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Individual Variability in Functional Connectivity Architecture of the Human Brain

Sophia Mueller,[1,2,3] Danhong Wang,[1] Michael D. Fox,[4] B.T. Thomas Yeo,[1,5] Jorge Sepulcre,[1,2,6] Mert R. Sabuncu,[1] Rebecca Shafee,[2] Jie Lu,[7,*] and Hesheng Liu[1,*]
[1]Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Charlestown, MA 02129, USA
[2]Harvard University, Center for Brain Science, Cambridge, MA 02138, USA
[3]Ludwig Maximilians University Munich, Institute of Clinical Radiology, Munich 81377, Germany
[4]Department of Neurology, Massachusetts General Hospital, Brigham and Women's Hospital, Boston, MA 02114, USA
[5]Neuroscience and Behavioral Disorders Program, Duke-NUS Graduate Medical School, Singapore 169857, Singapore
[6]Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA
[7]Department of Radiology, Xuanwu Hospital of Capital Medical University, Beijing 100053, China
*Correspondence: jielu@nmr.mgh.harvard.edu (J.L.), hesheng@nmr.mgh.harvard.edu (H.L.)
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SUMMARY

The fact that people think or behave differently from one another is rooted in individual differences in brain anatomy and connectivity. Here, we used repeated-measurement resting-state functional MRI to explore intersubject variability in connectivity. Individual differences in functional connectivity were heterogeneous across the cortex, with significantly higher variability in heteromodal association cortex and lower variability in unimodal cortices. Intersubject variability in connectivity was significantly correlated with the degree of evolutionary cortical expansion, suggesting a potential evolutionary root of functional variability. The connectivity variability was also related to variability in sulcal depth but not cortical thickness, positively correlated with the degree of long-range connectivity but negatively correlated with local connectivity. A meta-analysis further revealed that regions predicting individual differences in cognitive domains are predominantly located in regions of high connectivity variability. Our findings have potential implications for understanding brain evolution and development, guiding intervention, and interpreting statistical maps in neuroimaging.

INTRODUCTION

The human brain is characterized by striking interindividual variability in neuroanatomy and function (Frost and Goebel, 2012; Rademacher et al., 2001; Sugiura et al., 2007; van Essen and Dierker, 2007) that is reflected in great individual differences in human cognition and behavior. Such variability is a joint output of genetic and environmental influences that may differentially impact on different brain systems (Glendenning and Masterton, 1998). For example, structural variability of association cortex is less influenced by genetic factors during development (Brun et al., 2009), allowing more variable impact of postnatal environmental factors that lead to the diversity of neural connections beyond their genetic determination (Petanjek et al., 2011). A plethora of evidences suggest that neural systems subserving higher-order association and integration processes are more variable than those implicated in unimodal processing. Language areas for example exhibit overproportionally high variability in cytoarchitectonically defined volume (Amunts et al., 1999), as well as in fMRI-derived localization (Frost and Goebel, 2012). At a macroscopic scale, structural variability in cortical folding is higher in association areas than in the motor cortex (Hill et al., 2010a). In addition, long association white matter fiber tracts are more variable than the optic radiation and the corticospinal tract (Bürgel et al., 2006). In contrast to the large amount of work assessing structural variability across brain areas, individual variability in functional connectivity has not been systematically investigated and quantified.

An individual brain might be best characterized by its connectome (Seung, 2012). One powerful technique for assessing connectivity utilizes fMRI data obtained under resting conditions, often referred to as intrinsic functional connectivity (Fox and Raichle, 2007). Individual differences in intrinsic functional connectivity can predict individual performance variability in several cognitive domains in the healthy (Andrews-Hanna et al., 2007; Seeley et al., 2007; van den Heuvel et al., 2009) and symptom severity in neuropsychiatric disorders (Fox and Greicius, 2010; Greicius, 2008). Quantifying the spatial distribution of intersubject variability in connectivity could therefore provide new insights into the neural underpinnings of individual differences in human functions. This distribution could also have practical implications in guiding surgical mapping, interpreting imaging results (if results are averaged across subjects, it is less likely to obtain a significant effect in highly variable regions) and understanding which areas are the most likely to relate to variability in behavior.

In the present article, we collected intrinsic functional connectivity MRI data on 23 healthy subjects each scanned five times

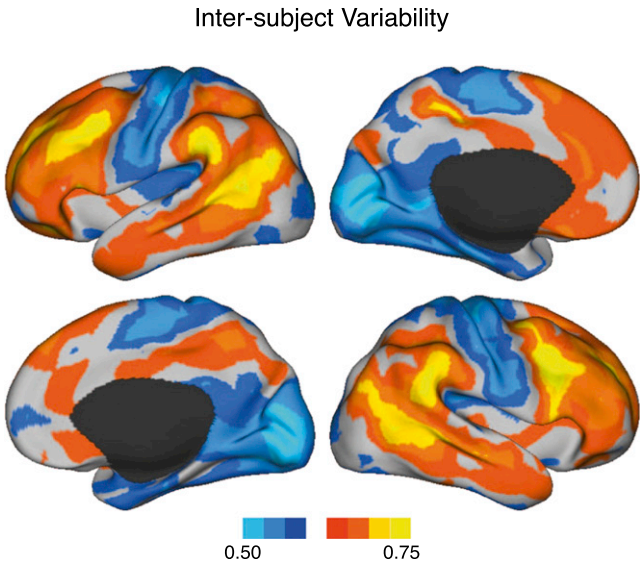

Figure 1. Intersubject Variability in Resting-State Functional Connectivity Is Heterogeneous across the Human Cortex

Intersubject variability was quantified at each surface vertex across 23 subjects after correction for underlying intrasubject variability. Values below the global mean are shown in cool colors while values above the global mean are shown in warm colors. See also Figure S1.

over 6 months. This unique data set allows us to assess the spatial distribution of intersubject variability while controlling for measurement instability based on intrasubject variance. This map of intersubject variability was then directly compared to maps of evolutionary cortical expansion, anatomical variability, and long-range integration and regional segregation (Sepulcre et al., 2010). Finally we performed a meta-analysis to explore how functional connectivity variability may relate to previously observed individual differences in cognition and behavior.

