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Differential age-dependent associations of gray matter volume and white matter integrity with processing speed in healthy older adults

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ABSTRACT

Slower processing speed (PS), a highly robust feature of cognitive aging, is associated with white matter (WM) deterioration and gray matter volume (GMV) loss. Traditional linear regression models assume a constant relationship between brain structure and cognition over time. To probe for variation in the association between WM and GMV and PS over time, we used a novel sparse varying coefficient model on data collected from 126 relatively healthy older adults (67 females, aged 58–85 years) evaluated with MRI and a standardized neuropsychological test-battery. We found that WM microstructural differences indexed by fractional anisotropy values in the fronto-striatal tracts (internal and external capsule) showed a stronger association with PS before the age of 70 years. Contrastingly, GMV values of the left putamen and middle occipital gyrus were more strongly correlated with PS after 70 years. Additionally, within GM and WM compartments, there was heterogeneity in the temporal sequence in which different cortical and subcortical elements were most strongly associated with PS. Together, these observations provide a more nuanced account of the relationships between different structural components of the aging brain and processing speed, a key cognitive domain affected in relatively healthy older adults.

Introduction

Reduced processing speed (PS) is a highly robust feature of cognitive aging (Salthouse and Ferrer-Caja, 2003) that may underlie age-related decline in several higher order cognitive abilities (Salthouse, 1995, 2010). Tests of processing speed incorporate both elements of sensorimotor response time as well as the ability to rapidly switch between recently encountered item mappings. Reduced gray matter volume (GMV) and degraded white matter (WM) integrity have individually been shown to correlate with age-related reduction in PS (Fjell and Walhovd, 2010).

Reduced GMV could potentially contribute to slower PS by increasing noise in neuronal signals with resultant slowing of information processing. In a prior cross-sectional analysis of relatively healthy elderly participants (N = 248, aged 55–86 years), we found a correlation between total cerebral volume and PS. Lower GMV of the inferior frontal, superior parietal, and lingual gyri also correlated with slower PS (Chee et al., 2009). Another cross-sectional study of adults aged 19–79 years found that the particular spatial patterns of frontal and cerebellar gray and white matter were related to slower PS (Eckert et al., 2010). PS differences have also been associated with thinner medial frontal and occipito-temporal cortices (Righart et al., 2013).

White matter degradation could contribute to reduced PS in healthy aging by affecting the speed of information transfer throughout the brain (Bendlin et al., 2010; Charlton et al., 2006; Lu et al., 2011; Madden et al., 2012; O'Sullivan et al., 2001; Shenkin et al., 2005; Vernooij et al., 2009; Voineskos et al., 2012). DTI measures of WM microstructure are useful in measuring healthy and pathological aging (Fjell and Walhovd, 2010; Sullivan and Pfefferbaum, 2006). Fractional anisotropy (FA), a commonly reported diffusivity measure of WM integrity and efficiency, indexes the directional coherence of water displacement. A decrease in PS has been related to a reduction of FA mainly in the frontal-subcortical tracts including the genu of the corpus callosum (Bennett et al., 2012; Bucur et al., 2008; Haasz et al., 2013; Kennedy and Raz, 2009a; Salami et al., 2012; Zahr et al., 2009), anterior limb of internal capsule (ALIC) (Madden et al., 2004; Sullivan et al., 2010), external capsule (EC), superior longitudinal fasciculus, and inferior fronto-occipital fasciculus (Borghesani et al., 2013; Kerchner et al., 2012; Salami et al., 2012), and anterior corona radiata (ACR) (Mori et al., 2005; Wakana et al., 2004) in healthy older subjects. Based on a sample of very old adults (aged 81–103 years) assessed twice with an interval of 2.3 years, decreases in perceptual speed were associated with changes in WM integrity of the corticospinal tract over time (Lovden et al., 2014).

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These findings establish the individual contributions of GMV loss and WM integrity deterioration to reduced PS (Kennedy et al., 2009; Kennedy and Raz, 2009a; Madden et al., 2009; Pfefferbaum et al., 2000, 2005; Sullivan and Pfefferbaum, 2006). However, it remains unclear as to how they jointly contribute to PS slowing as aging progresses (Fjell and Walhovd, 2010; Madden et al., 2009). Structural equation modeling has been applied to investigate how age and WM integrity influence cognitive performance in healthy subjects across the lifespan (Voineskos et al., 2012). Along similar lines, mediation analysis has been used to demonstrate how loss of WM integrity (FA) can mediate the relationship between age and PS (Kerchner et al., 2012). However, mediation models used in cross-sectional data may be biased (Lindenberger et al., 2011; Maxwell and Cole, 2007).

In contrast to the prevailing assumption that the contribution of a given brain structure to cognitive decline is constant over time, recent large-scale studies have identified nonlinear trajectories of age-related decreases in brain structural integrity (Ostby et al., 2009). A range of linear, quadratic, and cubic correlations between age and cortical thickness has been identified in different brain regions (Shaw et al., 2008; Sowell et al., 2003). Across the lifespan, the trajectories of GM and WM maturational and aging effects vary considerably across the cortex. Widespread reductions in GMV that are observed from middle age onward are preceded by changes restricted to the frontal cortex (Giorgio et al., 2010). In contrast, widespread WM microstructure changes are found from young adulthood onward, each white matter region exhibiting different linear or nonlinear lifespan trajectories (Giorgio et al., 2010; Kennedy and Raz, 2009b; Westlye et al., 2010). Indeed, initial decline in white matter integrity can begin as early as 23 years of age (Imperati et al., 2011), raising the possibility that WM degradation may exert a stronger influence on cognitive performance earlier in age than declines in GM volume.

