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AGING AND LARGE-SCALE FUNCTIONAL NETWORKS: WHITE MATTER INTEGRITY, GRAY MATTER VOLUME, AND FUNCTIONAL CONNECTIVITY IN THE RESTING STATE

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Abstract—Healthy aging is accompanied by neurobiological changes that affect the brain's functional organization and the individual's cognitive abilities. The aim of this study was to investigate the effect of global age-related differences in the cortical white and gray matter on neural activity in three key large-scale networks. We used functional–structural covariance network analysis to assess resting state activity in the default mode network (DMN), the fronto-parietal network (FPN), and the salience network (SN) of young and older adults. We further related this functional activity to measures of cortical thickness and volume derived from structural MRI, as well as to measures of white matter integrity (fractional anisotropy [FA], mean diffusivity [MD], and radial diffusivity [RD]) derived from diffusion-weighted imaging. First, our results show that, in the direct comparison of resting state activity, young but not older adults reliably engage the SN and FPN in addition to the DMN, suggesting that older adults recruit these networks less consistently. Second, our results demonstrate that age-related decline in white matter integrity and gray matter volume is associated with activity in prefrontal nodes of the SN and FPN, possibly reflecting compensatory mechanisms. We suggest that age-related differences in gray and white matter properties differentially affect the ability of the brain to engage and coordinate large-scale functional networks that are central to efficient cognitive functioning.

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Abbreviations: AD, axial diffusivity; BOLD, blood-oxygenation-level dependent; BSR, boot strap ratio; DMN, default mode network; EEG, electroencephalography; FA, fractional anisotropy; FPN, fronto-parietal network; FSL, FMRIB Software Library; LVs, latent variables; MD, mean diffusivity; MNI, Montreal Neurological Institute; PCC, posterior cingulate cortex; PLS, Partial Least Squares; RD, radial diffusivity; ROI, region of interest; SN, salience network; TE, echo time; TR, repetition time.

Key words: aging, resting state networks, white and gray matter, multimodal imaging, neural plasticity.

INTRODUCTION

The brain at rest consistently yields activity in the default mode network (DMN), which includes areas in the posterior cingulate cortex (PCC), precuneus, medial prefrontal areas, and the medial temporal lobes (Raichle et al., 2001; Greicius et al., 2003). The DMN was initially considered to represent neural baseline activity until further investigations showed that activity within the DMN is functionally related to internally driven mental states, such as self-referential processing, long-term memory, and mentalizing, and that its deactivation plays a functional role during externally directed tasks (Buckner et al., 2008; Kelly et al., 2008; Burianova et al., 2010; Mennes et al., 2010; Sambataro et al., 2010; Anticevic et al., 2012). In addition, an emerging view suggests that cognitive performance *in general* might rely on the dynamic interaction between the DMN and two other large-scale neural networks: the fronto-parietal task-positive network (FPN), which is associated with attention and cognitive control, and the salience network (SN) in anterior cingulate and fronto-insular cortex, which is involved in the selection of emotionally and motivationally relevant stimuli (Fox et al., 2005; Seeley et al., 2007; Sridharan et al., 2008; Chen et al., 2013; Spreng et al., 2013; Andrews-Hanna et al., 2014). These three neural networks are central to cognition, as they are engaged in a large number of functions, and their disruption has been associated with a variety of clinical syndromes, such as schizophrenia, traumatic brain injury, and Alzheimer's disease (Zhou et al., 2010; Manoliu et al., 2014; Sharp et al., 2014). In addition, evidence suggests that the disruption of the dynamic coordination of these large-scale networks constitutes one of the main causes of cognitive decline associated with aging (Andrews-Hanna et al., 2007; Sambataro et al., 2010), as shown by reduced neural activity in the DMN and SN at rest (Allen et al., 2011; Onoda et al., 2012) and increased activity in the FPN of older adults during visual tasks (Grady et al., 2010). However, it is an open question as to why and how aging

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affects the dynamic coordination of large-scale neural networks (Grady, 2012).

