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White Matter Tracts Associated with Set-Shifting in Healthy Aging

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Abstract

Attentional set-shifting ability, commonly assessed with the Trail Making Test (TMT), decreases with increasing age in adults. Since set-shifting performance relies on activity in widespread brain regions, deterioration of the white matter tracts that connect these regions may underlie the age-related decrease in performance. We used an automated fiber tracking method to investigate the relationship between white matter integrity in several cortical association tracts and TMT performance in a sample of 24 healthy adults, 21 – 80 years. Diffusion tensor images were used to compute average fractional anisotropy (FA) for five cortical association tracts, the corpus callosum (CC), and the corticospinal tract (CST), which served as a control. Results showed that advancing age was associated with declines in set-shifting performance and with decreased FA in the CC and in association tracts that connect frontal cortex to more posterior brain regions, including the inferior fronto-occipital fasciculus (IFOF), uncinate fasciculus (UF), and superior longitudinal fasciculus (SLF). Declines in average FA in these tracts, and in average FA of the right inferior longitudinal fasciculus (ILF), were associated with increased time to completion on the set-shifting subtask of the TMT but not with the simple sequencing subtask. FA values in these tracts were strong mediators of the effect of age on set-shifting performance. Automated tractography methods can enhance our understanding of the fiber systems involved in performance of specific cognitive tasks and of the functional consequences of age-related changes in those systems.

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Introduction

The Trail Making Test (TMT) (Reitan & Wolfson, 1985) is a commonly-used measure of executive functioning (Butler, 1991) that assesses cognitive flexibility, selective attention, visual scanning, and visual-motor tracking (Giovagnoli, et al., 1996; Reitan & Wolfson, 1985; Zakzanis, Mraz, & Graham, 2005). It is administered in two parts, A and B, both of which require visuomotor tracking. The cognitive flexibility necessary for the set-shifting requirement in Part B increases the executive demands of this subtask as evidenced by slower completion times for Part B relative to Part A (Arbuthnott, 2000; Olivera-Souza, et al., 2000).

Performance on the TMT, particularly on the set-shifting component, declines with advancing age (eg. Salthouse & Fristoe, 1995; Zakzanis, et al., 2005), and it has been suggested that compromise to frontal lobe structures underlies this decline (Gunning-Dixon & Raz, 2000; West, 1996). In support of this, evidence from lesion studies (Stuss & Levine, 2002), repetitive transcranial magnetic stimulation (Moser, et al., 2002), and functional magnetic resonance imaging (fMRI) (Moll, de Oliveira-Souza, Moll, Bramati, & Andreiuolo, 2002; Zakzanis, et al., 2005) have implicated the prefrontal cortex in TMT performance. However, functional imaging studies have also demonstrated that set-shifting in the TMT recruits temporal and parietal regions in addition to frontal regions (Moll, et al., 2002; Zakzanis, et al., 2005). This implies that TMT performance relies on communication among a number of broadly distributed, functionally-specialized brain regions. The integrity of the white matter tracts that connect these regions is thus likely to be a critical factor in TMT performance.

The development of diffusion tensor imaging (DTI) has enabled the assessment of white matter integrity *in vivo*. DTI is a variant of magnetic resonance imaging (MRI) that allows for assessment of white matter integrity (Basser, 1995) and for three-dimensional mapping of fiber tracts within the brain (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; Mori & van Zijl, 2002). White matter integrity can be quantified as fractional anisotropy (FA), a measure of the degree and orientation of diffusion of water molecules in the brain. Average FA can be assessed in discrete regions of white matter, or within fiber tracts generated by DTI fiber tracking methods (Xue, van Zijl, Crain, Solaiyappan, & Mori, 1999).