In light of these prior findings, we examined the differential age-dependent associations of regional WM FA and GMV with PS using the sparse varying coefficient (SVC) model (Daye et al., 2012). Unlike linear models used in previous studies, the SVC model does not assume constant association between a brain structure and PS across age, instead allowing for the association to vary with age. We hypothesized that (1) age-related reductions in the WM FA and GMV mainly within the fronto-striatal circuits and sensory cortices would be associated with slower PS and (2) the strength of the associations would not remain constant over time but instead vary with age. Specifically, based on prior evidence that WM microstructure metrics might decline earlier than GMV in aging, we expected deterioration in FA to correlate with PS earlier than GMV loss.

Methods

Participants

The participants were from the Singapore Longitudinal Aging Brain Study (Chee et al., 2009), a community-based convenience sample cohort comprising relatively healthy elderly adults. The current sample consisted of 126 participants (67 females, aged 58–85 years, all right-handed, age distribution in Supplementary Fig. 1B) who underwent both neuropsychological assessments and quality-controlled MRI and DTI scans during 2009–2010. They were of Han Chinese ethnicity and had no known active medical conditions other than treated, uncomplicated diabetes mellitus or hypertension (Table 1). They did not have any of the following: (1) a history of significant vascular events (i.e., myocardial infarction, stroke, or peripheral vascular disease); (2) a history of malignant neoplasia of any form; 3) a history of cardiac, lung, liver, or kidney failure; (4) active or inadequately treated thyroid disease; (5) active neurological or psychiatric conditions; (6) a history of head trauma with loss of consciousness; (7) a Mini Mental State Examination (MMSE) (Folstein et al., 1975) score of less than 26; or (8) a 15-point modified-Geriatric Depression Screening Scale (GDS) (Sheikh and Yesavage, 1986) score of greater than 9. The Institutional Review Board at the National University of Singapore granted approval for this study. All participants provided written informed consent prior to participation.

Table 1
Subject characteristics (N = 126).

Variables	Mean (SD)
Age (years)	69.3 (6.5)
Number of females	67
Education (years)	11.9 (3.4)
BMI (weight kg / height m^2)	23.4 (2.9)
Systolic blood pressure (mm Hg)	138.2 (16.9)
Diastolic blood pressure (mm Hg)	73.9 (9.9)
Mini Mental State Examination	28.2 (1.3)
Trail-Making Test A (seconds)	41.6 (14.9)
Symbol–Digit Modalities Test Written	44.3 (10.6)
Symbol–Digit Modalities Test Oral	51.1 (10.4)
Symbol search	27.3 (8.0)

Abbreviation: BMI = body mass index.

Neuropsychological assessments

Within 3 months of undergoing MR imaging, all participants underwent a comprehensive neuropsychological assessment that evaluated six cognitive domains: PS, attention, verbal memory, visuospatial memory, executive functioning, and language. To minimize the effects of language and culture, the included tests contained items that were relatively familiar to the study population (Chee et al., 2009). Here, we assessed PS using the Trail-Making Test A (Reitan and Wolfson, 1985), the Symbol–Digit Modalities Test (SDMT) (Smith, 1991), and symbol search test (Wechsler, 1997). The Trail-Making Test A recorded the time to complete the connection of 25 circles that contained numbers in an ascending order. The time in seconds was then multiplied by −1 to enable a higher score to indicate better performance. The SDMT required the participants to substitute a number for its corresponding geometric figure in both written and oral formats, with each format lasting 90 seconds. The raw score was the total number of correct answers. The symbol search test lasted for 120 seconds and required the participants to decide whether the target symbol appeared in a row of symbols. The raw score was the total number of correct answers. The raw scores of these three tests were normalized into *z*-scores across 126 participants. We generated one composite score for PS per participant by taking the average of the three *z*-scores to reduce the number of comparisons.

Image acquisition

MRI scans were conducted on a 3 T Siemens Magnetom Tim Trio System (Siemens, Erlangen, Germany). All 126 participants had DTI acquisition using a diffusion-weighted echo-planar imaging (EPI) sequence (30 non-collinear diffusion gradient directions at b = 1000 seconds/mm^2, six volumes of b = 0 seconds/mm^2, TR/TE = 9600/107 ms, FOV = 256 × 256 mm^2, matrix = 128 × 128, 54 contiguous slices, and voxel size = 2.0 × 2.0 × 2.0 mm^3). High-resolution T1-weighted structural MRI was acquired using MPRAGE (magnetization-prepared rapid gradient echo) sequence (192 continuous sagittal slices, TR/TE/TI = 2300/2.98/900 ms, flip angle = 9°, FOV = 256 × 240 mm^2, matrix = 256 × 256, isotropic voxel size = 1.0 × 1.0 × 1.0 mm^3, bandwidth = 240 Hz/pixel) for 119 participants and MEMPRAGE (multi-echo MPRAGE) (192 continuous sagittal slices, TR/TE/TI = 2530/2.98/1200 ms, flip angle = 7°, FOV = 256 × 256 mm^2, matrix = 256 × 256, isotropic voxel size = 1.0 × 1.0 × 1.0 mm^3, bandwidth = 651 Hz/pixel) for the remaining 7 participants.