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The structural connectivity of higher order association cortices reflects human functional brain networks

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ABSTRACT

Human higher cognition arises from the main tertiary association cortices including the frontal, temporal and parietal lobes. Many studies have suggested that cortical functions must be shaped or emerge from the pattern of underlying physical (white matter) connectivity. Despite the importance of this hypothesis, there has not been a large-scale analysis of the white-matter connectivity within and between these associative cortices. Thus, we explored the pattern of intra- and inter-lobe white matter connectivity between multiple areas defined in each lobe. We defined 43 regions of interest on the lateral associative cortex cytoarchitectonically (6 regions of interest – ROIs in the frontal lobe and 17 ROIs in the parietal lobe) and anatomically (20 ROIs in the temporal lobe) on individuals' native space. The results demonstrated that intra-region connectivity for all 3 lobes was dense and graded generally. In contrary, the inter-lobe connectivity was relatively discrete and regionally specific such that only small sub-regions exhibited long-range connections to another lobe. The long-range connectivity was mediated by 6 major associative white matter tracts, consistent with the notion that these higher cognitive functions arises from brain-wide distributed connectivity. Using graph-theory network analysis we revealed five physically-connected sub-networks, which correspond directly to five known functional networks. This study provides strong and direct evidence that core functional brain networks mirror the brain's structural connectivity.

Abbreviations: STG, superior temporal gyrus; LAT, lateral temporal pole; MED, medial temporal pole; MTG, middle temporal gyrus; ITG, inferior temporal gyrus; FG, fusiform gyrus; PhG, parahippocampal gyrus; HG, Heschl's gyrus; LG1, lingual gyrus next to fusiform gyrus; LG2, medial lingual gyrus; DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; p.Op, pars opercularis; p.Tri, pars triangularis; p.Orb, pars orbitalis; BA, Brodmann's areas; IPS, intraparietal sulcus; 5Ci, 5M, 5L, BA 5 (superior parietal cortex); 7PC, 7A, 7P, 7M, BA 7 (superior parietal cortex); PFop, PFt, PF, PFcm, PFm, supramarginal gyrus; PGa, PGp, angular gyrus.

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1. Introduction

The frontal, temporal and parietal lobes contain the majority of the tertiary association cortex, which are key substrates for higher cognition including executive function, language, memory and attention. Each cognitive domain arises from coordinated action between a widespread, distributed neural network within these regions. For example, the executive control network is embedded in subsets of frontoparietal areas (Seeley et al., 2007), the episodic memory system relies on a network connecting medial temporal areas to parietal and frontal regions (Alvarez & Squire, 1994), and language functions arise from an extensive network including Broca's and Wernicke's areas, as well as other prefrontal, temporal and parietal regions (Binder et al., 1997). Although other subcortical structures such as basal ganglia (Leisman, Braun-Benjamin, & Melillo, 2014) and thalamus (Mitchell et al., 2014) also contribute to these cognitive functions, we focused on cortico-cortical pathways between the major associative cortices in the current study.

Evidence spanning from lesion studies to functional connectivity have mapped functional networks by linking each cognitive activity to individual regions within a brain network. Multiple researchers have noted that the contributions of each brain region to large-scale network functions must be heavily shaped by their structural connectivity (Friston, 2002; Mesulam, 1990; Passingham, Stephan, & Kotter, 2002; Sporns, Tononi, & Kotter, 2005). Thus, it becomes necessary to investigate the white matter pathways that connect cortical areas in order to understand how each cognitive activity arises from the patterns of brain-wide distributed connectivity.