Many studies have reported age-related declines in global and regional white matter (eg. Ge, et al., 2002; Good, et al., 2001; Guttmann, et al., 1998; Nusbaum, Tang, Buchsbaum, Wei, & Atlas, 2001; Pfefferbaum, et al., 2000; Salat, et al., 2004; Walhovd, et al., 2005), with frontal white matter particularly affected (eg. Head, et al., 2004; Makris, et al., 2007; O'Sullivan, et al., 2001; Pfefferbaum, Adalsteinsson, & Sullivan, 2005; Salat, et al., 2005; Sullivan, Adalsteinsson, & Pfefferbaum, 2006). Recent results from fiber tractography studies have revealed a differential pattern of effects on major cortical, subcortical, callosal and cerebellar fiber tracts, with greater age effects on anterior than posterior, inferior than superior, and association than projection fiber tracts (Madden, et al., 2009; Ota, et al., 2006; Stadlbauer, Salomonowitz, Strunk, Hammen, & Ganslandt, 2008a, 2008b; Sullivan, et al., 2006; Sullivan, Rohlfing, & Pfefferbaum, 2008).

Evidence from studies of healthy and pathological aging suggests that declines in executive functions are associated with declines in frontal white matter integrity (eg. Charlton, et al., 2006; Correia, et al., 2008; Grieve, Williams, Paul, Clark, & Gordon, 2007; Gunning-Dixon & Raz, 2000; O'Sullivan, et al., 2001; Schmidt, et al., 1993; Schwartz, Sahlas, & Black, 2003). Most prior studies have examined FA relationships with cognition by performing voxelwise comparisons of anisotropy within restricted regions of white matter. Recently, however, a few studies have used tractography methods to investigate the relationship between cognitive task performance and FA in specific fiber systems, finding that declines in integrity

of specific fiber tracts are differentially correlated with declines in components of executive functions, including working memory, problem solving, categorical task switching and Stroop color-word interference (Madden, et al., 2009; Sullivan, et al., 2006; Zahr, Rohlfing, Pfefferbaum, & Sullivan, 2009). These initial results suggest that DTI tractography is useful for elucidating the neural architecture that underlies specific cognitive functions.

Here we take advantage of a newly developed method for automated white matter tractography in DTI data (Hagler, et al., 2008) to examine the influence of age-related changes in average FA in several major cortical tracts that connect regions that have previously been implicated in cognitive functions subserving TMT performance, including the inferior fronto-occipital fasciculus (IFOF, Duffau, 2008; Jellison, et al., 2004; Kraus, et al., 2007), the UF (Nakamura, et al., 2005), the ILF, (Catani, Jones, Donato, & Ffytche, 2003; Jellison, et al., 2004), the superior longitudinal fasciculus (SLF, Holzapfel, Barnea-Goraly, Eckert, Kesler, & Reiss, 2006; Karlsgodt, et al., 2008; Makris, et al., 2007), the cingulum (Carter, et al., 1998; MacDonald, Cohen, Stenger, & Carter, 2000; O'Sullivan, Barrick, Morris, Clark, & Markus, 2005), and the corpus callosum (Sullivan, et al., 2008; Zahr, et al., 2009). We hypothesized that average FA of these tracts would be inversely correlated with age and with time to completion on Part B, but not Part A, of the TMT. We further hypothesized that the association between age and task performance would be reduced after accounting for the effect of FA on performance, indicating a mediational effect of white matter integrity on age-related decrements in set-shifting performance. We included the corticospinal tract (CST) as a control, since average FA in this tract was not expected to be differentially correlated with performance on Part B of the TMT since the motor demands of Part A and B are similar.

Methods

Participants

Twenty-four right-handed, native English speaking volunteers (21 – 80 years of age, 11 males) participated in the study after providing written informed consent. This study was approved by the Institutional Review Board at the University of California, San Diego.

Exclusion criteria included any contraindication for MRI as well as any history of neurological illness, heart disease or diabetes, hospitalization for a psychiatric disorder, treatment for substance abuse or addiction to medication, current use of sedatives, stimulants or other psychoactive medications, consumption of three or more alcoholic beverages per day (or 21 or more per week), self-report of current depression or a score reflecting depressed mood on a standard assessment of depression, the Geriatric Depression Scale, (Sheikh & Yesavage, 1986) or Beck Depression Inventory-II, (Beck, 1996).

