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Age-Related Slowing in Cognitive Processing Speed is Associated with Myelin Integrity in a Very Healthy Elderly Sample

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Abstract

Performance on measures of cognitive processing speed (CPS) slows with age, but the biological basis associated with this cognitive phenomenon remains incompletely understood. We assessed the hypothesis that the age-related slowing in CPS is associated with myelin breakdown in late-myelinating regions in a very healthy elderly population. An in vivo MRI biomarker of myelin integrity was obtained from the prefrontal lobe white matter and the genu of the corpus callosum for 152 healthy elderly adults. These regions myelinate later in brain development and are more vulnerable to breakdown due to the effects of normal aging. To evaluate regional specificity, we also assessed the splenium of the corpus callosum as a comparison region, which myelinates early in development and primarily contains axons involved in visual processing. The measure of myelin integrity was significantly correlated with CPS in highly vulnerable late-myelinating regions but not in the splenium. These results have implications for the neurobiology of the cognitive changes associated with brain aging.

Keywords

Healthy Aging; Cognition; Information Processing Speed; Myelin; White Matter; Magnetic Resonance Imaging; Alzheimer's Disease; Dementia

INTRODUCTION

Performance on a wide-range of neuropsychological tests changes with age; for this reason, raw performance scores are typically adjusted for age to guide neuropsychological inference. In other words, the scores obtained are compared to an age-matched normative database. However, the biological basis for the age-related variance in different cognitive abilities is still not completely understood. Cognitive processing speed (CPS) is broadly defined as how fast one can execute the mental operations needed to complete a task at hand

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(Salthouse, 2000). Salthouse and others have argued that the age-related slowing in CPS underlies declines in other higher-order cognitive functions including memory and executive functioning (Hedden, Lautenschlager, & Park, 2005; Levitt, Fugelsang, & Crossley, 2006; Rabbitt et al., 2007; Salthouse, 1995; Salthouse, 1996; Salthouse, 2005; Salthouse & Coon, 1993; Salthouse & Ferrer-Caja, 2003).

Slowing in CPS with advancing age has high face validity and is arguably the most often replicated finding across studies of age effects on neuropsychological test performance. In clinical and laboratory settings, CPS is primarily measured using perceptual speed tasks, involving visual search, elementary comparison, and substitution operations. Cross-sectional (Gottsdanker, 1982; Salthouse, 2000; Salthouse, 2009; Tombaugh, 2004; Wilkinson & Allison, 1989) and longitudinal (Schaie, 2005) studies show that across the lifespan, speed of performance on these tasks has a quadratic trajectory that takes the shape of an inverted U; it reaches maximum efficiency around the mid-30's then shows a generally linear decline thereafter. Recent studies have increasingly focused on the role of white matter as the biological basis underlying this basic cognitive phenomenon (Bartzokis et al., 2007; Bucur et al., 2008; Charlton et al., 2006; Deary et al., 2006; Kemper, 1994; Kennedy & Raz, 2009; Madden et al., 2009; Marner, Nyengaard, Tang, & Pakkenberg, 2003; O'Sullivan et al., 2001; Tang, Nyengaard, Pakkenberg, & Gundersen, 1997; Tuch et al., 2005; Turken et al., 2008; Vernooij et al., 2009).

Axon myelination results in saltatory conduction of action potentials (AP) that increases signal transmission speed by more than 10-fold (Waxman, 1977). Myelination also markedly decreases the refractory time (time needed for repolarization before a new AP can be supported by the axon) by as much as 34-fold (Felts, Baker, & Smith, 1997; Sinha, Karimi-Abdolrezaee, Velumian, & Fehlings, 2006). Thus, intact myelin enhances the integration of information across spatially distributed neural networks supporting cognitive and motor functions (Bartzokis et al., 2001; Fuster, 1999; Lutz, Koeneke, Wustenberg, & Jancke, 2005; Mesulam, 2000; Srinivasan, 1999). The protracted myelination process of the human brain results in a quadratic (inverted U) trajectory of myelin content and integrity as it peaks in the mid-30's followed by breakdown and loss with advancing age (Bartzokis et al., 2001; Bartzokis et al., 2003; Benes, Turtle, Khan, & Farol, 1994; Ge et al., 2002; Jernigan & Gamst, 2005; Kemper, 1994; Walhovd et al., 2005). This course of myelin development and breakdown resembles the pattern of performance on CPS measures across the lifespan, suggesting a relationship between these brain and cognitive measures (Salthouse, 2000; Salthouse, 2009; Schaie, 2005). Furthermore, slowed information processing speed has been consistently documented in multiple sclerosis (MS), a demyelinating disease that affects the central nervous system (Archibald & Fisk, 2000; Diamond, Johnson, Kaufman, & Graves, 2008; Kail, 1998; Lengenfelder et al., 2006; Litvan, Grafman, Vendrell, & Martinez, 1998).

