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The association between higher order abilities, processing speed, and age are variably mediated by white matter integrity during typical aging

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ABSTRACT

Although aging is associated with changes in brain structure and cognition it remains unclear which specific structural changes mediate individual cognitive changes. Several studies have reported that white matter (WM) integrity, as assessed by diffusion tensor imaging (DTI), mediates, in part, age-related differences in processing speed (PS). There is less evidence for WM integrity mediating age-related differences in higher order abilities (e.g., memory and executive functions). In 165 typically aging adults (age range 54–89) we show that WM integrity in select cerebral regions is associated with higher cognitive abilities and accounts variance not accounted for by PS or age. Specifically, voxel-wise analyses using tract-based spatial statistics (TBSS) revealed that WM integrity was associated with reasoning, cognitive flexibility and PS, but not memory or word fluency, after accounting for age and gender. While cerebral fractional anisotropy (FA) was only associated with PS; mean (MD), axial (AD) and radial (RD) diffusivity were associated with reasoning and flexibility. Reasoning was selectively associated with left prefrontal AD, while cognitive flexibility was associated with MD, AD and RD throughout the cerebrum. Average WM metrics within select WM regions of interest accounted for 18% and 29% of the variance in reasoning and flexibility, respectively, similar to the amount of variance accounted for by age. WM metrics mediated ~50% of the age-related variance in reasoning and flexibility and different proportions, 11% for reasoning and 44% for flexibility, of the variance accounted for by PS. In sum, (i) WM integrity is significantly, but variably, related to specific higher cognitive abilities and can account for a similar proportion of variance as age, and (ii) while FA is selectively associated with PS; while MD, AD and RD are associated with reasoning, flexibility and PS. This illustrates both the anatomical and cognitive selectivity of structure-cognition relationships in the aging brain.

1. Introduction

The neurobiologic underpinnings of age-related cognitive decline remain unclear. Although cerebral atrophy and neuronal death occur in select brain regions during specific diseases (e.g., hippocampal cell loss in Alzheimer's disease), it appears that a majority of non-specific age-related cerebral volume loss is the result of reduced neuronal complexity and loss of connections (Fjell & Walhovd, 2010). Since the coordinated activity of both local and global neural networks relies on cortical–cortical connections, white matter (WM) integrity, i.e., the "intactness" of cortical connections, must be essential for normal cognitive function and loss of WM integrity likely contributes to age-related cognitive decline (Bartzokis et al., 2004; Deary, Penke, & Johnson, 2010).

Age-related cognitive decline is observed in many domains important in the maintenance of everyday function including memory, executive function and processing speed (PS) (Hedden & Gabrieli, 2004). While reliance of higher order abilities on PS is complex (Park & Reuter-Lorenz, 2009), it has been hypothesized that reductions in PS may account for much of the age-related cognitive change in higher order abilities (Finkel, Reynolds, McArdle, Hamagami, & Pedersen, 2009; Salthouse, 1996, 2010). Thus we sought to determine if WM integrity is related to higher order cognitive abilities after accounting for age or PS, and whether WM integrity mediates the associations between higher order cognitive abilities, age and PS.

Both higher order abilities (e.g., executive function and episodic memory) and PS have been variably associated with WM integrity

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(Gold, Powell, Xuan, Jicha, & Smith, 2010; Kennedy & Raz, 2009; O'Sullivan et al., 2001; Turken et al., 2008; Vernooij et al., 2009). However, few studies have tried to determine if reduced WM integrity accounts for the association between higher order abilities and PS. Bucur et al. (2008) reported that WM integrity in prefrontal regions partially mediates the association between PS and episodic memory while Salami, Eriksson, Nilsson, and Nyberg (2011) reported that although WM integrity partially mediates the association between age and PS, it is not strongly related to age-related changes in higher cognitive functions (Bucur et al., 2008; Salami et al., 2011). Thus it remains unclear if WM integrity mediates the association between age-related changes in higher order abilities and declining PS (Madden, Bennett, & Song, 2009a).

Age-related changes in WM integrity (i.e., microstructure) can be assessed with diffusion tensor imaging (DTI). DTI allows for the in situ assessment of WM integrity since water diffuses more freely parallel to myelinated axons (i.e. axial diffusivity (AD)) than perpendicular to them (i.e., radial diffusivity (RD)) (Le Bihan, 2003). Fractional anisotropy (FA) is essentially the ratio of AD to RD while mean diffusivity (MD) is the average diffusion across all directions. Major WM tracts have high FA. Loss of WM integrity is typically defined by reduced FA, perhaps reflecting the loss/degeneration of axons, and increased MD, perhaps reflecting demyelination and loss of parenchymal complexity (Jones, 2008). Aging is associated with decreasing FA and increasing MD throughout much of the cerebral WM (Bennett, Madden, Vaidya, Howard, & Howard, 2010; Burzynska et al., 2010; Damoiseaux et al., 2009; Madden, Bennett et al., 2009; Sullivan & Pfefferbaum, 2003) that is linearly related to average cortical thickness (Kochunov, Glahn, Lancaster et al., 2011). While AD and RD have also been shown to increase with age (Michielse et al., 2010) it is less clear how they are related to cognitive changes during typical aging (Madden et al., 2012). Some evidence points to greater RD changes with aging than AD (Burzynska et al., 2010) while others report equal or greater AD changes (Sala et al., 2010).

