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The organisation of the elderly connectome

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ABSTRACT

Investigations of the human connectome have elucidated core features of adult structural networks, particularly the crucial role of hub-regions. However, little is known regarding network organisation of the healthy elderly connectome, a crucial prelude to the systematic study of neurodegenerative disorders. Here, whole-brain probabilistic tractography was performed on high-angular diffusion-weighted images acquired from 115 healthy elderly subjects (age 76–94 years; 65 females). Structural networks were reconstructed between 512 cortical and subcortical brain regions. We sought to investigate the architectural features of hub-regions, as well as left–right asymmetries, and sexual dimorphisms. We observed that the topology of hub-regions is consistent with a young adult population, and previously published adult connectomic data. More importantly, the architectural features of hub connections reflect their ongoing vital role in network communication. We also found substantial sexual dimorphisms, with females exhibiting stronger inter-hemispheric connections between cingulate and prefrontal cortices. Lastly, we demonstrate intriguing left-lateralized subnetworks consistent with the neural circuitry specialised for language and executive functions, whilst rightward subnetworks were dominant in visual and visuospatial streams. These findings provide insights into healthy brain ageing and provide a benchmark for the study of neurodegenerative disorders such as Alzheimer's disease (AD) and frontotemporal dementia (FTD).

1. Introduction

The human brain is a large-scale complex network known as the human "connectome" (Sporns et al., 2005). The application of graph theoretical analysis to human neuroimaging data has uncovered topological features of the connectome that mirror other complex systems (Fornito et al., 2013; Sporns, 2013). These network features include "small-worldness" (Achard et al., 2006; Sporns and Zwi, 2004; Stephan et al., 2000), highly-connected "hubs" (Hagmann et al., 2008; van den Heuvel and Sporns, 2011, 2013b), and a modular structure (Hagmann et al., 2008; Meunier et al., 2009). Knowledge of the connectome has accelerated through recent advances in diffusion-weighted imaging, including optimal acquisition parameters (Sotiropoulos et al., 2013; Tournier et al., 2013), improved reconstruction algorithms (Behrens et al., 2003; Tournier et al., 2010), and diffusion models (Aganj et al., 2011; Behrens et al., 2007; Jbabdi et al., 2012; Tournier et al., 2008).

A crucial architectural feature of the adult human connectome is the presence of highly-connected regions ("hubs"), that are also densely connected with each other (van den Heuvel and Sporns, 2013b). These regions form what is known as a "rich-club", and occur in cortical regions such as the precuneus, cingulum (anterior and posterior), insula, superior frontal and parietal areas, temporal regions, and also subcortical structures (van den Heuvel and Sporns, 2011, 2013b). Rich-club connections in human (Collin et al., 2013; van den Heuvel et al., 2012), macaque (Harriger et al., 2012) and cat cortices (de Reus and van den Heuvel, 2013) have high topological efficiency, longer anatomical fibres, increased inter-modular connectivity and route a large proportion of network traffic. The structural rich-club may thus act as a central backbone that integrates communication between segregated brain regions (van den Heuvel and Sporns, 2013b). This is exemplified by the disproportionate reduction in network "communicability" and/or "efficiency" when hub-regions or their connections are artificially lesioned (Crossley et al., 2013; de Reus et al., 2014; van den Heuvel and Sporns, 2011).

These hub-regions overlap with transmodal areas known to be pivotal within-and-between core neurocognitive systems such as the cognitive control, default mode, and salience network (Crossley et al., 2013; Dwyer et al., 2014; Sepulcre et al., 2012; Spreng et al., 2013; Tomasi and Volkow, 2011; Uddin et al., 2011; van den Heuvel and Sporns, 2013a). Interestingly, alterations in functional connectivity of these large-scale systems in elderly populations have been associated

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with changes in working memory, processing speed and executive functions (Campbell et al., 2012; Damoiseaux et al., 2008; He et al., 2014; Lim et al., 2014; Wang et al., 2010). These disruptions are thus suggestive of topological changes occurring to hub connections with ageing. Hub-regions are also metabolically costly, evident through their increased metabolic expenditure and wiring cost (Collin et al., 2013; Liang et al., 2013; van den Heuvel et al., 2012). This increased energy expenditure of hub-regions further highlights their potential for age-related changes, as their high metabolic cost has been shown to potentially render such regions more vulnerable to pathological processes in neurodegenerative disorders (Crossley et al., 2014; Liang et al., 2013; Tomasi et al., 2013). Indeed, hub-regions have shown to be more likely susceptible to normal ageing processes such as amyloid deposition (Buckner et al., 2009; Toga and Thompson, 2014).

During cognitively demanding tasks, older adults increase their recruitment of contralateral brain regions, suggesting compensatory mechanisms (Cabeza et al., 2002; Davis et al., 2012; Park and Reuter-Lorenz, 2009). Left-hemisphere networks are well known to be dominant in language tasks, whilst the right-hemisphere is associated with visuospatial abilities (Geschwind and Galaburda, 1985; Herve et al., 2013; Toga and Thompson, 2003). Although connectomic investigations (Caeyenberghs and Leemans, 2014; Nielsen et al., 2013; Tomasi and Volkow, 2012b) have examinated lateralized organisation at the nodal-level, no study has specifically investigated lateralization of the elderly connectome.