RESULTS

Intersubject Connectivity Variability Is Nonuniformly Distributed across Brain Networks

Intersubject variability in intrinsic functional connectivity was quantified at each vertex of the brain surface after correction for nuisance variance (see Figures S1A and S1B, available online, and Experimental Procedures for the details). Intersubject variability demonstrated a nonuniform distribution across brain regions (Figure 1). Individual differences were largest in heteromodal association cortex including the lateral prefrontal lobe and the temporal-parietal junction and minimal in unimodal sensory and motor cortices. Functional variability was also assessed within 7 specific brain networks (Yeo et al., 2011; Figure 2, top row). Intersubject variability within the boundary of each network was averaged and compared (Figure 2). We found that frontoparietal control and attentional networks demonstrated a high level of functional variability, whereas sensory-motor and visual systems were least variable. The default network demonstrated a moderate level of variability,

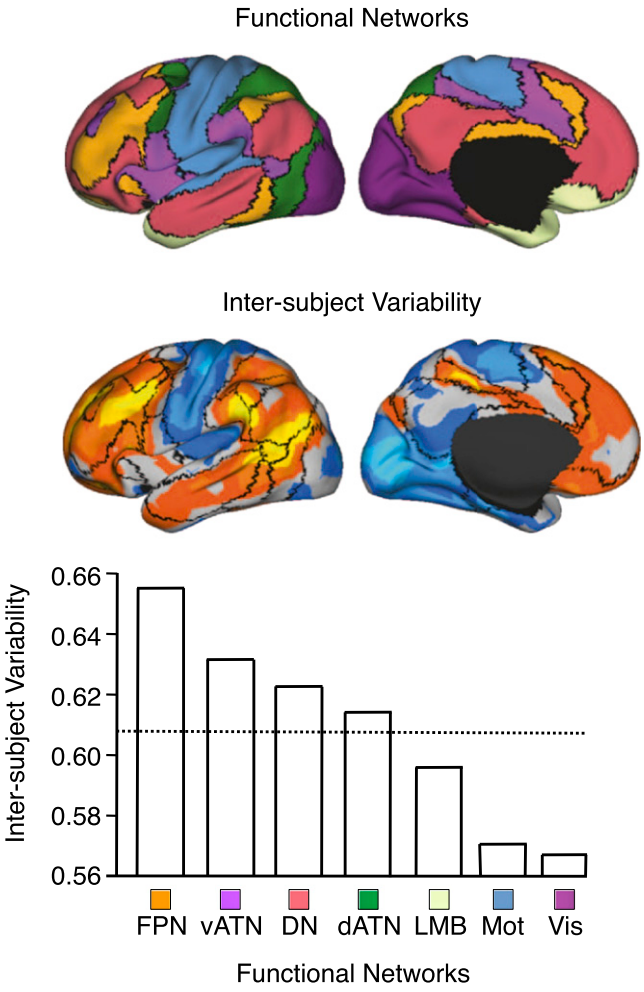

Figure 2. Functional Connectivity Variability Quantified across Cortical Networks

The analysis was based on our prior parcellation of the cerebrum (Yeo et al., 2011) into seven functional networks (top row), namely the frontoparietal control (FPN), ventral and dorsal attention (vATN, dATN), default (DN), limbic (LMB), sensory-motor (Mot), and visual (Vis) networks. Intersubject variability within the boundary of each network (black curves in the middle row) was averaged and plotted (bars in the bottom row). The dotted line indicates the global mean of intersubject variability in the entire cerebral cortex. See also Figure S2.

which is lower than that of frontoparietal and attentional networks, but higher than the variability of sensorimotor and visual networks.

Functional Connectivity Variability Is Highly Correlated with Evolutionary Cortical Surface Expansion

Functional connectivity variability was found to be highest in frontal, temporal, and parietal association cortex areas. These brain regions are phylogenetically late-developing regions (Kaas, 2006; Smaers et al., 2011) that are essential to complex and human specific cognitive functions like reasoning and language (Goldman-Rakic, 1988). As evolutionary history is usually represented by the phylogenetic tree, the fact that higher

