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The structural, connectomic and network covariance of the human brain

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ABSTRACT

Though it is widely appreciated that complex structural, functional and morphological relationships exist between distinct areas of the human cerebral cortex, the extent to which such relationships coincide remains insufficiently appreciated. Here we determine the extent to which correlations between brain regions are modulated by either structural, connectomic or network-theoretic properties using a structural neuroimaging data set of magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) volumes acquired from $N = 110$ healthy human adults. To identify the linear relationships between all available pairs of regions, we use canonical correlation analysis to test whether a statistically significant correlation exists between each pair of cortical parcels as quantified via structural, connectomic or network-theoretic measures. In addition to this, we investigate (1) how each group of canonical variables (whether structural, connectomic or network-theoretic) contributes to the overall correlation and, additionally, (2) whether each individual variable makes a significant contribution to the test of the omnibus null hypothesis according to which no correlation between regions exists across subjects. We find that, although region-to-region correlations are extensively modulated by structural and connectomic measures, there are appreciable differences in how these two groups of measures drive inter-regional correlation patterns. Additionally, our results indicate that the network-theoretic properties of the cortex are strong modulators of region-to-region covariance. Our findings are useful for understanding the structural and connectomic relationship between various parts of the brain, and can inform theoretical and computational models of cortical information processing.

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Introduction

It is widely appreciated that complex structural, functional and morphological relationships exist between distinct areas of the human cerebral cortex. Among the most telling of these relationships is that of structural connectivity, where distinct gyral and sulcal gray matter (GM) structures are physically connected by white matter (WM) tracts. Structural connectivity patterns aid one in understanding how different areas of the brain process inputs, exchange information, and respond to either exogenous or endogenous stimuli. For this reason, the study of connectivity patterns in the brain is an active topic of scientific investigation (Achard et al., 2006; Bassett and Bullmore, 2006; De Luca et al., 2006; Eguiluz et al., 2005; Greicius et al., 2009; Hagmann et al., 2010; Honey et al., 2007). In addition to structural connectivity, however, various areas of the brain can also share intricate relationships as a consequence of genetic, developmental and environmental factors which can alter the structural and functional relationships between brain regions (Chen et al., 2008; He et al., 2007; Lerch et al., 2006). At the macroscopic scale, the most obvious structural delineation scheme for the cortex involves dividing the cerebral surface into gyri and sulci, given that the morphometric, areal and volumetric properties of these structures can be resolved using currently available neuroimaging methodologies. Thus, to understand how different parts of the brain can interact with each other, it is very helpful to elucidate the extent to which the structural properties of gyri and sulci (such as their cortical thickness, area, curvature, etc.) co-vary across subjects (He et al., 2007).

In addition to the structure of covariance between the anatomic and connectivity properties of different brain regions, it is also useful and enlightening to investigate the individual place of each brain region within the full ensemble of brain connections (Gong et al., 2009). In the context of network theory, brain regions and WM fibers can be conceptualized as nodes and edges, respectively, and local network topology can be explored by quantifying the relative prominence of various nodes at the local or at the global level (Chen et al., 2008). By studying the covariance patterns of network properties between different nodes across subjects, one can identify the roles of various brain regions within their overarching networks, as quantified using graph-theoretic measures such as degree, betweenness centrality, local efficiency, etc.

In this article, we seek to determine the extent to which the patterns of correlation between brain regions are modulated by structural, connectomic and/or network-theoretic properties. Starting from a

Abbreviations: DTI, diffusion tensor imaging; FA, fractional anisotropy; Fro, frontal; GM, gray matter; HIPAA, Health Insurance Portability and Accountability Act; IDA, integrated data archive; Ins, insula; Lim, limbic; LOD, lower order design; LONI, Laboratory of Neuro Imaging; MRI, magnetic resonance imaging; Par, parietal; Tem, temporal; Occ, occipital; WM, white matter.

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structural neuroimaging data set of magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) volumes acquired from $N = 110$ healthy human adults, we use automated image processing methods to segment and parcel the brain of each subject into 165 regions and to compute the structural, connectomic and network-theoretic properties of each region. To identify the co-linear relationships between all available pairs of regions, we use canonical correlation analysis to test whether a statistically significant correlation exists between each pair of cortical parcels as quantified via structural, connectomic or network-theoretic measures. In addition to this, we investigate (1) how each group of canonical variables (whether structural, connectomic or network-theoretic) contributes to the overall correlation and, additionally, (2) whether each individual variable makes a unique contribution to the test of the omnibus null hypothesis according to which no correlation between regions exists across subjects. Our findings are useful for understanding the structural and connectomic relationship between various parts of the brain, provide an overarching picture of brain connectedness, and can inform theoretical and computational models of cortical information processing.