One possible reason for altered large-scale network activation with increasing age is that aging leads to widespread neurobiological changes, which impact the structural organization and integrity on which large-scale networks critically depend (Van den Heuvel et al., 2008; Greicius et al., 2009; Teipel et al., 2010; Horn et al., 2013). Thus, structural changes related to aging would, in part, account for the *functional* changes associated with cognitive decline. This view is supported by studies that found correlations between functional integration of anterior and posterior medial regions and fractional anisotropy (FA) of connecting white matter tracts (Andrews-Hanna et al., 2007), between activity in the DMN during fixation and age-related decreases in FA across the whole white matter skeleton (Burzynska et al., 2013), and between functional connectivity in bilateral prefrontal cortex and FA of corpus callosum (Davis et al., 2012). In addition, there is evidence that the white matter networks of older adults are organized less efficiently and with less functional connectivity within the DMN, FPN, and SN than those of younger adults (Achard and Bullmore, 2007; Zhu et al., 2012; Geerligs et al., 2014; for a recent review of this body of evidence, see Ferreira and Busatto, 2013). These studies show correlations between functional activity in the DMN and indicators of white matter integrity for specific brain regions. However, no study has comprehensively addressed the relationship between whole-brain structural changes related to healthy aging and changes in functional connectivity across the three central large-scale neural networks. Therefore, the aim of this study was to investigate age-related differences in global white and gray matter properties and their relationship to functional activity in three large-scale neural networks (DMN, FPN, and SN) in the resting state.

We hypothesized that age-related neurobiological changes related to the processing and transmission of information would affect functional connectivity, and that indicators of white and gray matter integrity, such as FA, mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD), cortical thickness, volume, and surface area, would significantly correlate with neural activity as measured by fMRI in each of the three networks. Specifically, we predicted that global age-related decline in microstructural integrity of white matter tracts as measured by decreasing FA and increasing MD, RD, and AD, would be indicative of reduced global efficiency of long-distance connections and lead to less functional connectivity in all three networks of older adults. Similarly, we expected to find that age-related reduction in gray matter thickness, surface area, and volume would affect efficiency of neural information processing in nodes of each network and further contribute to altered large-scale network activity in older adults.

EXPERIMENTAL PROCEDURES

16 older participants (mean age = 66 years; range = 59–81 years; 9 males) and 16 young participants (mean age = 30 years; range = 23–37 years; 7 males) took part in the experiment. All participants were right-handed, with normal or corrected to normal vision, native English speakers, and received a comparable number of years of formal education (mean older adults = 17 years, mean younger adults = 18 years). All older participants were considered cognitively intact, scoring in the high range of the Mini-Mental State Examination (MMSE; average score = 29.3; range = 26–30). Only participants that met the following criteria were included in the study: no previous head injury, no known neurological or psychological conditions, no history of alcohol or substance abuse, no blood-thinning medication.

All participants took part in a 6-min eyes-closed resting state experiment, followed by a 13-min diffusion weighted acquisition on a Siemens 3-T Magnetom Verio scanner with a standard 32-channel radiofrequency head coil at the Macquarie University Private Hospital. The Human Research Ethics Committee at Macquarie University approved this study and written consent was obtained from all participants.

Gray matter data acquisition and analysis

For each participant, a T1-weighted volumetric anatomical MRI was acquired with the following parameters: 176 slices sagittal magnetization-prepared rapid acquisition with gradient echo (MP-RAGE); $0.94 \times 0.94 \times 0.94$ mm isotropic volume; repetition time (TR) = 2110 ms; echo time (TE) = 3.52 ms; flip angle = 9°; FOV = 240 mm. T1 weighted images were analyzed with the default processing pipeline of Freesurfer 5.1 (http://surfer.nmr.mgh.harvard.edu/), which includes brain extraction, intensity normalization, segmentation, generation of white and pial surfaces, surface topology correction, inflation of surfaces to a sphere, and spherical registration to the average surface based on a measure of surface shape (Dale et al., 1999; Fischl et al., 1999a,b, 2004; Fischl and Dale, 2000; Fischl et al., 2001; Ségonne et al., 2004). Average whole-brain values of cortical volume, surface area, and thickness were extracted for each individual and compared statistically. To correct for differences in head size, volume measures were examined as percentage of total intracranial volume. Measures showing significant group differences between young and older adults were used as covariates for functional–structural covariance network analysis (see below).

DWI data acquisition and analysis

Diffusion-weighted images were acquired along 64 gradient directions with the following parameters: TR = 11500 ms, TE = 85 ms, b-value = 1200 s/mm^2, voxel size = $2 \times 2 \times 2$ mm, 55 axial slices. To obtain diffusivity measures, images were analyzed using the FMRIB Software Library (FSL 5.0; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). After eddy-current correction, Gaussian diffusion tensor models were fitted to each voxel with DTIfit and eigenvectors and eigenvalues, as well as FA maps were computed (Behrens et al., 2007). Additionally, maps of different diffusivity measures, such as mean diffusivity (MD $= (\lambda 1 + \lambda 2 + \lambda 3)/3$), radial diffusivity