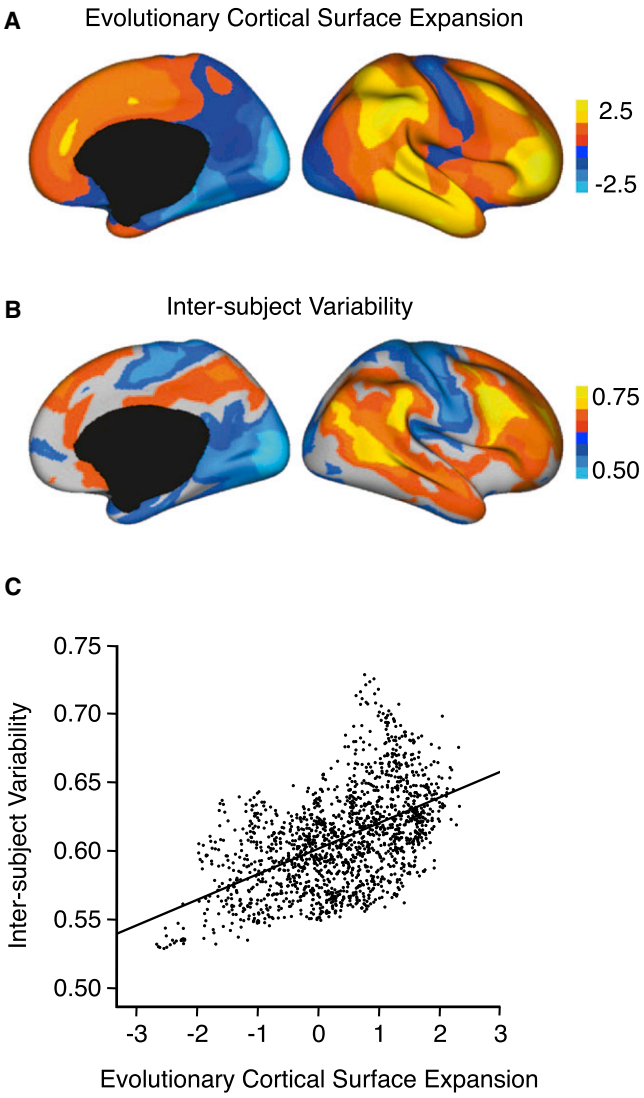

Figure 3. Functional Connectivity Variability and Evolutionary Cortical Expansion Are Highly Correlated

(A) The regional evolutionary cortical expansion between an adult macaque and the average human adult PALS-B12 atlas. Data were provided by van Essen and colleagues (van Essen and Dierker, 2007). On a whole-surface level, evolutionary expansion and functional variability (B) were significantly associated ($r = 0.52$, $p < 0.0001$). The correlation was shown in the scatter plot (C) where each 100th vertex is represented by a small circle.

variability exists in the phylogenetically late regions may indicate an evolutionary root of the variability in functional connectivity. To test this hypothesis, we compared the functional variability map (Figures 1 and 3B) to a map of regional evolutionary cortical expansion between an adult macaque and the average human adult PALS-B12 atlas (Figure 3A) provided by David van Essen and colleagues (Hill et al., 2010b; van Essen and Dierker, 2007; http://sumsdb.wustl.edu/sums/directory.do?id=7601585). On a whole-surface level, evolutionary expansion and functional variability were significantly correlated ($r = 0.52$, $p < 0.0001$; Figure 3C), indicating that the extent of functional variability is related to the evolutionary cortical expansion. To verify that this correlation is not influenced by the spatial dependence between neighboring vertices, we randomly sampled 7% of the vertices 1,000 times and computed the correlation coefficient based on these subsets of vertices. These vertices were spatially independent as confirmed by Durbin-Watson test (see Experimental Procedures). All of the reported correlation coefficients in our paper have been tested using this procedure and were not affected by spatial dependence between neighboring vertices.

Functional Connectivity Variability Is Associated with Brain Folding Pattern but Not Cortical Thickness

It has been well recognized that across individuals the cortical folding patterns are consistent in some regions but highly variable in some other regions (Hill et al., 2010a). Here, we investigated how the functional connectivity variability may relate to the known anatomical variability. Sulcal depth (see Experimental Procedures for definition and caveats) and cortical thickness were estimated for each subject using FreeSurfer (Figures 4A and 4B). To properly model the anatomical variability, we employed the intraclass correlation (ICC; see Experimental Procedures) with the intrasubject variance sufficiently accounted for. Consistent with previous findings (Hill et al., 2010a), sulcal depth variability was most pronounced in lateral frontal and temporoparietal regions but was low in the motor cortex. The default network showed moderate sulcal depth variability. In contrast, cortical thickness demonstrated a very distinct pattern with high variability in the motor area but low variability in the frontoparietal network (see also Figure S3 for a quantification across seven functional networks). When quantified on the whole brain surface, sulcal depth variability showed a moderate but significant correlation with functional variability ($r = 0.30$, $p < 0.0001$), while cortical thickness variability was uncorrelated with functional variability ($r = 0.05$, $p > 0.05$).

Functional Variability Is Positively Associated with the Degree of Long-Range Connectivity but Negatively Associated with Local Connectivity

It has been suggested that developmental reorganization of functional connectivity is characterized by a shift of functional connectivity hubs from sensory-motor cortex toward default (Fransson et al., 2011) and frontoparietal network areas (Power et al., 2010). In adults, functional connectivity is known to form preferentially local connections within sensory and motor cortical regions, while hubs of distant connections are located in phylogenetically and ontogenetically later multimodal association cortices (Sepulcre et al., 2010). Here, we explored whether this special network organization of the human brain is related to functional variability. The degree of distant and local functional connectivity was quantified at each voxel in the brain volume according to Sepulcre et al. (2010). Distant connectivity was defined as the connection ($r > 0.25$) between two regions with a distance larger than 25 mm. Local connectivity was define as the connection ($r > 0.25$) within 12 mm. The percentage of distant connectivity (Figure 5A) demonstrated a moderate but significant correlation with the functional variability ($r = 0.32$, $p < 0.0001$) across the entire cerebral cortex (Figure 5B). Within the regions