Methods

Subjects

T_1-weighted MRI volumes from $N = 110$ healthy, right-handed human subjects aged 25–36 were obtained from the Integrated Data Archive (IDA; http://ida.loni.ucla.edu) of the Laboratory of Neuro Imaging (LONI) at the University of California, Los Angeles. Data were obtained from a variety of projects in which subjects provided their informed written consent as required by the Declaration of Helsinki, U.S. 45 CFR 46, and with the approval of local ethics committees at their respective research institutions. All subjects were healthy normal controls with no neurological pathology or history of psychiatric illnesses. Data sets deposited in the LONI IDA are fully anonymized for the purposes of sharing, re-use, and re-purposing, and linked coding or keys to subject identity are not maintained. Consequently, in accordance with the U.S. Health Insurance Portability and Accountability Act (HIPAA; http://www.hhs.gov/ocr/privacy), our study does not involve human subjects' materials.

Image processing

The LONI Pipeline environment (http://pipeline.loni.ucla.edu) was used for all major image processing operations, including bias field correction, skull stripping, image alignment, etc. This program is a graphical environment for the construction, execution and validation of neuroimaging data analysis and facilitates automated data format conversion while providing a large library of computational tools (Dinov et al., 2009, 2010; MacKenzie-Graham et al., 2008). DTI data were analyzed in native subject space using second-order Runge–Kutta tractography in the Diffusion Toolkit component of the TrackVis (http://trackvis.org) software package for white matter fiber tract reconstruction. The 3D Slicer (http://slicer.org) program, an openly available software platform from the National Alliance for Medical Image Computing (NA-MIC; http://www.na-mic.org) was used for visualization. Segmentation and regional parcellation were performed using FreeSurfer (Dale et al., 1999; Fischl et al., 1999, 2002) following methodology described by Destrieux et al. (2010). For each hemisphere, 74 cortical structures were identified in addition to 7 subcortical structures and to the cerebellum. One midline structure (the brain stem) was also included, for a total of 165 parcels for the entire brain. The cortex was divided into 7 lobes, with the number of parcels in each being equal to 21 (frontal, Fro), 8 (insula, Ins), 8 (limbic, Lim), 11 (temporal, Tem), 11 (parietal, Par), and 15 (occipital, Occ). Cortical surface area, GM volume, mean curvature and mean thickness were extracted for each parcellated region.

Connectivity calculation and representation

To compute connectivity between regions for each subject, the location of each fiber tract end-point extremity within the brain was identified, while the GM volume associated with every parcel was also delineated. For those fibers which both originated as well as terminated within any two distinct parcels of the 165 available, each fiber extremity was associated with the appropriate parcel. For each such fiber, the corresponding entry in the connectivity matrix of the subject's brain was appropriately updated to reflect an increment in fiber count (Hagmann et al., 2008, 2010). To compute relative connectivity density, each subject's connectivity matrix was normalized over the total number of fibers within that subject. The average length of the fibers connecting every pair of regions was also recorded, as was the average fractional anisotropy (FA) of each fiber line as reconstructed via second-order Runge–Kutta tractography (Basser et al., 2000). Processing workflows to compute inter-regional connectivity matrices were constructed using purpose-built software.

Connectogram design

Connectivity was represented circularly using a framework based on Circos software (Krzywinski et al., 2009). Parcellated regions were displayed as a circle of radially aligned elements (a 'connectogram') representing the left and right hemispheres positioned symmetrically on the corresponding side of the vertical axis. Parcellated regions were assigned unique RGB colors as shown in Fig. 3, and all RGB codes are provided in (Irimia et al., 2012). Arrangement of parcellations within each lobe of the connectogram was performed in the order of their locations along the antero-posterior axis of the cortical surface associated with the published FS normal population atlas (Destrieux et al., 2010). Cortical lobes were assigned unique color schemes: black to red to yellow (Fro), charlotte to turquoise to forest green (Ins), primrose to lavender rose (Lim), etc. Subcortical structures were colored light gray to black. An unambiguous abbreviation scheme was created to label each parcellation. Within the outermost circle which represents cortical parcellations, five circular heat maps were created to encode one of the five structural measures associated with the corresponding parcellation. Proceeding towards the center of the circle, these measures are total GM volume, total area of the surface associated with parcellation, mean cortical thickness, mean curvature and connectivity per unit volume. This latter measure was calculated as the density of fibers with endings within that parcellation divided by the parcellation's total GM volume. The value of each structural measure was encoded as a color using a color scheme mapping that ranged from the minimum to the maximum of the data set. Specifically, the cortical thickness t with values in the interval $[t_{\min}, t_{\max}]$ was normalized as $t_1 = (t - t_{\min})/(t_{\max} - t_{\min})$. The value of t_1 was associated with a unique color; for example, nuances at the extremities of the color map correspond to $t_{\min}$ and $t_{\max}$, as required. For the brain stem, cerebellum and subcortical structures, values for area, thickness and curvature were unavailable from FS and their appropriate heat map entries were drawn in white. The methodology for generating connectograms is described in detail elsewhere (Irimia et al., 2012).

Network metrics

Nodes here are denoted by parcellated regions and edges are represented by fiber tracts. Network metrics were computed for each subject and included measures of global and local influence and segregation. As metrics of influence, the degree, betweenness centrality and participation coefficient of each node were computed. The node