Myelin breakdown associated with healthy aging has been thoroughly demonstrated in animal models (Kemper, 1994; Marner et al., 2003; Peters et al., 1996; Peters & Sethares, 2003; Peters & Sethares, 2004; Peters, Sethares, & Killiany, 2001; Sloane, Hinman, Lubonia, Hollander, & Abraham, 2003; Tang et al., 1997) and humans (Pakkenberg et al., 2003). Studies using ultrastructural electron microscope reveal that age-related myelin breakdown results in microvacuolations consisting of splits in the myelin sheath layers (Kemper, 1994; Nielsen & Peters, 2000; Peters & Sethares, 2002). This creates microscopic fluid-filled spaces that increase tissue water (Bartzokis et al., 2004; Peters et al., 1996). Consequently, the structural integrity of myelin sheaths can be indirectly measured *in vivo* with magnetic resonance imaging (MRI) by estimating the transverse relaxation rates (R_2, derived from the reciprocal of transverse relaxation time or T_2). Intuitively, R_2 measures how rapidly the MRI signal dissipates, and this rate is sensitive to the local molecular

environment. Relaxometry measures, such as R_2, are markedly sensitive to small changes in the proportion of tissue water (Oldendorf & Oldendorf, 1988). Myelination reduces white matter water content (Ferrie et al., 1999; Paus et al., 2001) and thereby increases R_2; conversely, myelin breakdown increases tissue water and decreases R_2 (Fazekas, Schmidt, & Scheltens, 1998; Takao et al., 1999; Dyakin et al., 2010). Histopathologic studies on animals have shown that certain toxins, such as vigabatrin (VBG), cause intramyelinic edema resulting in microvacuolations (Jackson et al., 1994; Peters et al., 1996; Peyster et al., 1995; Weiss et al., 1994); this damage is reversible with discontinuation of VGB treatment. MRI T_2 signal intensity changes in concert with the extent of myelin microvacuolation, confirming that toxin-induced myelin breakdown and the subsequent recovery process can be detected and tracked with MRI (Jackson et al., 1994; Peyster et al., 1995; Qiao et al., 2000; Weiss et al., 1994) (reviewed in Cohen, Fisher, Brigell, Peyster, & Sze, 2000).

R_2 measures have also been used to assess myelin integrity in humans during the development/myelination phase (birth to mid life) when R_2 increases (Miot-Noirault, Barantin, Akoka, & Le Pape, 1997; Bartzokis et al., 2003) as well as in aging and a variety of myelin-damaging conditions in which R_2 decreases (Takao et al., 1999; Bartzokis et al., 2003; House et al., 2006; Neema et al., 2007; Vermathen et al., 2007). Severity of myelin damage and associated R_2 changes are on a continuum that ranges from focal lesions (Takao et al., 1999; Neema et al., 2007; Vermathen et al., 2007) visible to the unaided eye (referred to as T_2 "hyperintensities" on radiology reports) to diffuse changes that occur in "normal appearing white matter" detectable only with *quantitative* R_2 measures (Bartzokis et al., 2003; House et al., 2006; Neema et al., 2007; Vermathen et al., 2007). In disease processes such as multiple sclerosis or phenolketonuria, myelin destruction is *qualitatively* observable on MRI images but more subtle changes are also detectable quantitatively with R_2 measures in "normal appearing white matter" (Neema et al., 2007; Vermathen et al., 2007). Similarly, age-related R_2 changes in normal appearing white matter have been quantitatively demonstrated in healthy aging as well as more pronounced changes associated with genes that increase risk of developing Alzheimer's disease (AD), pre-AD conditions such as mild cognitive impairment, and AD itself (Bartzokis et al., 2003; House et al., 2006; Bartzokis et al., 2007). Herein the terms myelin "integrity" and "breakdown" will be used to refer to R_2 measures.

Recent studies have reported on the correlation between age and white matter integrity using diffusion tensor imaging (DTI) markers (Bucur et al., 2008; Charlton et al., 2006; Deary et al., 2006; Kennedy & Raz, 2009; Madden et al., 2009; O'Sullivan et al., 2001; Turken et al., 2008; Vernooij et al., 2009). DTI is a MRI modality that provides information about the microstructural integrity of WM by measuring the magnitude and direction of water diffusion (Pierpaoli & Basser, 1996; Basser & Pierpaoli, 1996). Fractional anisotropy (FA) describes the directional selectivity of the random motion of water molecules within a tissue and is thought to reflect the structure of axonal cell membranes and myelin sheaths (Pierpaoli & Basser 1996). Analysis of other DTI parameters such as directional diffusivities may provide additional information on the potential pathophysiology underlying the white matter changes. Increased radial diffusivity (perpendicular to the white matter tract) is related to myelin breakdown whereas changes in axial diffusivity (parallel to the primary fiber orientation) reflect axonal damage (Sun et al., 2006; Song et al. 2003, 2005). However, crossing fibers, such as those found in the frontal lobes, can artificially reduce FA values, the most frequently used index of white matter integrity, if they are computed from the standard single-tensor model (Zhan et al., 2009), but the R_2 measure used here has been validated to be sensitive to myelin content (Bartzokis et al., 2004; Jackson et al., 1994; Peyster et al., 1995; Qiao et al., 2000; Weiss et al., 1994) and is not influenced by fiber orientation (Bartzokis et al., 2003; Bartzokis et al., 2004; House, St Pierre, Foster, Martins,

& Clarnette, 2006) and therefore lends itself to precise regional hypothesis testing of structure-function relationships.