Herein we examine where higher order cognitive abilities and PS are associated with WM integrity and whether regional WM integrity mediates the associations between higher order abilities, PS and age. This is important because if changes in WM integrity can explain the association between PS and age-related cognitive decline, it would suggest that WM pathology, and not cell loss, account for cognitive changes during typical aging. To determine where higher order abilities and PS are associated with WM integrity we used tract based spatial statistics (TBSS), a 3D voxel-wise approach that assesses local maximum DTI values (the presumed core of cortical WM tracts (Smith et al., 2006)). We hypothesize that PS will be more strongly and globally related to WM integrity than higher order abilities (Wen et al., 2011) and that executive abilities will be most related to WM integrity in the frontal lobes. In addition, given that flexibility is more associated with PS than other higher order abilities (Schaie, Dutta, & Willis, 1991) we predict that flexibility may be more related to WM integrity than other higher order abilities. To determine if WM integrity can account for the associations between higher order abilities, PS and age, mediation analysis using average regional WM metrics is used. In mediation analysis three conditions must be met (Baron & Kenny, 1986); (i) the cognitive abilities must be correlated with age and PS, (ii) WM integrity must be correlated with age and PS and (iii) WM integrity should account for significant variance in multiple regressions that include the "mediated" variable. This approach has been used in prior studies (Bucur et al., 2008; Madden, Spaniol et al., 2009; Salami et al., 2011) although the mediation effects of WM integrity on age were not explored (Bucur et al., 2008) or only found for PS and not higher order abilities (Madden, Spaniol et al., 2009; Salami et al., 2011). Finally, we hypothesize that WM integrity will account for unique variance in cognitive abilities beyond that explained by either age or PS.

2. Materials and methods

2.1. Participants

The present study involved 188 subjects who were selected to undergo MRI in 2006–2007 from the Seattle Longitudinal Study (SLS), a cohort-sequential longitudinal study of the relationship between aging, health, cognition and life-style (Schaie, 2005). Imaging data from 165 subjects was used secondary quality control measures (see *Image Analysis* below). SLS members at recruitment represent a stratified-by-age and gender sample from the Group Health Cooperative of Puget Sound, a large HMO in western Washington State. This study has been approved by the University of Washington Medical Center and the Group Health Cooperative of Puget Sound Institutional Review Boards. Participants were selected from the larger group sample ($n=572$) of SLS subjects who had been cognitively assessed in middle age; selection criteria were; (i) had undergone 2 or more cognitive assessments in midlife and/or old age, (ii) participated in the 2005 SLS data collection, and (iii) were willing and capable of undergoing MRI. A vascular risk score (0 to 3) was assigned to each subject based on self-reported diagnoses of hypertension, diabetes or hyperlipidemia (each risk factor being given an equal weight of 1 point). APOE genotyping was performed at Northwest Lipid Research Laboratories (Seattle WA, USA).

2.2. Cognitive assessment

SLS participants were assessed on a broad battery of psychometric abilities in two, 2.5-hour sessions (Schaie, 2005; Schaie, Willis, & Caskie, 2004). Cognitive testing was performed independently of the MRI and occurred on average 24 weeks prior to scanning (s.d. 34 weeks, range 2 years prior to 1.25 years after). The testing-MRI interval was not correlated with age ($r=-0.01$), any DTI metric (all p values >0.05, uncorrected for multiple comparisons) or any other demographic factor. However, the testing-MRI interval was correlated with immediate recall (partial correlation $\rho=-0.28$ $p<0.01$), delayed recall ($\rho=-0.23$ $p<0.01$), word fluency ($\rho=-0.23$ $p<0.01$), cognitive flexibility ($\rho=-0.16$ $p<0.05$) and PS ($\rho=-0.28$ $p<0.01$) but not reasoning, after accounting for age and gender. This suggests that at any given age at scanning, those taking the test earlier (i.e., prior to the MRI) had slightly better scores than those scanned later (i.e., after the MRI) as expected if scores decline with age.

All subjects were cognitively normal based on neuropsychological assessment and consensus review (MMSE ranged from 24–30 with 2 individuals scoring 24 and one individual scoring 25). Two measures of episodic memory (immediate and delayed recall), word fluency, two measures of executive function (reasoning and cognitive flexibility), and a measure of PS were used in this analysis. All cognitive measures were converted into t-scores using first occasion data from the entire SLS sample for standardization to permit quantitative, longitudinal comparisons across measures with different metrics (Schaie, Willis, & Pennak, 2005).

2.2.1. Episodic memory

Both immediate and delayed recall measures were used (Zelinski, Gilewski, & Schaie, 1993); (Zelinski & Kennison, 2007). For immediate recall, participants studied a 20-word list for 3.5 min followed by 3.5 min of free recall. Delayed recall involved free recall after 1-hour of interim activities (test-retest reliability $r=0.7$) (Zelinski & Lewis, 2003). Words correctly recalled are scored. Immediate and delayed recall are highly correlated ($r=0.92$, $p<0.001$) and generated qualitatively identical results in all analyses. Combining immediate and delayed recall into a factor score resulted in qualitatively identical results to each individual score, e.g., DTI parameters were not associated with the factor score.

2.2.2. Word fluency

The Primary Mental Abilities (PMA) word fluency test (Thurstone & Thurstone, 1949) requires participants to recall as many words as possible according to a lexical rule in a 5-minute period (e.g., words starting with the letter "S"). In factor analytic work it has been shown to load on verbal memory and ability (Schaie et al., 1991). No factor score for word fluency is available as factor analysis has shown that word fluency is a complex ability with loading on memory, verbal and speed factors (Willis, unpublished results).

2.2.3. Reasoning

The PMA reasoning test (Thurstone & Thurstone, 1949) requires participants to view a series of letters (e.g., abXcdXefXghX…) that are arranged according to one or more rules. Participants are asked to discover the rule(*s*) and mark the letter that should come next in the series. In the preceding example, normal alphabetical progression is interrupted with an "x" after every second letter and the solution would be the letter "i". Scores represent the number of items (out of 30) that are