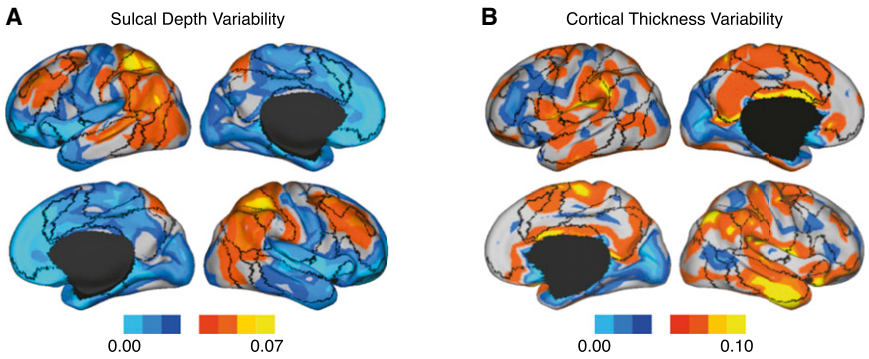

Figure 4. Relationship between Functional and Anatomical Variability

Functional connectivity variability is significantly associated with the variability in sulcal depth (A) but not the variability in cortical thickness (B). Intersubject anatomical variability was calculated using intraclass correlation (ICC), with the intra-subject variance properly accounted for. Sulcal depth variability showed a significant correlation with functional variability ($r = 0.30$, $p < 0.0001$) while cortical thickness variability was uncorrelated with functional variability ($r = 0.05$, $p > 0.05$). See also Figure S3.

dominated by local connectivity (blue regions in Figure 5A), functional variability showed a negative correlation ($r = -0.33$, $p < 0.0001$) to the degree of local connectivity (Figure 5C). The relation between functional variability and the degree of connectivity is exemplified in the default network. It has been reported that the default network is a hybrid hub of both local and long-range cortical-cortical interactions (Sepulcre et al., 2010). In our data, we have observed a moderate level of functional variability in the default network, consistent with the notion that functional variability is associated with the degree of long-range connectivity but negatively correlated with the degree of local connectivity.

Regions Predicting Individual Differences in Cognitive and Behavioral Domains Are Predominantly Located in Regions of High Functional Connectivity Variability

Intrinsic functional connectivity has been shown to reflect individual performance variability in several cognitive domains in healthy individuals (Seeley et al., 2007; van den Heuvel et al., 2009). To determine if these regions previously shown to relate to individual differences in performance overlap with the currently identified regions of high intersubject variability, we performed a PubMed-based search of studies that reported associations between functional connectivity measures and individual differences in cognitive or behavioral domains including personality traits, memory performance, anxiety, risk seeking behavior, response inhibition, intelligence, and visual perception (for inclusion criteria, see Experimental Procedures; for a list of included studies, see Table S1). A total of 15 studies, comprising 573 subjects and 139 foci were retrieved. Quantification was performed on the brain surface (Figure 6) and the results revealed that about 73% percent of the clusters overlap with regions of high functional variability. Regions of high variability were defined as regions displaying variability above the global mean and covered about 51% of the cortical surface.

Ruling Out Potential Confounding Factors

To rule out the possibility that the observed functional connectivity variability was dominated by intersubject differences in head motion during the scan sessions, we calculated the mean relative displacement (Van Dijk et al., 2012) for each session of each subject. We chose a subset of ten subjects that displayed higher intra- than intersubject variance in head motion and quantified intersubject variability in functional connectivity using the same procedure as in Figure 1. The functional variability map derived from this subset of subjects displayed the same characteristic topography as shown in Figure 1 ($r = 0.77$, $p < 0.0001$), suggesting that the functional variability observed was not due to the intersubject variance in head motion.

Higher degree of convolution in association cortex areas may also lead to lower fidelity of intersubject alignment in these regions (van Essen, 2005). To investigate this potential confound we regressed out sulcal depth variability, which comprises variability due to alignment error, from the functional variability map. Figure S3 demonstrates that the overall pattern of functional connectivity variability remains stable after regression. Nevertheless, this approach only partially accounts for alignment errors as it disregards cytoarchitectonic information of cortical areas, whose positions in relation to gyral and sulcal folds are themselves variable. We therefore further quantified functional connectivity variability in several histologically defined architectonic brain areas (Fischl et al., 2008) that are known to show different susceptibility to misalignment. Previous studies have suggested that MT had a larger alignment error than BA 44/45 (Yeo et al., 2010). We found that MT, although more prone to alignment variability, showed lower variability (0.60) in functional connectivity than BA 44/45 (0.64 and 0.65, respectively). This discrepancy may suggest that functional variability is influenced but not dominated by alignment variability. However, future investigation on architectonic variability across the brain will be useful to better address this potential confound.

Two left-handed subjects had been included in our data set in order to roughly represent the handedness distribution in the healthy population. To investigate the potential impact of this handedness variability on our results, intersubject functional connectivity variability was recalculated after excluding the left-handed subjects (Figure S1C). The variability maps derived from these two data sets were highly correlated ($r = 0.99$), suggesting that the observed variability distribution was not dominated by the handedness variability in the data set.

