 1998). Although primary sensory pathways also involve parallel anatomical connections in distributed areas (Kravitz and others 2013), the special emphasis on long-range rather than

local processing in the association cortices is prominent in functional connectivity (Sepulcre and others 2010). The ratio between long- and short-range functional connectivity is greatest in the association areas. In contrast, regions within or near primary sensory and motor areas display high local connectivity consistent with a modular organization (Fig. 2B).

With an enlarged brain volume and elongated neural pathways, the cost of maintaining the physical connections and the pressure for speed of signal transmission both increase. The negotiation between "lowering the wiring cost and improving adaptive value" during evolution (Kaiser and Hilgetag 2006) could have led to emergence of more efficient connectivity configurations that became markers of individual differences. A particularly important marker is hemispheric specialization. This topological property can enable efficient processing (Ringo and others 1994) through segregation and integration, which is related to an increased capacity to process multiple tasks in parallel (Rogers and others 2004). A specialized network organization also reduces the need for cross-hemispheric interaction on top of the within-hemispheric connections that are already slow in the enlarged brain. Cross-hemispheric information transfer occurs by way of the anterior and posterior commissures and, most importantly, via the corpus callosum. As the majority of the fibers in human corpus callosum are under 1 μm in diameter (Aboitiz and others 1992; Tomasch 1954), interaction between hemispheres is time-consuming and requires additional energy on top of the intra-hemispheric processing. For example, a one-way cross-hemispheric transfer between the temporal lobes could introduce a delay of over 25 ms in addition to the within-hemisphere traffic (Aboitiz and others 1992). The temporal constraint will be alleviated if local circuits within a single hemisphere become specialized for time-critical tasks without relying on the feed-forward and feedback projections between two hemispheres. Not coincidentally, hemispheric specialization of functional connectivity is most prominent in higher-order cognitive regions (Liu and others 2009; Wang and others 2013), particularly in regions related to language, memory, and spatial processing. In contrast, unimodal sensory and motor functions are more bilaterally represented (see Gazzaniga 2000 for a review). Higher specialization of the cognitive functions is most likely to be driven by the higher pressure for processing efficiency in the expanded association cortices. Specialization heterogeneity across functional systems can also be reflected in the anatomical arrangement in the corpus callosum. The thick, highly myelinated, fast-conducting fibers are mainly located in callosal regions connecting the primary and secondary sensorimotor areas, while thin, poorly myelinated fibers are densest in callosal regions connecting higher-order association areas in the frontal, parietal, and temporal lobes (Aboitiz and others 1992). Using resting-state functional connectivity, we recently computed the degree of hemispheric specialization at each brain voxel according to the imbalance between within-hemispheric connections and cross-hemispheric connections (Wang and others 2012). The assumption was that a brain region involved in a lateralized function would rely more on within-hemispheric connectivity, rather than cross-hemispheric connectivity, as supported by ample anatomical and physiological evidence. We found that the association areas demonstrated prominent specialization, whereas the sensory and motor areas exhibited less specialization (Fig. 2C). Interestingly, the frontoparietal control network, which is suggested to be an evolutionarily novel (Mantini and others 2013) or expanded (Buckner and Krienen 2013) network in humans, demonstrated particularly strong specialization in both hemispheres. Although lateralization of motor functions such as handedness is well-recognize and can be related to anatomical and language lateralization (Amunts and others 1996), functional connectivity in motor regions is relatively symmetric compared to association areas (Wang and others 2013; Wey and others 2013), possibly reflecting that the coordination of parts on both sides of the body is a more distinctive feature of motor function rather than lateralization.

Comparing the regional variation of evolutionary cortical expansion, the relative density of long-range connectivity, the degree of hemispheric specialization, and the intersubject variability of connectivity architecture revealed close relations among them (Fig. 2). It has been previously demonstrated that the regions showing the most prominent intersubject variability are also the regions showing the most rapid expansion during human brain evolution, and these regions are dominated by long-range connections (Mueller and others 2013). Complementing these findings, here we showed a significant spatial correlation (Spearman rank correlation $r = 0.45$, $P < 0.0001$) between hemispheric specialization and intersubject variability, indicating that regions of high specialization were also the regions that were most variable across individuals. A correlation (Spearman rank correlation $r = 0.49$, $P < 0.0001$) between hemispheric specialization and evolutionary cortical expansion was also observed, supporting the relation between optimized connectivity architecture and cortical expansion.

These observations may support our hypothesis that evolutionary cortical expansion has initiated a series of changes in connectivity architecture, and it is these changes that make human brains particularly variable. This hypothesis could gain further support from developmental studies, as evolutionary history is often reflected by the developmental trajectories. In humans, the association cortices demonstrate the greatest postnatal

enlargement and a slow maturation rate (Hill and others 2010), providing a higher degree of freedom in space and time for environmental factors to act on. Consistent to this proposition, it is suggested that the developmental reorganization of functional connectivity hubs experiences a shift from the sensory and motor cortices, which are dominated by local connectivity, toward the default network (Fransson and others 2011) and the frontoparietal areas (Power and others 2010) that are characterized by long-distance connectivity. The postnatal cortical expansion and the development of long-distance connectivity may drive the maturation of hemispheric specialization in the association cortex. Indeed, longitudinal studies have revealed that language lateralization demonstrates an almost linear increase during development (Holland and others 2001; Szaflarski and others 2006).

Summary

The extraordinary success of humans among other species might have profited from the unimaginable richness and diversity of human capacity. The extent to which human brains can differ is remarkable and understanding individual variability has strong implications for basic neuroscience research and clinical practices. The spatial heterogeneity of intersubject variability is likely to be the outcome of evolutionary cortical expansion that triggered a series of changes in connectivity architecture, including prominent hemispheric specialization. These changes not only differentiate us from our evolutionary ancestors but also enable each one of us to develop more uniquely, an outcome that may benefit humanity as a whole through natural selection.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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