The heterogeneity in chronology of brain development may underlie the regionally specific pattern of myelin breakdown seen in aging, which appears to have a reverse trajectory from development, beginning from later-myelinating regions and progressing to earlier-myelinating regions (Bartzokis, 2004a; Braak & Braak, 1999; Flechsig, 1901; Kemper, 1994; Nielsen & Peters, 2000; Peters, Moss, & Sethares, 2000). Regions that myelinate later in brain development include the frontal lobes and the genu of the corpus callosum (which connects the prefrontal cortices of the left and right hemispheres). These regions are comprised of smaller axons and the myelin sheaths have fewer myelin lamellae (Chia, Thompson, & Moscarello, 1983). Therefore, these regions tend to be more vulnerable to breakdown by a variety of brain insults as well as the effects of normal aging (Kemper, 1994; Marner et al., 2003; Tang et al., 1997). In contrast, the splenium of the corpus callosum contains primarily sensory (visual) axons that tend to be fully and heavily myelinated in early childhood (Lamantia & Rakic, 1990; Pandya & Seltzer, 1986; Yakovlev & Lecours, 1967).

Here we examined associations between cognitive processing speed (CPS) and selected regional measures of myelin integrity. To assess the normal aging process, as far as possible, we studied a well-characterized healthy elderly sample selected to minimize risk of incipient Alzheimer's disease (AD; e.g., under age 80, absence of family history of dementia and other risk factors). The use of the R_2 measure, which is highly reliable and reproducible (Bartzokis et al., 2003; 2004), more specifically assesses myelin fiber integrity and is not limited by crossing fibers prevalent in regions such as the frontal lobes. We specifically chose to analyze frontal lobe white matter (FLwm) and genu of the corpus callosum (Gwm) and combine them into a single measure because they both represent late-myelinating white matter (LMwm) and are most vulnerable and maximally affected by the aging process. For a contrasting region, we analyzed the splenium (Swm), which is heavily myelinated and more resistant to age-related breakdown. The CPS tasks chosen for this study (Digit Symbol and Trails A) use a broad range of cognitive, perceptual, and motor processes and are sensitive to the integrity of late-myelinating fiber systems that are responsible for speed and efficiency of task execution (Turken et al., 2008); therefore, we would expect CPS to be associated with myelin integrity in LMwm region but not in the Swm.

METHODS

Participants

Normal adult volunteers were between the ages of 55 to 80. Age 80 was chosen as the upper age limit as the risk of developing AD peaks at this age for carriers of the apolipoprotein E (ApoE) ε4 allele (Raber, Huang, & Ashford, 2004). They were recruited from the community and hospital staff for a study of healthy aging. Subjects were excluded if they had a history of neurological disorder, psychiatric illness (including drug or alcohol abuse), or head injury resulting in loss of consciousness for more than 10 minutes. Additional exclusion criteria aimed at reducing risk of underlying AD pathology included family history of AD or other neurodegenerative disorders and failed glucose tolerance test. The subjects were physically very healthy and were excluded if they were obese (defined as body mass index [BMI] of > 30kg/m^2), or if they had a history of diabetes, hypertension, or cardiovascular disease. The participants were independently functioning and had no complaints or evidence of neurocognitive impairment or gross neurological abnormalities on clinical interview and brief neurological examination (GB). Analyses were based on a total of 152 individuals with mean age of 67.0 (sd=5.9) and a mean education level of 15.5 years (sd=2.6). There were 62 men and 90 women in the sample and their racial composition was

comprised of 113 Caucasian (74%), 25 Asian (16%), 12 African-American (8%), and 2 Hispanic (1%) subjects.

All subjects received written and oral information about the study and signed written informed consents approved by the local institutional review board prior to study participation. Neurocognitive measures

***Trailmaking Test - Part A* (Reitan & Wolfson, 1985)—**Part A of the Trailmaking Test (Trails A) assesses speed of visual scanning, information processing, and graphomotor tracking. Subjects are required to rapidly connect twenty-five consecutively numbered circles. Time to complete the task serves as the variable of interest.

***Digit Symbol subtest* from the WAIS-R (Wechsler, 1981)—**This test involves rapid copying of symbols and integrates several cognitive processes including psychomotor speed, visual scanning, simple constructional ability, and short-term memory. The score reflects the number of symbols copied after 90 seconds.

Cognitive Processing Speed (CPS)—The dependent variable examined in all the analyses was a composite measure of cognitive processing speed computed by standardizing the scores from Trails A [log transformed due to positive skew then multiplied by -1 because lower time indicates faster performance] and Digit Symbol, using the means and standard deviations from the present healthy adult sample, then averaging the z-scores.

