Neurobiology of Aging 36 (2015) 2830–2837

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

The relation of structural integrity and task-related functional connectivity in the aging brain

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ARTICLE INFO

Article history:
Received 24 December 2014
Received in revised form 2 July 2015
Accepted 5 July 2015
Available online 10 July 2015

Keywords:
Structural integrity
Functional connectivity
White matter
Gray matter
Age-related compensation

ABSTRACT

The relations among structural integrity, functional connectivity (FC), and cognitive performance in the aging brain are still understudied. Here, we used multimodal and multivariate approaches to specifically examine age-related changes in task-related FC, gray-matter volumetrics, white-matter integrity, and performance. Our results are two-fold, showing (i) age-related differences in FC of the working memory network and (ii) age-related recruitment of a compensatory network associated with better accuracy on the task. Increased connectivity in the compensatory network correlates positively with preserved white-matter integrity in bilateral frontoparietal tracks and with larger gray-matter volume of right inferior parietal lobule. These findings demonstrate the importance of structural integrity and FC in working memory performance associated with healthy aging.

1. Introduction

Healthy aging is associated with structural and functional changes in the brain and a decline in behavioral performance on a variety of cognitive tasks. Efficiency of cognitive functioning necessarily depends on the integrity of cerebral gray matter (GM) and white matter (WM); yet, little is known about the relation among age-related changes in structure, behavior, and task-related functional connectivity (FC). Despite widespread anatomic variability, converging evidence demonstrates age-related cortical thinning and reduction in GM volume (Tisserand et al., 2002) and a loss of integrity in WM microstructure (Guttmann et al., 1998). Functionally, theories of cognitive aging concur that two distinct phenomena take place in the aging brain: dedifferentiation, that is, reduced distinctiveness of neural representations in domain-specific areas (Li et al., 2001), and compensation, that is, over-recruitment of alternate brain circuits to compensate for age-related processing deficiencies in the existing circuitry that subserves a specific cognitive function (Cabeza et al., 2002; Grady, 2012; Reuter-Lorenz et al., 2000). Increased engagement of prefrontal and other brain areas is interpreted as compensatory when associated with maintained performance in older adults (Davis et al., 2008; Grady, 2002; Grady et al., 2002; Madden et al., 2004) or when activity in these over-recruited areas is positively correlated with behavior in older adults (Burianová et al., 2013; Davis et al., 2008; Grady et al., 2002). It is argued that the strongest evidence for compensation is the recruitment of additional neural resources in older adults, that is, higher levels of mean activity or stronger FC, and that this recruitment is related to better performance in older adults (Cabeza and Dennis, 2013; Grady, 2008). Although compensation links functional activity and behavior, the interplay between compensation and structural integrity is still unclear. It is of importance to note that albeit two distinct phenomena, the dedifferentiation and compensation processes have been shown not to be mutually exclusive (Burianová et al., 2013). Thus, the brain may show reduced neural selectivity in the domain-specific regions and use a different network of areas to compensate for this deficiency in neural distinctiveness.

Concurrent investigations of age-related alterations in structure and function are necessary because the mechanisms underlying changes in structural integrity may likely mediate changes in FC

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http://dx.doi.org/10.1016/j.neurobiolaging.2015.07.006

and performance on cognitive tasks. Recent studies have reported an association between age-related changes in WM microstructure and cognitive performance (Burzynska et al., 2013) and between age-related decline in GM volume and performance (Steffener et al., 2012), thereby demonstrating significant covariance between better structural integrity and higher cognitive functioning in aged adults. Although standard in vivo imaging methods preclude drawing of direct causal inferences regarding structure-function-behavior relations, multimodal imaging approaches may provide convergent evidence for complex macroscopic principles that facilitate age-related plasticity.

The objective of the present study was to use multimodal imaging and multivariate analysis methods to investigate the relation among changes in FC of a task-related network, behavioral performance, and structural integrity in an aging population. Specifically, we used a validated cognitive task (*n*-back) to delineate the working memory network, which engages essential load-dependent frontoparietal (FP) nodes (Honey et al., 2002), and examined the relation between the strength of FC in this network and task performance. Older adults often compensate for deficits in posterior brain regions by increasing frontal activity (Grady et al., 2002); thus, we examined GM volumetrics of the network's FP nodes and WM microstructure of their connecting WM tract, the superior longitudinal fasciculus (SLF, Petrides and Pandya, 2002). We hypothesized that, in contrast with young adults, (i) older adults would show stronger FC to the frontal regions under low load, as aging has been associated with increased recruitment of available frontal resources at lower levels of cognitive load (Reuter-Lorenz and Cappell, 2008) and (ii) older adults who perform better on the working memory task would recruit brain regions outside of the working memory network to aid their performance under high cognitive load, when available resources would have reached their limit. In addition to its association with more accurate performance, this compensatory recruitment would relate to greater structural integrity, as we propose that intact brain structure may play a biologically permissive role in functional compensation (Murphy and Corbett, 2009).