Characteristics of the study sample, stratified into three age groups to allow comparison of demographic information across the age range, are shown in Table 1. A univariate analysis of variance (ANOVA) showed that groups did not significantly differ on estimated verbal IQ, as assessed with the Vocabulary subtest of the Wechsler Abbreviated Scale of Intelligence ($F < 1$, $p > .1$). Although chi square tests of association showed no significant differences in gender distribution by age group ($\chi^2 = 4.13$; $p < .1$) the youngest group had a higher male to female ratio; whereas the older groups had higher female to male ratios.

Task

The Halstead-Reitan Trail Making Test (Reitan & Wolfson, 1985) was administered to all subjects. Total time to completion served as the primary dependent variable of task performance.

Magnetic Resonance Imaging

MRI data were acquired using a General Electric 1.5 Tesla EXCITE HD scanner with an 8-channel head coil. The protocol included two T1-weighted 3D structural scans (TE = 4.87, TR = 10.73, flip angle = 8°, bandwidth = 31.25 Hz/pixel, FOV = 25.6cm, matrix = 256 × 192, slice thickness = 1.00mm) and one diffusion-weighted scan (b=1000 s/mm², 51 diffusion gradient directions plus one b=0 volume). Diffusion data were acquired using single-shot echo-planar imaging with isotropic 2.5mm voxels (FOV = 24.0cm, matrix size = 96 × 96, axial slices, slice thickness = 2.5mm), covering the entire cerebrum without gaps. An additional b=0 volume with reversed phase-encode polarity was collected for use in nonlinear B0 distortion correction.

Image Processing

Image files in DICOM format were transferred to a Linux workstation for processing with a customized, automated, processing stream written in MATLAB and C++. The two T1-weighted images were rigid body registered to each other and reoriented into a common space. Images were corrected for non-linear warping caused by non-uniform fields created by the gradient coils (Jovicich, et al., 2006). Image intensities were corrected for spatial sensitivity inhomogeneities in the 8-channel head coil by normalizing with the ratio of a body coil scan to a head coil scan. Four pre-processing steps were performed on the diffusion-weighted images. 1.) Within-scan motion was removed by calculating diffusion tensors, synthesizing of diffusion-weighted volumes from those tensors, and rigid body registering each data volume to its corresponding synthesized volume. 3.) Image distortion in the diffusion-weighted volumes caused by eddy currents was minimized by nonlinear optimization. 4.) Image distortion caused by magnetic susceptibility artifacts was minimized with a nonlinear B0-unwarping method using paired images with opposite phase-encode polarities (Chang & Fitzpatrick, 1992; Morgan, Bowtell, McIntyre, & Worthington, 2004; Reinsberg, Doran, Charles-Edwards, & Leach, 2005). 5.) Images were resampled using linear interpolation to 1.875 mm³ isotropic voxels.

Fiber Tracking and Fractional Anisotropy Calculations

The IFOF, UF, ILF, SLF, cingulum, CC, and CST (Figure 1) were automatically derived for each subject using a newly developed automated method for labeling white matter tracts in individual subjects based on a probabilistic diffusion tensor atlas of fiber tract locations and orientations (Hagler, et al., 2008). The probabilistic fiber atlas was constructed by Hagler et al. (2008) by manually tracing fiber tracts of 42 subjects with DTI Studio (John Hopkins University, Baltimore, MD) using the multiple region of interest (ROI) procedure described by Wakana et al (2004). All fibers tracts were subsequently thresholded to exclude voxels with FA < 0.15. Data from this manual training set were used to create the probabilistic fiber atlas that consisted of averaged information about the locations and local orientations of the chosen fiber tracts (Hagler, et al., 2008). Here, we used the probabilistic fiber atlas to derive the 13 fiber tracts in each subject, and to calculate the average FA within each fiber tract for each subject. T1-weighted images were used to map the brain into a common space and diffusion tensor orientation estimates were compared to the atlas to obtain a relative probability that a voxel belonged to a particular fiber given the similarity of diffusion orientations. Average FA was calculated for each tract from the eigenvalues obtained from the diffusion images as described by Pierpaoli et al. (1996) and Nucifora et al. (2007). For each tract, a weighted average of FA in each voxel showing a non-zero probability of belonging to that tract was calculated, using the fiber probability as the weighting, after first excluding voxels with an FA < .0.15.