MRI protocol

All subjects were scanned using the same 1.5 Tesla MR instrument (Picker Instruments, Cleveland, Ohio), and all scans used the same imaging protocol. Details of the protocol have been published previously (Bartzokis et al., 2003; Bartzokis et al., 1994; Bartzokis et al., 2004) and are only summarized here. Two pilot sequences were obtained to specify the location and spatial orientation of the head and the position of the axial image acquisition grid. The axial image acquisition sequence acquired interleaved contiguous slices using a Carr Purcell Meiboom Gill dual spin-echo sequence TR/TE/NEX=2500/20,90/2, 3 mm slice thickness, 256×192 acquisition matrix, and 25 cm field of view.

Image analysis

Transverse relaxation time (T_2) was calculated at each voxel by an automated algorithm from the two signal intensities (TE = 20 & 90) of the robust dual spin-echo sequence that used 90 degree refocusing pulses to produce gray-scale encoded T_2 maps of the brain (Bartzokis et al., 1994). T_2 measures were extracted using a Macintosh configured image analysis workstation. The image analysis software (Medvision 1.4, Evergreen Technologies, Castine, ME) permitted the rater to delineate the region-of-interest (ROI) using a mouse.

For all three regions, two contiguous slices were chosen for analysis. To analyze the frontal lobe white matter, a circular ROI sample of supraorbital white matter was placed manually by the rater in the frontal lobe white matter on the second and third contiguous slices above the last image containing orbitofrontal cortex (Bartzokis et al., 2003). For analysis of the genu of the corpus callosum, the two slices on which the angle formed by the left and right sides of the genu appeared the most linear were chosen. This was done to obtain a sample that would be consistently in the middle of the structure, which contains primarily fibers connecting the prefrontal cortices (Bartzokis, Sultzer, et al., 2004). Values from these two regions formed the late myelinating white matter measure (LMwm) (Figure 1). For the contrasting early-myelinating region, the lower half of the splenium of the corpus callosum (Swm) was chosen. The second and third lowest slices on which the fibers of the splenium

connected in the midline were chosen in order to sample primarily the lower half of the splenium that contains predominantly early-myelinating primary sensory (visual) fibers (Lamantia & Rakic, 1990; Pandya & Seltzer, 1986) (Figure 1).

Once the choice of slices and position of the ROIs were completed, the rater excluded gray matter regions of the central sulcus, T_2 hyperintensities, or other hyperintense structures such as periventricular halos (for further details please see Bartzokis, et al., 2003; Bartzokis, Sultzer, et al., 2004). While the general image analysis protocol describes the removal of T_2 hyperintensities or other hyperintense structures if present, the white matter ROIs were not affected by T_2 hyperintensities in this sample of very healthy older adults who were screened and excluded for vascular-related risk factors such as hypertension, diabetes, and cardiovascular disease. The ROIs were then transferred onto the corresponding T_2 maps. All voxels that had a T_2 value above the right side inflection point of the histogram of the ROI were removed, to eliminate voxels that partially contained CSF structures or lesions (Bartzokis, et al., 1994).

T_2 data for each ROI were obtained from contiguous pairs of slices. The relaxation rate (R_2) was calculated as the reciprocal of T_2, and then multiplied by 1000 (by convention). The average R_2 of the two slices from both hemispheres were the final measures used in the subsequent analyses. Test-retest reliability of the R_2 measurement was assessed by computing intraclass correlation coefficients on 2 ratings done at least 1 month apart by the same rater for 13 of the scans. Reliability was very good for all three regions (Frontal lobe white matter: R_{xx}=0.91, F=21.3, df=1,12, p<.0001; genu of the corpus callosum white matter: R_{xx}=0.99, F=138.0, df=1,11, p<.0001; splenium of the corpus callosum white matter: R_{xx}=0.95, F=20.5, df=1,11, p<.0001).

Data Analysis

The primary hypothesis was that there would be a significant relationship between CPS and R_2 in late-myelinating regions (LMwm; composed of the average R_2 for the frontal and genu of the corpus callosum white matter regions) but not in the early-myelinating region (Swm). We compared age-related linear change in R_2 in late- and early-myelinating regions using multivariate multiple regression with age as the independent variable, testing the difference in the regression coefficients for the R_2 measure in the two regions. A simple linear regression model was used to examine age-related change in the measure of CPS. To complement the regression analysis, Pearson correlations were computed separately between measures of R_2 in the two regions and age, CPS and age, and between R_2 and CPS. Differences between these correlations were tested using a normal curve test based on Fisher's z-transformation. Significance tests are unadjusted for multiple comparisons and are reported as significant at p=.05 (two-tailed).