Diffusion neuroimaging and tractography methods allow researchers to reveal white matter fibre structure and to map white matter cortico-cortical projections at high spatial resolution, *in vivo* and *en masse* (Conturo et al., 1999; Parker & Alexander, 2005). Such studies generate a matrix of inter-regional connectivity which can be further explored using mathematical techniques such as graph-theory (for the review, see Bullmore & Sporns, 2009; Gong et al., 2009; Hagmann et al., 2007; Iturria-Medina, Sotero, Canales-Rodriguez, Aleman-Gomez, & Melie-Garcia, 2008). Previous diffusion neuroimaging studies have tended to focus on either reconstructed major associative fasciculi (Catani & Thiebaut de Schotten, 2008; Makris et al., 2009) or have demonstrated topological properties within discrete targeted structural networks, with particular reference to primary sensory and motor regions/function (Gong et al., 2009; Hagmann et al., 2007). In addition, most studies using these methods have not yet fully covered the whole brain owing to susceptibility-induced geometric distortion of the MRI signal which leads to erroneous fibre tracking (Embleton, Haroon, Morris, Lambon Ralph, & Parker, 2010). This is particularly problematic around the rostral temporal cortices which are known to be important for semantic memory, language and visual processes (Binney, Parker, & Lambon Ralph, 2012; Shimotake et al., 2015). Therefore, the current study utilised targeted diffusion datasets that overcome the magnetic susceptibility artefacts by adopting new and advance DWI and tractography methodologies (Embleton et al., 2010; Haroon, Morris, Embleton, Alexander, & Parker, 2009; Jeurissen, Leemans, Jones, Tournier, & Sijbers, 2011; Parker & Alexander, 2005) (see the Materials and methods for the details).

In the current study, we explored the pattern of intra- and inter-lobe white matter connectivity between multiple areas defined within each lobe. In order to examine this large-scale frontal, temporal and parietal network, regions of interest (ROIs) were defined anatomically in temporal lobe (20 ROIs covering from anterior to posterior temporal cortices) and cytoarchitectonically in lateral frontal (6 ROIs) and parietal lobe (17 ROIs). To map the connectivity among ROIs systematically, we employed probabilistic tractography of distortion-corrected diffusion-weighted imaging at high angular resolution, which overcomes the signal dropout and image distortion within anteroventral temporal areas (Embleton et al., 2010; Parker & Alexander, 2005). In addition, graph-theory network analysis was conducted to quantify the network properties in our tractography results and thus reveal the underlying topology of the intra/inter-regional structural connectivity for frontal, temporal and parietal lobes. To the best of our knowledge, this is the first attempt to look into the structural patterns of connectivity of specifically targeted sub-regions that cover the majority of the human tertiary association cortices.

2. Materials and methods

2.1. Participants

Twenty-four participants (11 females; mean age = 25.9, range = 19–47) participated in this study, which was approved by the local ethics boards. All were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). Written informed consent was obtained from all participants.

2.2. Diffusion weighted imaging and distortion correction

Imaging data were acquired on a 3-T Philips Achieva scanner (Philips Medical System, Best, Netherlands), using an 8 element SENSE head coil. Diffusion weighted imaging was performed using a pulsed gradient spin echo-planar sequence, with TE = 59 msec, TR ≈ 11,884 msec, $G = 62\ \mathrm{mTm^{-1}}$, half scan factor = .679, 112 × 112 image matrix reconstructed to 128 × 128 using zero padding, reconstructed resolution 1.875 × 1.875 mm, slice thickness 2.1 mm, 60 contiguous slices, 61 non-collinear diffusion sensitization directions at $b = 1200$ s $\mathrm{mm^{-2}}$ ($\Delta = 29.8$ msec, $\delta = 13.1$ msec), 1 at $b = 0$, SENSE acceleration factor = 2.5. Acquisitions were cardiac gated using a peripheral pulse unit positioned over the participants' index finger or an electrocardiograph. For each gradient direction, two separate volumes were obtained with opposite polarity k-space traversal with phase encoding in the left-right/right-left direction to be used in the signal distortion correction procedure (Embleton et al., 2010). A co-localized T2 weighted turbo spin echo scan, with in-plane resolution of .94 × .94 mm and slice thickness 2.1 mm, was obtained as a structural reference scan to provide a qualitative indication of distortion correction accuracy. A high resolution T1-weighted 3D turbo field echo

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