Statistical analysis

The SPSS statistical software package (SPSS, Inc., Chicago, IL) was used for statistical comparisons. Initial examination of the behavioral data indicated that neither sex nor IQ were significant predictors of performance or of tract FA, therefore simple Pearson's correlations were performed to determine the relationships between age and TMT performance; between age and average FA of each tract; and between average FA of each tract and TMT performance. One-tailed tests were used to assess the significance of our directional hypotheses, and a modified Bonferroni procedure, as described by Holm (1979), was used to correct for multiple comparisons, while maintaining a type I error rate of 5%. To determine the significance of differences in the correlations between tracts in the two hemispheres, the Hotelling-Williams test was used. Stepwise linear regression, using all tracts as input variables, was performed to determine the tract(s) that best predicted performance.

Following approaches used by Baron and Kelly (1986) and Madden et al. (2008), we also used a hierarchical regression approach to investigate whether average FA in the tracts that predicted TMT part B performance mediated the effect of age on task performance. The amount of variance accounted for by age when age was entered after tract FA was compared to the amount of variance explained when age was used as the sole predictor. Due to concern over the wide age range employed here, and the strong correlation of age with performance and with FA, we repeated the mediation analyses on a truncated age range to investigate whether the pattern of results obtained in the full sample were observed among the older adults only (> 45 years).

Finally, to determine whether tract FA was related to performance independently of the effects of age, we correlated average FA in each tract with TMT performance after controlling for the effects of age.

Results

Trail Making Test Performance

Age showed a significant positive correlation with TMT Part B completion time ($r = 0.631$; $p = .001$), with increasing age associated with longer completion times (Figure 2). In contrast, age showed a small, positive correlation with TMT Part A completion time that failed to reach significance ($r = 0.378$; $p = .069$).

White Matter Integrity and Age

Correlations between advancing age and average FA for each of the 13 fiber tracts are shown in Table 2. Generally, advancing age was associated with decreased FA. The relationship between age and FA was significant, after controlling for multiple comparisons, for all tracts connecting frontal regions to more posterior regions (IFOF, UF, SLF), the CC, and the left cingulum. Modest inverse correlations that failed to reach significance were observed for the ILF bilaterally. FA in the CST was not related to age.

The difference between right and left hemisphere correlations differed significantly only for the IFOF ($t=2.12$; $p < .05$), with the left IFOF showing a higher correlation with age than the right.

White Matter Integrity and Trail Making Test Performance

There were no significant correlations between TMT Part A completion time and average FA in any of the tracts (all r 's $< .38$). Generally, increased time to completion on TMT Part B performance was associated with decreased FA (Figure 3). This relationship was significant, after correcting for multiple comparisons, for all tracts connecting frontal regions to more posterior regions (IFOF, UF, SLF), and for the right ILF (Table 3). Modest inverse correlations

that failed to reach significance were observed for the cingulum bilaterally. FA in the CST was not related to performance. The difference in left and right hemisphere correlations with performance approached significance for the SLF ($t = 2.07$; $p > .05$) only. In the stepwise linear regression analysis the right IFOF was selected as the single best predictor of TMT Part B performance (standardized beta = -0.742 ; $p < .001$). We note that the left IFOF is an equally good predictor of performance, and is highly correlated with the right IFOF ($r = 0.926$). If the right IFOF is excluded from the input list, the sole best predictor is the left IFOF (standardized beta = -0.742 ; $p < .001$).