RESULTS

In this sample, the slope of the associations between measures of myelin integrity (R_2) and age were negative for both regions, but the slope of R_2 with age was steeper for LMwm than in Swm (LMwm: −.040 per year, SE=.006, p<.0001; Swm: −.011 per year, SE=.007, p=.133; multivariate F=14.92, df=1, 150, p=.0002). A steep slope was also seen for the association between CPS and age (−.055 per year, SE=.010, p<.0001). We computed Pearson correlations which revealed a significant negative relationship between LMwm and age (r=−.473, df=150, p<.0001) but not between Swm and age (r=−.123, df=150, p=.133). The difference in correlation coefficients between the LMwm and Swm groups were statistically significant and mirrored the regression result (Fisher's z-test: t=4.49, df=149, p<.0001). Significant negative relationship was also observed between CPS and age (r=−.423, df=150, p<.0001). These associations are graphically displayed in Figures 2A–C.

Pearson correlation analyses showed that CPS was significantly associated with R_2 in the LMwm (r=.225, df=150, p=.005) but not Swm (r=−.004, df=150, p=.961). Correlation coefficients between the two regions were compared via z-transformation, and the difference was statistically significant (t=2.66, df=149, p=.009) indicating a significant regional difference in the association between CPS and R_2. The relationship between LMwm R2 and CPS was no longer statistically significant after adjusting for the effects of age using partial correlation analysis (r=.031, df=149 p=.702).

Figure 3A shows the scatterplot and the trend line of the hypothesized association between LMwm R_2 and CPS for the healthy adult group, while Figure 3B shows the absence of this association in the contrasting region of Swm.

DISCUSSION

Our data confirm prior observations that CPS slows significantly with age (Gottsdanker, 1982; Salthouse, 2000; Salthouse, 2009, Tombaugh, 2004; Schaie, 2005; Wilkinson & Allison, 1989) and that LMwm was more susceptible to age-related myelin breakdown than the earlier-myelinating Swm region (Bartzokis, Sultzer, et al., 2004; House et al., 2006). As hypothesized, the R_2 was correlated with CPS only in the late-myelinating region, confirming regional specificity in this structure-function relationship. The relationship between LMwm R_2 and CPS was no longer statistically significant after adjusting for age indicating that both measures are strongly affected by the aging process.

By middle age, the developmental process of myelination produces a continuum of increasingly vulnerable oligodendrocytes from less vulnerable early-myelinating regions such as the visual pathways to more vulnerable later-myelinating association brain regions such as the frontal lobes (Bartzokis, Sultzer, et al., 2004; Flechsig, 1901; Meyer, 1981). Later-differentiating oligodendrocytes ensheath increasing numbers of axons with smaller axon diameters (Lamantia & Rakic, 1990; Pandya & Seltzer, 1986). As a result of increased complexity and metabolic demands, these more vulnerable myelin sheaths are disproportionately lost with age (27–45% reduction) (Bartzokis, Sultzer, et al., 2004; Braak & Braak, 1991; Kemper, 1994; Marner et al., 2003; Tang et al., 1997). The uniquely extensive myelination of the human brain makes myelin maintenance critical for sustaining our high CPS. The data support the hypothesis that during normal aging, the myelin-breakdown process in highly vulnerable late-myelinating regions is associated with a degradation of CPS (Bartzokis, 2004a, 2005, 2009).

Present findings provide a potential biological substrate for the “frontal aging hypothesis,” which proposes that the frontal lobes, a late myelinating region, are most vulnerable to age-related deterioration and thus underlie the neuropsychology of aging (Dempster, 1992; Greenwood, 2000). However, “frontal aging” may be preceded and mediated by the more basic cognitive phenomenon of processing speed as Salthouse and others have argued that the age-related slowing in CPS underlies declines in other higher-order cognitive functions such as memory and executive functioning (Hedden et al., 2005; Levitt et al., 2006; Rabbitt et al., 2007; Salthouse, 1995; Salthouse, 1996; Salthouse, 2005; Salthouse & Coon, 1993; Salthouse & Ferrer-Caja, 2003). This is consistent with large longitudinal studies of cognitive performance across the lifespan, which show that the decline in CPS performance begins at an earlier age and progresses at a steeper rate compared to memory functioning, which declines later in life (Amieva, Rouch-Leroyer, Letenneur, Dartigues, & Fabrigoule, 2004; Schaie, 2005). The CPS-R_2 associations observed in the present study, when considered in conjunction with the DTI literature demonstrating that integrity of specific white matter tracts can mediate age-related slowing in cognitive processing speed (Madden et al., 2009; Bucur et al., 2008; Gold et al., 2010), support the proposition that myelin

breakdown may represent one biological source of age-related decline in cognition. This has also been shown in non-human primates (Peters et al., 2000; Peters & Sethares, 2002), and explains the need for age adjustments in determining "normal" neuropsychological performance.

Studies relating white matter microstructure to cognition have received increased attention in recent years, but our current study represents a unique contribution to the existing literature because 1) our strict entry criteria attempt to create a model that best represents healthy brain and cognitive aging in humans, 2) the use of the R_2 measure more specifically assesses myelin fiber integrity as opposed to general white matter or axon health indicated by DTI markers employed by the majority of studies (Vernooij et al., 2009). To our knowledge, this is the only imaging study on healthy aging that aggressively screened out risks of incipient AD (e.g., no family history of AD, under age 80, no subjective concerns or objectively documented cognitive problems, normal glucose tolerance testing, no head trauma, excellent physical health, etc.). This minimizes the possibility that age-related changes in cognition and myelin integrity are driven by AD pathology. This study design replicates myelin-cognition associations observed *post mortem* in non-human primates, which do not develop AD (Peters et al., 2000; Peters & Sethares, 2002).