2. Methods

2.1. Participants

Twenty-three healthy older adults (mean age = 66 years, standard deviation [SD] = 5 years, 13 females) and 22 healthy young adults (mean age = 29 years, SD = 6 years, 10 females) participated in the study. All participants were right handed, had normal or corrected-to-normal vision, and had no history of neurological impairment or psychiatric illness. The 2 groups of participants were education matched. Older adults were cognitively intact and achieved an average score of 28.9 (SD = 1.1 and range 27–30), on the Mini-Mental State Examination (Folstein et al., 1975). All participants provided written informed consent approved by the University of Queensland Human Research Ethics Committee.

2.2. Experimental design

Participants underwent a 45-minute experimental session, which consisted of 3 components: structural magnetic resonance imaging (MRI), diffusion-weighted imaging (DWI), and functional MRI (fMRI). During fMRI, participants were presented with a continuous series of letters and performed an *n*-back task with 3 experimental conditions: 0-back, 1-back, and 2-back. During the 0-back condition, participants were required to press "1" if the letter "A" was presented or "2" if any other letter was presented. During the 1-back and 2-back conditions, participants were required to press "1" if the current letter matched the letter 1 or 2 letters earlier, respectively, or "2" if it did not match. Letters were presented in a blocked design, with 4 blocks of each experimental condition, 20 letters per block, and 4–6 targets per block. Each block consisted of a 3-s instruction, 500-ms stimulus presentation, and 1-s interstimulus interval. Three 20-s fixation blocks were presented at the beginning, middle, and end of each of the functional runs. Before the experimental session, the task was verbally and visually explained to the participants who subsequently took part in a short practice session, which ensured a proper familiarization with the task's instructions and timing.

2.3. MRI acquisition and analysis

T1-weighted volumetric structural MRIs were acquired using a 3-dimensional magnetization-prepared rapid gradient-echo sequence (192 sagittal slices, time repetition [TR] = 1900 ms, time echo [TE] = 2.32 ms, time inversion = 900 ms, field of view = 230 mm, voxel size = 0.9 mm^3, and flip angle = 9°). Estimates of cortical volume were obtained using the default preprocessing steps of FreeSurfer software (http://surfer.nmr.mgh.harvard.edu). For each participant, brains were extracted and intensities normalized. Then, GM, WM, and noncortical structures were segmented, and a triangular mesh was used to generate the pial and cortical surfaces, which was followed by a manual quality control check of gross structural abnormalities, occurrence of artifacts, and accuracy of registration (Dale et al., 1999; Toro et al., 2008). For each participant, average values of cortical volume were extracted for inferior parietal lobule (IPL) and the rostral division of the middle frontal gyrus (MFG) in each hemisphere, using the Desikan-Killiany atlas (Desikan et al., 2006). Volume measures were normalized as percentage of total intracranial volume, to correct for difference in head size. All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS, version 21; SPSS, Inc, Chicago, IL, USA). Individual values of cortical volume of the regions of interest were used as covariates in task-related FC analysis (see subsequently).

2.4. DWI acquisition and analysis

High–angular resolution DWIs were acquired along 85 gradient directions using spiral acquisition (Sepehrband et al., 2015; 55 slices, TR = 9400 ms, TE = 112 ms, *b* value = 3000 s/mm^2, and voxel size = 2.5 mm^3) and processed using Dipy software (Garyfallidis et al., 2014; http://nipy.org/dipy/). DWIs were first corrected for motion and residual eddy current–induced distortions using ExploreDTI software with B-matrix adjustments (Leemans and Jones, 2009; http://www.exploredti.com/). Then, after skull and nonbrain tissue were removed from the image using median Otsu segmentation (Garyfallidis et al., 2014), the tensor model was fitted to each voxel using nonlinear regression, and, finally, fractional anisotropy (FA) maps were calculated (Basser et al., 1994). FA is considered a general marker of WM integrity, reflecting coherence within a voxel and fiber density (Beaulieu, 2002), yet, in the absence of other diffusivity measures, it is generally accepted as a nonspecific marker of microstructural change (Alexander et al., 2007). To maximize specificity, we obtained additional maps of different diffusivity measures from the tensor, namely, radial diffusivity (RD), a marker of demyelination (Song et al., 2005), and axial diffusivity (AD), a marker of axonal damage or loss (Sun et al., 2006).

Group differences for these diffusivity measures were assessed for the whole WM skeleton using tract-based spatial statistics (Smith et al., 2006) included in functional magnetic resonance imaging of the brain (FMRIB's) Software Library (FSL, http://fsl.fmrib.ox.ac.uk/). All diffusivity maps, including a common WM skeleton for all participants, were linearly coregistered to the avgMNI152 template using FSL's FMRIB's linear image registration