For the fiber tracts that showed significant correlations with age and with TMT Part B performance, preconditions for mediational analyses (Baron & Kenny, 1986.), we examined the extent to which the contribution of age to performance was attenuated by first accounting for the contribution of each of the tracts independently. The effect of age no longer significantly contributed to TMT Part B performance variability, after accounting for average FA of the left or right IFOF, UF, or right SLF. Age accounted for a very small amount of performance variability after accounting for the effects of average FA of the left SLF or right ILF (Table 4). A similar pattern of results was observed when the analyses were repeated in the truncated age range (>45 years, $N = 11$). In this small sample, the right and left IFOF, left UF, right SLF, and the CC showed significant ($p < .05$; unadjusted for multiple comparisons) correlations with age (absolute r 's > 0.53) and with TMT Part B performance (r 's > 0.55). The relationship between age and performance ($r^2 = 0.490$) was substantially reduced after accounting for average FA in each tract separately (maximum r^2 change with age after tract FA = 0.217).

Finally, when controlling for the effects of age, only the right IFOF ($r = -0.546$ $p = .004$) was significantly associated with TMT Part B performance, after adjusting for multiple comparisons. However, strong trend-level effects were observed for the relationship between TMT Part B performance and FA in the left IFOF ($r = -0.511$, $p = .006$) right UF ($r = -.509$, $p = .006$), and right SLF ($r = -.462$, $p = .013$) after controlling for the effects of age.

Discussion

In this study, we explored the relationships among age, performance on a task of set-shifting ability, and integrity of several major fiber tracts, automatically derived using a comprehensive probabilistic DTI fiber atlas. In agreement with prior studies, we found that advancing age was associated with significantly slower performance on the set-shifting subtask of the TMT (Salthouse, Fristoe, McGuthry, & Hambrick, 1998; Salthouse & Fristoe, 1995; Zakzanis, et al., 2005), and with decreases in average FA (eg. Grieve, et al., 2007; Makris, et al., 2007; O'Sullivan, et al., 2001; Pfefferbaum, et al., 2005; Salat, et al., 2005; Sullivan, et al., 2008; Zahr, et al., 2009). We also observed significant relationships between decreases in average FA of several tracts and performance on the set-shifting task, indicating that age-related degradation of these tracts may have functional consequences.

Fiber tracking methods have recently emerged as a method for examining aging effects on major white matter tracts *in vivo*. Significantly greater decreases in tract integrity have been observed for association versus projection fibers (Makris, et al., 2007; Stadlbauer, et al., 2008a); for anterior versus posterior tract systems (Ota, et al., 2006; Stadlbauer, et al., 2008b; Sullivan, et al., 2006; Sullivan, et al., 2008), and for superior lateral versus inferior lateral fibers (Sullivan, et al., 2008). Consistent with this, we found that the CST was resistant to the effects of age, but that the CC and cortical association fibers, particularly those that connect frontal regions to more posterior regions (eg. IFOF, UF, SLF) are significantly negatively affected by age. We also observed greater age effects on FA in the SLF than in the ILF. Although Stadlbauer et al. (2008b) reported that FA of the cingulum, averaged over left and right hemisphere tracts, was resistant to the effects of age, we found a significant

relationship between age and FA of the left but not right cingulum. Similarly Zahr et al. (2008) reported significantly lower FA for older than younger subjects in the left superior and inferior cingulum but not in the right hemisphere measures, and Correia et al. (2008) observed a trend level effect of age on the left cingulum with no effect of age on the right cingulum in their sample of adults over the age of 40 years. Taken together, these findings suggests that there is a hemispheric asymmetry in aging effects on the cingulum, with the left hemisphere tract showing great vulnerability to the effects of age. The general consistency of the age effects observed in our study and those of prior reports provides further validation for the automated, atlas-based fiber tracking algorithm employed here (Hagler, et al., 2008).