Recent studies have reported similar results using DTI markers, namely significant relationships between FA of anterior brain regions and tests of cognitive functions, including measures of information processing speed (Bucur et al., 2008; Charlton et al., 2006; Kennedy & Raz, 2009; Stebbins et al., 2001; Turken et al., 2008; Vernooij et al., 2009) and executive functioning involving attentional set-shifting and working memory (Charlton et al., 2006; Kennedy & Raz, 2009; O'Sullivan et al., 2001). In addition, lower FA in the anterior limb of the internal capsule was found to be associated with slower reaction time in older individuals (Madden et al., 2004) while FA in the splenium and parietal pericallosal region significantly correlated with alternated finger tapping (Sullivan et al., 2001). We did not find a significant association between splenium R_2 and finger tapping speed (Bartzokis et al., 2010) or the CPS measures in the present study. The discrepant results may reflect differential sensitivity of R_2 and FA measures to aspects of splenium cellular structure that correlate with finger tapping. R_2 and DTI, depending on the indices used and regions examined, may demonstrate similar or different patterns of development and breakdown with age. Specifically, R_2 of frontal lobes shows a quadratic, inverted-U trajectory (Bartzokis et al., 2003) consistent with *post mortem* data (Benes et al., 1994; Kemper, 1994). While several studies have reported that FA in the same region declines approximately linearly with age beginning from early adulthood (Grieve, Williams, Paul, Clark, & Gordon, 2007; Salat et al., 2005; Hsu et al. 2010), recent literature has demonstrated non-linear, quadratic relationships between FA and age in specific regions such as the body of the corpus callosum (Hsu et al., 2010; Sala et al., 2010), limbic pathways, and association and corticospinal tracts (Sala et al., 2010). In summary, R_2 and DTI offer different methods for assessing myelin content/white matter integrity, but the two approaches are complementary and their combined use will likely yield greater insight into the underlying pathophysiology of white matter changes.

Several study limitations should be acknowledged. The selection of very healthy individuals and the exclusion of family history with dementia may limit potential confounds and contributors that affect the trajectory of brain and cognitive changes, but the present findings are likely to underestimate the R_2-CPS relationship compared to the general population. A number of tissue changes such as subtle edema, alteration in regional vasculature, or alterations of axons unrelated to myelin breakdown could result in small changes in regional water content, affecting CPS and R_2. This possibility is less likely as all subjects had been thoroughly assessed and found to be in excellent health, and had few risk factors for

vascular disease or significant history of head trauma. The measures that comprise the CPS all involve graphomotor demands, thus performance may be adversely impacted by physical limitations and ailments (e.g., arthritis); subsequent studies may choose to employ cognitive processing speed measures devoid of a motor component. Finally, in a cross-sectional study, interpretation of age-related differences as "changes" or as "cause and effect' should be avoided (Kraemer, Yesavage, Taylor, & Kupfer, 2000; Schaie, 2005). Although more time-consuming and costly, prospective studies may be advantageous to more accurately model trajectories of change.

There is an urgent need to understand the biological and functional changes associated with brain aging, as age is the most potent risk factor for developing AD. The ability to measure age-related breakdown of myelin *in vivo* and the associated decline in CPS provides a biological framework to interpret changes in cognition associated with brain aging. Furthermore, measures of myelin integrity hold promise as a possible surrogate biomarker of assessing cognitive decline and outcome for primary prevention trials. Future studies can extend the present findings to examine the contribution of myelin breakdown to the trajectory of decline from normal cognitive functioning into MCI and AD.