DISCUSSION

Several findings in the current article add to our understanding of individual differences in functional connectivity. We demonstrated that functional connectivity variability has a specific topographic distribution with heteromodal association cortex being most variable and unimodal sensorimotor regions being

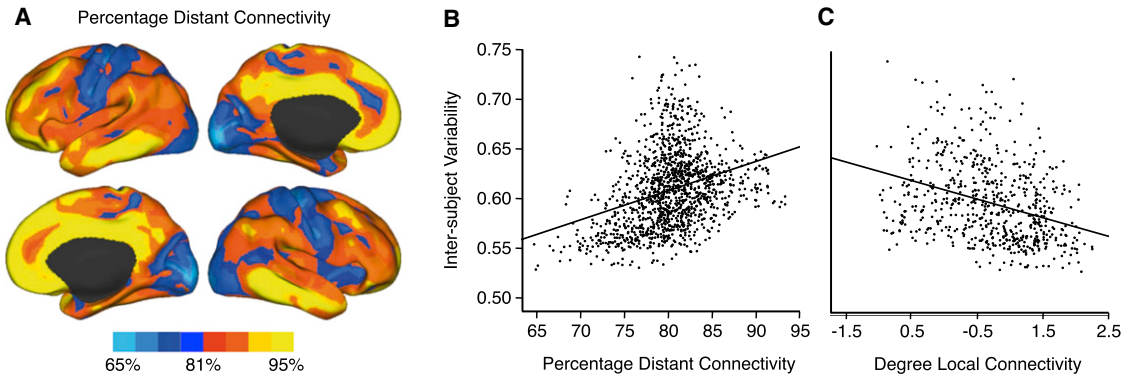

Figure 5. Functional Connectivity Variability Is Positively Associated with the Degree of Long-Range Functional Connectivity but Negatively Correlated with Local Connectivity

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 projected to the brain surface (A). Regions above the global mean are shown in yellow; regions below the global mean are shown in blue. Significant correlation ($r = 0.32$, $p < 0.0001$) was found between the functional connectivity variability and the percentage of distant connectivity across the entire cerebral cortex (B). In the regions dominated by local connectivity, functional connectivity variability was negatively correlated ($r = -0.33$, $p < 0.0001$) with the degree of local connectivity (C).

least variable. This functional connectivity variability is related to evolutionary cortical expansion and variability in cortical folding pattern but not cortical thickness. Further analyses revealed that functional connectivity variability is associated with network properties of functional integration and segregation. Finally, we demonstrated that our map of functional connectivity variability overlaps well with prior reports linking individual differences in functional connectivity to behavioral performance.

Potential Causes of Strong Variability in Association Cortex

Functional variability in human cerebral cortex is likely to be the result of evolution that has shaped a unique distribution of susceptibility to genetic and environmental influences. Association cortex areas, where functional architecture appeared to be most variable, are phylogenetically late-developing regions that underwent a disproportionate enlargement during human evolution (Kaas, 2006; Smaers et al., 2011; van Essen and Dierker, 2007). Evolutionary trajectories can be partially retraced in individual development (Clancy et al., 2000), where association cortex exhibits the most protracted course of white (Yakovlev and Lecours, 1967) and gray (Gogtay et al., 2004; Shaw et al., 2008) matter maturation and most pronounced postnatal cortical expansion (Hill et al., 2010b). This prolonged maturation course of association cortex implicates a prolonged exposure to variable extrinsic experience during a time of high neuroplasticity (Petanjek et al., 2011). In addition, structural variability of late maturing association cortex is probably less genetically influenced during development (Brun et al., 2009), again enabling more variable impact of postnatal environmental factors that lead to the diversity of neural connections beyond their genetic determination (Petanjek et al., 2011; but also see Chen et al., 2011; Rimol et al., 2010; Thompson et al., 2001 for different explanations). Besides this prior evidence on heritability of anatomical properties, functional connectivity, e.g., of the default network, is known to be influenced by genetic factors, which cannot necessarily be attributed to anatomical variability (Glahn et al., 2010). Nevertheless, the spatial distribution of the heritability of functional connection strength across the entire brain is yet to be unveiled. Finally, the dynamics of synaptic overproduction in early childhood and consecutive synaptic pruning may contribute to a similar functional hierarchy, where synaptic overproduction is highest in the prefrontal cortex and lowest in primary sensory regions (Elston et al., 2009; Jacobs et al., 1997). High synaptic overproduction may provide more freedom for selective stabilization to operate on during development. Taken together, a protracted maturation, weaker genetic influence on structure and more synaptic over-production may jointly contribute to the high functional variability of multimodal association cortices as reported in this study.

Functional Variability Is Related to Evolutionary Cortical Expansion and Cortical Folding

Functional variability is correlated with variability of sulcal depth, a proxy of cortical folding. From an evolutionary perspective, the degree of gyrification is highest in phylogenetically young association cortex and lowest in phylogenetically older occipital and motor cortex (Zilles et al., 1997), resulting in highest sulcal depth variability and positional variability in association cortex (Hill et al., 2010a). It is striking how well the regional evolutionary cortical expansion and sulcal depth variability maps match the distribution of variability in functional connectivity as revealed in this study. In contrast, no significant correlation was found between cortical thickness variability and functional variability. This finding is consistent with the fact that brain evolution has been characterized by huge surface expansion (e.g., ten-fold between macaque and human [Preuss, 1995]) without a significant increase in cortical thickness (Rakic, 1995).