Although prior studies have reported relationships between global (Correia, et al., 2008; Grieve, et al., 2007;) or regional (O'Sullivan, et al., 2001) measures of white matter integrity and set shifting performance, we extend the literature by reporting the relationship between TMT performance and measures of white matter integrity in several specific major fiber systems. We found that performance on the set-shifting subtask of the TMT, but not the simple sequencing subtask, was moderately to strongly correlated with decreased FA in the CC and in cortical association tracts that connect regions of the frontal lobe to more posterior regions, including the IFOF, UF, and SLF. Integrity of the right ILF was also significantly associated with TMT Part B performance. In contrast, FA in the CST and cingulum was not correlated with performance on the TMT, highlighting the selectivity of the relationships observed between tract integrity and set-shifting performance.

The IFOF, UF, SLF, ILF and CC connect distributed functional regions that are involved with the various cognitive processes required for successful performance of TMT Part B. Although there are few reports in the literature of the relationship between the integrity of these tracts and set-shifting ability, a variety of evidence from other conditions that affect white matter integrity have suggested that the integrity of these fiber tracts are important for set-shifting ability. Converging evidence for the importance of these tracts in set-shifting ability, and the putative roles of these tracts in TMT Part B performance, are briefly reviewed below.

The IFOF is a long-range cortical association fiber pathway that connects frontal to occipital cortices (Jellison, et al., 2004; Kier, Staib, Davis, & Bronen, 2004), providing a substrate for top-down attentional modulation of oculomotor and visuospatial processing in prefrontal and posterior parieto-occipital areas by dorsolateral prefrontal cortex (Petrides & Pandya, 2006). The dorsolateral prefrontal cortex plays a critical role in attentional set-shifting and damage to lateral prefrontal regions of either hemisphere impairs set-shifting performance (McDonald, Delis, Norman, Tecoma, & Iragui-Madozi, 2005; Stuss & Levine, 2002; Yochim, Baldo, Nelson, & Delis, 2007). Thus degradation of the fiber tracts that connect this region to posterior regions can be expected to affect set-shifting performance. We observed the strongest relationships between TMT Part B performance and FA in the IFOF. Average FA in the IFOF was the single best predictor of performance, and mediational analyses showed that it was a strong mediator of age effects on performance. The right IFOF was associated with TMT performance even after controlling for age, suggesting that normal variability of FA in this tract may influence set-shifting performance independently of age effects on this tract.

Although average FA in the IFOF showed the strongest relationship with set-shifting performance, average FA in the CC, UF, SLF and right ILF were significantly related to TMT Part B performance, supporting the view that connectivity among multiple brain regions is important for TMT Part B performance. The UF connects orbitofrontal cortex to temporopolar and limbic regions (Petrides & Pandya, 2007). Ventromedial prefrontal damage has been associated with impairments in tasks that require cognitive flexibility (Cato, Delis, Abildskov, & Bigler, 2004). Decreased integrity of the left UF has been associated with elevated time to completion on TMT Part B in late life depression (Sheline, et al., 2008) and in patients with

schizotypal personality disorder (Nakamura, et al., 2005). We found that average FA in both the left and right UF were strong mediators of the effect of age on TMT Part B performance.

The SLF connects dorsolateral prefrontal areas to supplementary motor areas, superior temporal areas and occipital cortex (Petrides & Pandya, 2006). A subcomponent of this tract connects the dorsolateral prefrontal cortex with parietal areas involved in visuospatial abilities, providing for attentional control of movement in space (Petrides & Pandya, 2006). Relationships between SLF integrity and executive functions, including set-shifting, have been observed in moderate to severe TBI (Kraus, et al., 2007). Our results show a somewhat stronger relationship with set-shifting performance for the right than left SLF, possibly reflecting the greater role of the right hemisphere in the sustained attentional processes necessary for complex task performance (Stuss & Levine, 2002).

The ILF connects anterior temporal regions with occipital areas, connecting functional regions important for visual memory (Catani, et al., 2003). Since memory for the locations of stimuli is likely to affect performance speed, the age-related reduction in FA of the ILF may contribute to the slowing in TMT performance. We found that decreased FA in the right, but not the left ILF, was a significant mediator of the age effect on set-shifting performance, possibly reflecting a greater role of right than left hemisphere regions in visuospatial memory.