Sexual dimorphism has also been an active area of research for the last few decades, with increasing interest from connectomic investigations (Dennis et al., 2013; Duarte-Carvajalino et al., 2012; Gong et al., 2009; Ryman et al., 2014). Across the lifespan, males have been shown to demonstrate greater performance in visuospatial tasks, whilst females excel on verbal tasks (Gur et al., 2012; Hoogendam et al., 2014; Kimura, 2004). Preferential wiring for inter-hemispheric structural connections was recently observed in female adolescents, whilst localised intra-hemispheric connectivity characterises cortical networks in young men (Ingalhalikar et al., 2014). Whether such topological differences persist into late adulthood is not known.

Hitherto, the structural connectomes of healthy elderly populations have been investigated through lifespan longitudinal studies (Betzel et al., 2014; Caeyenberghs and Leemans, 2014; Gong et al., 2009). Whilst these incorporate sufficiently large numbers of subjects across the life span, the number of elderly subjects is invariably modest. The organisation of healthy older connectomes hence remains relatively unknown and has not benefitted from recent advances in the acquisition and analysis of structural connectomes. The present study addresses this gap by characterising network topology in elderly structural connectomes generated from high-angular resolution fibre bundles. For comparative purposes, structural networks of a young adult population (17–30 years old) are also investigated.

2. Methods

2.1. Participants

143 cognitively healthy elderly individuals were drawn from the Sydney Memory and Ageing Study (Tsang et al., 2013). The longitudinal study involves community-dwelling older adults aged 76–94 years, randomly recruited from the electoral roll. Inclusion criteria for all participants were performance above (1.5 standard deviations) normative published values on all neuropsychological test measures. Exclusion criteria included the diagnosis of Mild Cognitive Impairment, decided by a clinical case panel chaired by neuropsychiatrists, psychogeriatricians, and psychologists (Sachdev et al., 2010) using international consensus criteria (Winblad et al., 2004). Other exclusion criteria included dementia, mental retardation, schizophrenia, bipolar disorder, multiple sclerosis, motor neuron disease, active malignancy, or inadequate comprehension of English to complete a basic assessment.

2.2. Diffusion MRI acquisition

Diffusion MRI data were acquired from all subjects on a Philips 3T Achieva Quasar Dual MRI scanner (Philips Medical System, Best, The Netherlands), using a single-shot echo-planar imaging (EPI) sequence (TR = 13,586 ms, TE = 79 ms). For each diffusion scan, 61 gradient directions ($b = 2400$ s/mm^2) and a non-diffusion-weighted acquisition ($b = 0$ s/mm^2) were acquired over a 96 mm^2 image matrix (FOV 240 mm × 240 mm^2); with a slice thickness of 2.5 mm and no gap, yielding 2.5 mm isotropic voxels.

2.3. Diffusion image pre-processing

The diffusion MRI scan of each participant was visualised within FSLView (Smith et al., 2004). Participants were excluded from the study if their scan revealed the presence of artefact due to motion effects. Twenty-two participants were excluded due to diffusion artefact, along with six others whose networks were not completely connected. We thus analysed the structural connectomes from 50 males and 65 females (see Table 1).

The FMAM (Fit Model to All Measurements) method (Bai and Alexander, 2008) was used to correct for eddy current and motion effects using ANTS software (Avants et al., 2009). To correct for head motion, the gradient direction matrix was rotated (Leemans and Jones, 2009). Next, to reduce spatial intensity inhomogeneities, intensity normalisation was performed on the b0 image and subsequently applied to all diffusion-weighted (DW) images (Sled et al., 1998). Lastly, a Higher Order Model Outlier Rejection model (Pannek et al., 2012) identified voxels with residual outliers in the DW signal.

2.4. Whole-brain fibre tracking

We employed the probabilistic streamline algorithm (iFOD2) (Tournier et al., 2010) to generate high-resolution whole-brain fibre tracks until 5 million in number were reached. The orientation of fibre distributions (FOD) were estimated within MRtrix software (Tournier et al., 2012), by performing constrained spherical deconvolution (CSD, $lmax = 8$) of the diffusion signal (Tournier et al., 2008). Using the default parameters for images of such acquisition (step size = 1.25 mm, minimum length = 12.5 mm, max length = 250 mm, FA termination = 0.1, max angle = 45°), iFOD2 tracked the most probable fibre propagations by sampling a probability density function of the FOD at points along each candidate path. iFOD2 has been shown to improve the accuracy of reconstructing high-angular fibre bundles (Tournier et al., 2012) and prevent biases caused by overshoot (Tournier et al., 2010).

2.5. Construction of whole-brain structural networks

The standard AAL template (Tzourio-Mazoyer et al., 2002) was subdivided into 512 cortical and sub-cortical parcellation regions (SI 1 Table 1) of approximately uniform size (Zalesky et al., 2010b). The AAL parcellation is widely used in structural network investigations (Bai et al., 2012; Caeyenberghs and Leemans, 2014; Gong et al., 2009; Lo et al., 2010; Shu et al., 2012; Shu et al., 2011), but does not include information on the WM–GM boundary for each parcel. We note that the echo-planar readout in diffusion acquisition induces geometric

Table 1
Demographic information.

Gender (M/F)	Male (N = 50)	Female (N = 65)
	Mean ± SD	Mean ± SD
Age (years)	83.35 ± 4.74	82.89 ± 4.06
Education (years)*	13.37 ± 3.87	11.64 ± 2.93

* $p < .01$ (t-test).

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