Functional Variability Is Related to the Need for Long-Range Information Exchange

The human brain possesses a complex architecture with some areas highly specialized for local, modular processing and certain areas connecting and integrating these otherwise

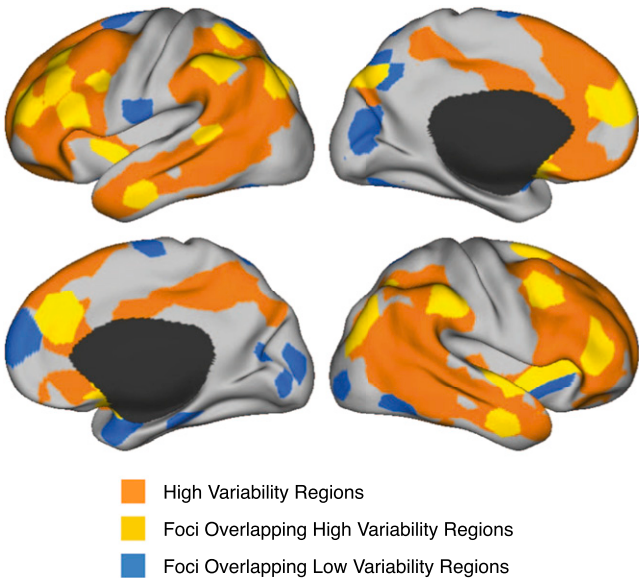

Figure 6. Loci that Predict Individual Differences in Behavioral and Cognitive Domains Are Predominantly Located in Cortical Areas of High Functional Connectivity Variability

Loci were derived from a meta-analysis that included 15 studies that found associations between functional connectivity and individual differences in cognitive and behavioral domains. Loci were merged in the volume. Frequency of contributing foci was estimated for each voxel. Results were smoothed, normalized, and projected to the surface. Quantification revealed that about 73% of the clusters associated with individual differences are located in cortical regions that display high functional connectivity variability (above the global mean, 51% of the cortical surface in total). For an overview of included studies, see Table S1.

segregated brain regions or systems (Buckner et al., 2009; Sepulcre et al., 2010). Such arrangement may maintain high information processing efficiency given that the human brain has tripled the size over past several million years. The ratio of local to distributed areal projections is suggested to be critical to the evolution of higher-order cognitive functions including language, reasoning, and foresight (Kaas, 2005; Semendeferi et al., 2001). We have previously reported that regions within or near primary sensory and motor areas display high local connectivity consistent with a modular organization. In contrast, distant connectivity is prominent across association areas in parietal, lateral temporal, and frontal cortices as well as paralimbic cortex including posterior cingulate (Sepulcre et al., 2010). Here, we extend these insights by showing that functional variability is strongly correlated with the degree of distant connectivity but negatively correlated with the degree of local connectivity. A potential inference from this observation is that functional variability may not become prominent until distant connectivity emerges, i.e., species with smaller brains dominated by local, modular processing may have limited functional variability, hence the more uniform and predictable behavior.

A particularly intriguing observation is that the default network, which represents a hybrid hub for local and distant connections (Sepulcre et al., 2010), exhibited moderate variability in functional connectivity across subjects. Given that the DMN has been described as a network that subserves mostly internal thought processes and human specific functions such as autobiographical memory retrieval (Svoboda et al., 2006), imagining the future (Schacter et al., 2007), and mind wandering (Mason et al., 2007) one would predict the DMN to be among the most variable networks, both across and within subjects. Neither of those two predictions was proven correct in this study. The DMN showed low intrasubject variability (Figure S1B) and intermediate intersubject variability (Figures 2 and S2). Taking into account that the DMN is present in rodents (Lu et al., 2012) and anaesthetized monkeys (Vincent et al., 2007) it seems plausible that the DMN subserves both phylogenetically older, putatively less complex functions and human specific higher order cognitive functions. This could be reflected in the intermediate variability of the DMN where information processing that involves modular computation could be consistent across subjects, whereas processing which associates distributed information from key limbic, parietal, and prefrontal regions exhibits strong individual differences.

Clinical Relevance of Individual Differences

While functional variability in association cortex has important implications for the evolution of higher-order cognitive abilities, it might also relate to an increased susceptibility to the formation of abnormal circuitry as manifested in neuropsychiatric disorders. Here, we demonstrate that individual differences in mental domains such as personality traits can be linked to brain regions of high functional variability. A caveat is that based on the available literature the majority of included studies investigated individual differences in higher cognitive functions, which might constitute a publication bias favoring higher order association cortex areas in displaying individual differences.

Functional development of the human brain is characterized by a general trend toward increases in connectivity across widely distributed regions, conceptualized as the development of a 'local to distributed' organization (Fair et al., 2009). Studies have suggested that abnormal development leading to variable disconnection of focal brain regions, especially regions that are functionally integrated network hubs, might be present in many neuropsychiatric disorders (Zhang and Raichle, 2010). In this context, it is noteworthy that many neuropsychiatric diseases such as anxiety disorders, bipolar disorder, depression, eating disorder, psychosis (including schizophrenia), and substance abuse most commonly emerge during adolescence (Kessler et al., 2007), a period critical for the establishment of long-range connection hubs that signify functional variability. Brain circuits susceptible to neuropsychiatric diseases may therefore be identified based on the abnormal range of connectivity variability in patients. Knowing cortical areas of highest individual variability may furthermore help guide investigations into individual differences in disease susceptibility.

As clinical practice moves ever closer to the goal of individualized therapy, knowing the distribution of individual differences in brain connectivity is likely to be important. For example, functional and connectivity data are playing an increasing role in guiding operative approaches (Liu et al., 2009). Knowing that a surgical resection is near an area of high intersubject variability may inform acquisition of preoperative imaging. Similarly, there is increasing evidence that therapeutic brain stimulation might

be guided by differences in connectivity (Fox et al., 2012). Knowing whether a target of brain stimulation is in an area of high or low individual variability will be important for determining whether one can target based on group averages or if one should obtain information on a patient's specific connectivity pattern.