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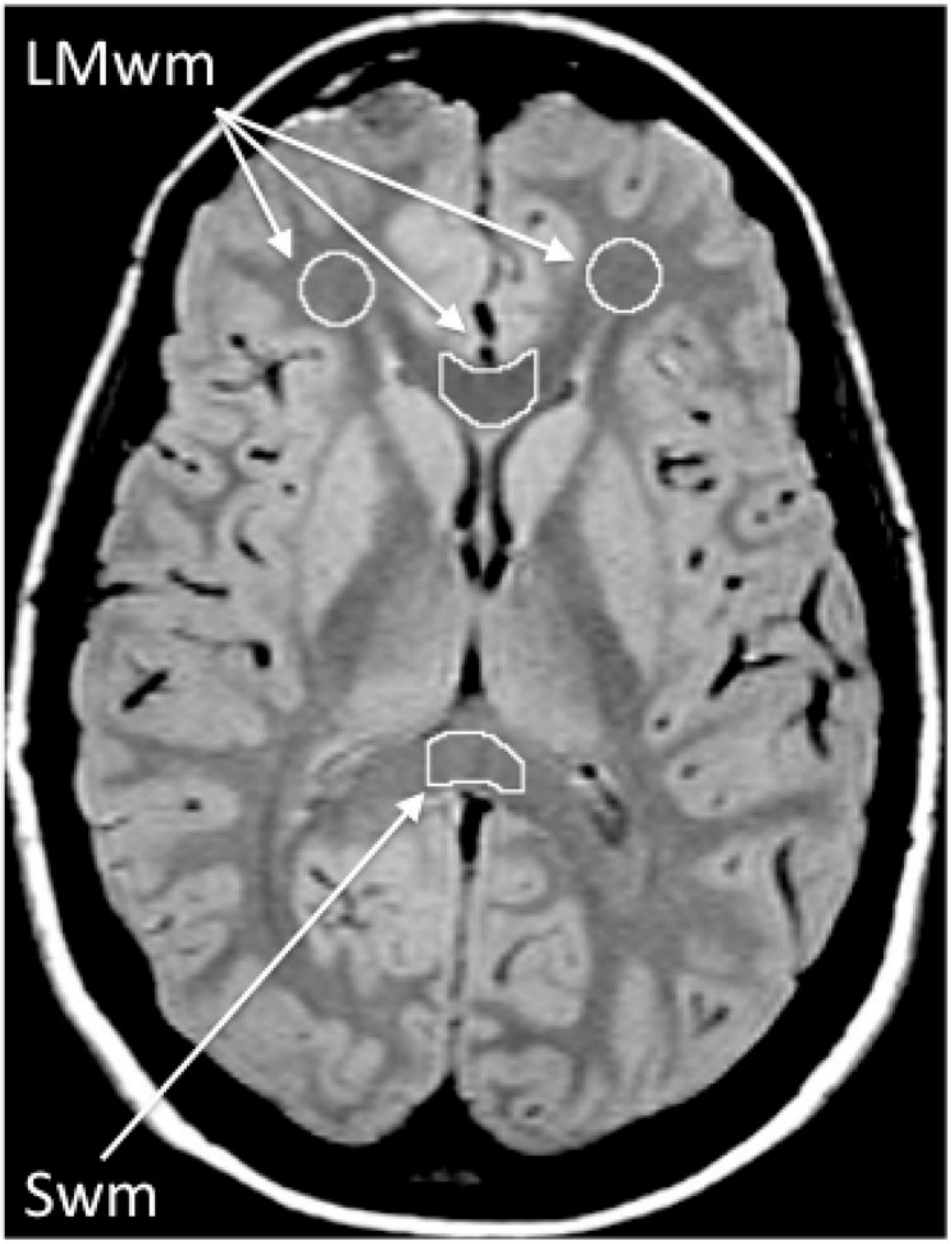

Figure 1.

White matter regions of interest (ROI). The ROIs are depicted on an early echo (TE=20) axial MRI image that has good contrast between gray matter (light gray) and white matter (dark gray). The TE=90 (not shown) has optimal contrast between brain (appears gray) and CSF (white). Both TE=20 and TE=90 images are used to draw each ROI as this combination of slices maximizes contrast needed for optimal ROI definition. Frontal lobe white matter: The ROI is manually edited to exclude any hyperintensities or gray matter. Genu and splenium for the corpus callosum: For each of the two corpus callosum regions, a standard rectangular ROI template is first positioned on the midline, and then the anterior and posterior borders are manually edited using the contrast provided by the TE=20 and TE=90 images to exclude non-corpus callosum tissue. Lateral borders are defined by the dimensions of the rectangular template. For the genu, this positioning results in a sample consistently in

the middle of the structure, which contains primarily fibers connecting the prefrontal cortices. For the splenium, this positioning samples primarily the lower half of the structure, which contains predominantly primary sensory (visual) fibers. This subject's image was chosen as an example because the head positioning was such that frontal lobe, genu, and splenium white matter were measured on the same slices. For the majority of subjects; however, these regions are measured on different slices.
LMwm = Late-myelinating white matter (average of frontal lobe and genu of corpus callosum white matter). Swm = Splenium of corpus callosum white matter (early-myelinating region).