Relevance to Interpretation of Group Maps in Neuroimaging

Regardless of whether one is studying functional connectivity or task-based activations, neuroimaging results are generally presented as a statistical map computed across a group of subjects. The creation of these statistical maps necessarily incorporates the variance across the group. As such, the map of individual differences presented here is highly relevant for interpretation of these statistical images. Specifically, one is more likely to get a significant result in areas of low individual variability such as primary sensory or motor cortex and less likely to get a significant result in areas of high individual variability. Therefore, the risk of false-positives and false-negatives in neuroimaging is likely non-uniformly distributed across the human cortex. Variance maps from an independent data set such as the one presented here might eventually be used to formally correct for this heterogeneity in creating statistical images.

EXPERIMENTAL PROCEDURES

Participants and Data Collection

Twenty-five healthy subjects (age 51.8 ± 6.99, 9 female) were recruited for a longitudinal fcMRI study. The data was collected as a control sample of a longitudinal stroke study. Therefore the age range is slightly higher than what would be expected for a study of healthy adult subjects. The data set also included two left-handed subjects, roughly representing the handedness distribution in the healthy population (Connolly and Bishop, 1992). Participants were screened to exclude individuals with a history of neurologic or psychiatric conditions as well as those using psychoactive medications. Participants provided written informed consent in accordance with guidelines set by institutional review boards of Xuanwu Hospital. Each subject underwent five scanning sessions within 6 months (7, 14, 30, 90, and 180 days from the enrollment). All participants performed two or three rest runs per session (6 m 12 s per run) to estimate intrinsic functional connectivity. After quality control, 23 subjects who had at least two good runs (tSNR > 100) in each session were included in this study (mean = 2.02 runs). All data were acquired on a 3 Tesla TimTrio system (Siemens) using the 12-channel phased-array coil supplied by the vendor. Functional data were obtained using a gradient echo-planar pulse sequence (TR, 3,000 ms; TE, 30 ms; flip angle, 90°; 3 mm isotropic voxels, transverse orientation, 47 slices fully covering cerebral cortex and cerebellum). Subjects were instructed to stay awake and keep their eyes open; no other task instruction was provided. Structural images were acquired using a sagittal MP-RAGE three-dimensional T1-weighted sequence (TR, 1600 ms; TE, 2.15 ms; flip angle, 9°; 1.0 mm isotropic voxels; FOV, 256 × 256).

Data Preprocessing

Resting-state fMRI data were processed using previously described procedures (Van Dijk et al., 2010; Yeo et al., 2011). Structural data was processed using the FreeSurfer version 4.5.0 software package (http://surfer.nmr.mgh.harvard.edu). Surface mesh representations of the cortex from each individual subject's structural images were reconstructed and registered to a common spherical coordinate system (Fischl et al., 1999). The structural and functional images were aligned using boundary-based registration (Greve and Fischl, 2009). The resting-state BOLD fMRI data were then aligned to the common spherical coordinate system via sampling from the middle of the cortical ribbon in a single interpolation step. See Yeo et al. (2011) for details.

In this study, a symmetric surface template of the cerebral cortex (unpublished) was constructed using FreeSurfer. fMRI data of each individual were then registered to this template. The data were resampled on this template with a mesh of 1,284 vertices. For each vertex in this mesh, the nearest vertex in the higher resolution template was extracted and if multiple nearest vertex existed, the values on these vertices were averaged. We have used this lower resolution template to achieve computational efficiency but this re-sampling procedure may introduce noise. This was mitigated by a smoothing preprocessing step that we have taken.

Estimating Intersubject Functional Variability

Functional correlation maps were computed by taking each of the 1,284 vertices as the seed, resulting in 1,284 maps for each subject and session. The correlation map based on each seed vertex can be denoted as $F_i(s,t)$, where $i = 1, 2, \ldots 1284$, and F_i is a 1 × 1284 vector, s indicates the subject, t indicates the session.

For a given seed vertex i, the similarity between the 23 maps derived from 23 subjects was quantified by averaging the correlation values between any two maps:

$$R_i(t) = E[corr(F_i(s_p,t), F_i(s_q,t))], \text{where } p,q = 1,2,\ldots 23; p \neq q.$$

The intrasubject variance was estimated using the 5 maps derived from 5 scanning sessions of each subject:

$$N_i(s) = 1 - E[corr(F_i(s,t_m), F_i(s,t_n))], \text{where } m,n = 1,2,\ldots 5; m \neq n.$$

The intrasubject variance was then averaged across 23 subjects and assigned to the seed vertex i (see Figure S2 top row):

$$N_i = E[N_i(s)].$$

Note that the intrasubject variance consists of the variance caused by technical noise, which may be reflected by the tSNR of the BOLD signal (Figure S1B, middle row), as well as the biological variance related to the brain state change within subjects (Figure S1B, bottom row).

To estimate intersubject variability, the similarity map $R_i(t)$ was first inverted (by subtraction from 1; see Figure S1A) and then the intrasubject variance was regressed out using ordinary least-squares regression (i.e., a general linear model, GLM). The residual map was taken as the estimate of functional variability,

$$V_i(t) = [1 - R_i(t)] - \beta N_i - c,$$

where β and c are parameters determined via ordinary least-squares. Variability maps derived from each session t are averaged and shown in Figure 1.