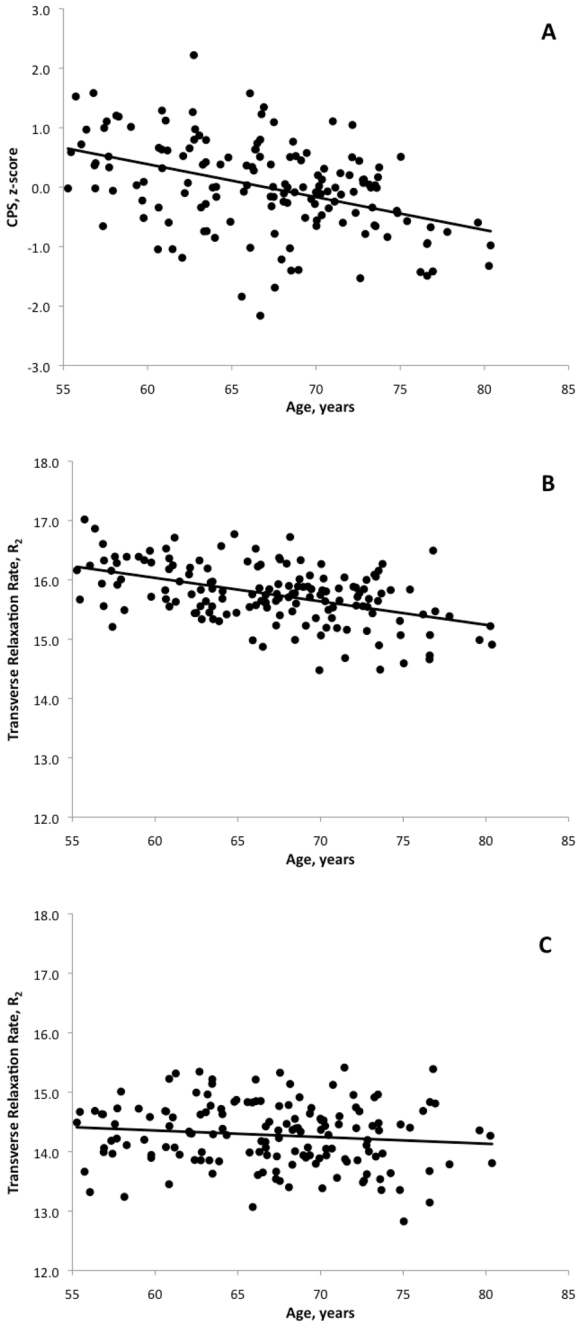

Figure 2.

Figures 2A–2C. Scatterplots and age-regression lines of cognitive processing speed (CPS) (A) late-myelinating white matter (B), and splenium of the corpus callosum (C).

Figure 3A.

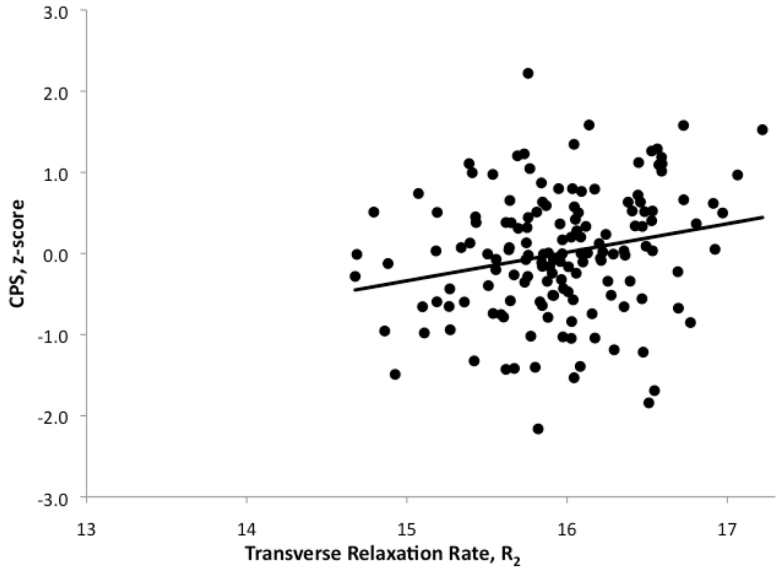

Figure 3B.

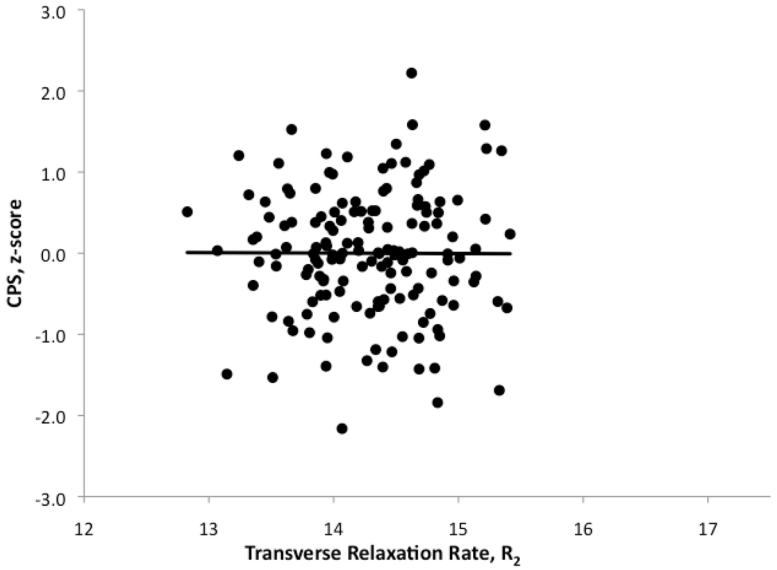

Figure 3.

Figures 3A and 3B. Scatterplots of Cognitive Processing Speed (CPS) versus Transverse Relaxation Rate (R_2) in late-myelinating white matter (3A) and splenium of the corpus callosum (3B) of healthy elderly subjects.