Parcellation and Seed-Based Network Analysis

To quantify variability in specific functional networks, we used the functional atlas derived from a clustering approach (http://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation_Yeo2011; Yeo et al., 2011). The boundaries of seven networks were projected to the symmetric surface template. Intersubject variability values were then averaged within each network (Figure 2A).

For the ROI-based analysis described in Figure S2, we used a group of regions of interest (ROI) associated with different brain functions (Van Dijk et al., 2012), including the ATN (paraCG, FEF, MFG, Insula, MTplus, TPJ, sPL), the FPN (aPFC, ApCC, dlPFC, SFG, IPL), the DN (PCC, aMPFC, dMPFC, LPC, SFG, LTC), the motor cortex (hand, foot, tongue region), the visual cortex (medial and lateral V1), and the auditory cortex (STG). Seeds were created by projecting the center of each volume ROI (MNI152 volumetric space) to the FreeSurfer spherical surface model and constructing a circle (radius = 8 mm, defined as the arc length on the sphere) around each projected peak vertex on the sphere. The coefficient of variance of the correlation strength between a given pair of seeds was computed as the standard deviation divided by the mean across 23 subjects. To account for the measurement instability, the raw intersubject variance was normalized by the mean intrasubject variance for each seed pair. The coefficient of variance was then averaged across all seed pairs of one network. The surface-based ROIs may correspond to different sizes of brain volume but this source of variability is not significantly affecting the result. The ROI-based analyses described above were repeated

using standard volumetric spherical seeds in the volumetric space, the reported ranking of variability among functional networks remained unchanged.

Relation to Evolutionary Cortical Expansion

The map of regional evolutionary cortical expansion between an adult macaque and the average human adult PALS-B12 atlas was published previously (Hill et al., 2010b; van Essen and Dierker, 2007) and made publicly available. The right hemisphere evolutionary expansion map and the functional variability map were projected to the Conte69 164k_fs_LR mesh (van Essen et al., 2012) (http://sumsdb.wustl.edu/sums/directory.do?id=8291494&dir_name=CONTE69). The data were extracted using the Caret Surface Statistics Toolbox (Diedrichsen, 2005) for the correlation analysis. The absolute expansion ratio was normalized by taking the logarithm and subtracted with a constant.

Relation to Anatomical Variability

Sulcal depth and cortical thickness measurements were calculated using FreeSurfer (Fischl et al., 1999). The sulcal depth estimated by FreeSurfer is not a direct measure of distance to the outer cortical margin, but the integrated dot product of the movement vector with the surface normal during inflation. It highlights large-scale geometry as deep regions consistently move outward and get a positive value while superficial regions move inward and get a negative value. Intersubject variability in sulcal depth and cortical thickness was estimated vertex-wise using intraclass correlation (Shrout and Fleiss, 1979) with the intrasubject variance accounted for. The Pearson's correlation coefficient was calculated between functional variability and anatomical variability across the whole brain. To demonstrate the topological impact of anatomical variability on functional variability, a GLM approach was applied to regress out sulcal depth and cortical thickness variability from the functional variability map.

Testing the Potential Impact of Spatial Dependence on Correlation Analyses

To test the potential impact of spatial dependence between neighboring vertices on correlation analysis, we performed a repeated (n = 1,000) random sampling of 7% of the vertices and computed the correlation coefficient on the subsets of the vertices. For each subset, the Durbin-Watson test was performed to estimate the spatial dependence (DW > 2). Correlation coefficients were averaged across the 1,000 iterations.

Meta-analysis of Individual Differences Predicted by Functional Connectivity

We performed a voxel-wise frequency-based meta-analysis. A PubMed search was conducted using three sets of search terms: (1) search: individual differences, intrinsic connectivity; (2) search: individual differences, resting-state fMRI; (3) search: individual differences, connectivity, MRI. After accounting for redundancies, this resulted in 182 studies to be reviewed. The following inclusion criteria were applied: healthy, adult human subjects, original research, fMRI study, reported cerebral/cortical coordinates in standardized stereotaxic space (Talairach or Montreal Neurological Institute [MNI] template) and association between an individual cognitive/behavioral/psychological trait and a functional connectivity measure. Fifteen studies met inclusion criteria. The meta-analysis was conducted in MNI space. For studies that reported coordinates in Talairach space (Talairach and Tournoux, 1988), used SPM or FSL, and did not specify the use of Lancaster transformation (Laird et al., 2010), conversion to MNI coordinates was performed using the reversed Brett transformation (Brett et al., 2001). For studies that reported coordinates in Talairach space and used neither SPM nor FSL, conversion to MNI coordinates was performed using the (reversed) Lancaster transformation (Laird et al., 2010). Three millimeter spheres around each focus were merged in MNI 152 volumetric space. For each voxel, the number of contributing foci was calculated. The resulting volume map was spatially smoothed (FWHM 12 mm), normalized (z score) and projected to the surface.

Visualization

Since the main analyses were performed in FreeSurfer symmetric surface space, the final results of both hemispheres were projected only to the left hemisphere of the inflated PALS cortical surface using CARET (van Essen, 2005) for the purpose of visualization. The right hemisphere results shown in the figures were mirrored from the results rendered on left CARET surface.

SUPPLEMENTAL INFORMATION

Supplemental Information includes three figures and one table and can be found with this article online at http://dx.doi.org/10.1016/j.neuron.2012.12.028.

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