The cingulum connects the anterior cingulate cortex, an area implicated in conflict monitoring and divided attention (Carter, et al., 1998; MacDonald, et al., 2000), with posterior cingulate regions (Vaccarino & Melzack, 1992; Zhang, et al., 2007). A significant association between mean diffusivity in individual voxels within the cingulum and performance on TMT Part B in adults (O'Sullivan, et al., 2005) and a significant association between average FA in the bilateral cingulum and set-shifting performance in monkeys (Makris, et al., 2007) have been reported. We found modest relationships that failed to reach significance between set-shifting performance and average FA of the cingulum bilaterally suggesting that while the cingulum may be involved with set shifting performance, age effects on these tracts have less influence on performance than age effects on association fibers that connect frontal cortex to posterior association areas, or commissural fibers in the CC.

The CC, which serves as the main substrate for interhemispheric transfer, has been implicated in executive function performance with age (Madden, et al., 2009; Sullivan, et al., 2006; Zahr, et al., 2009). Consistent with this, we found that average FA in the CC was a strong mediator of the effect of age on set shifting performance. In contrast, average FA in the CST was not associated with performance in either subtask of the TMT. This is consistent with the minimal and equivalent motor demands of the two subtasks.

There are several limitations to this study. First, the small sample size may have limited our ability to observe subtle relationships between FA and task performance, particularly with regard to hemisphere asymmetries and associations between FA and task performance that are independent of the effects of age. The sample was also biased towards greater representation of females than males in the older ages, leading to a potential confound of the effects of sex and age. In contrast to strong effects of age on FA that have been found in many prior studies, there have been fewer investigations of sex differences in FA, and results are conflicting. Some studies have reported significant differences in FA between men and women in specific regions (Huster, Westerhausen, Kreuder, Schweiger, & Wittling, 2009; Oh, et al., 2007; Sullivan, et al., 2008; Westerhausen, et al., 2004). Thus there is the potential that some of the aging effects observed here may be driven by, or masked by, the sex differences in our sample. The high verbal IQ of our participants is another limitation of the sample. While this limits the generalizability of the findings to the full aging population, the results nevertheless indicate that decreased FA occurs with aging even in highly functioning individuals, and that this

decrease is associated with functional consequences. The correlational nature of this study, which precludes conclusions of causation is also a limitation of the study, as is the cross-sectional design. Larger study samples, with balanced gender distribution, and incorporating longitudinal measures are needed to further understanding of the relationship between changes in white matter integrity and cognitive function in aging.

Conclusion

The results of this study suggest that age-related degradation of cortical association fiber tracts that form functional connections between frontal regions and posterior association areas are important contributors to the decrement in set-shifting performance observed with age. Automated methods for deriving fiber tracts within individual subjects will facilitate exploration of the relationship between white matter integrity of specific fiber tracts and specific cognitive functions, enhancing our understanding of the neural architecture that supports cognition.

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Figure 1. The fiber tracts assessed in this study

The top row shows horizontal (left) and sagittal (middle) views of the 13 automatically generated tracks for a single subject. The corpus callosum (CC) is shown superimposed on the subject's T1 images on the right. The two rows below show left hemisphere tracts superimposed on the subject's T1-image. Lighter shading indicates that the fiber tract extends through the plane of the T1 underlay. CC = Corpus Callosum, IFOF = Inferior Fronto-Occipital Fasciculus, UF = Uncinate Fasciculus; SLF = Superior longitudinal fasciculus (SLF), ILF = Inferior Longitudinal Fasciculus; CST = Corticospinal Tract.

Figure 2. Relationship Between Age and Time to Complete TMT A and B

Completion time on TMT Part A was not significantly affected by age whereas completion time on TMT Part B was significantly slower with advancing age.

Figure 3. Relationship between Time to Complete TMT B and average FA in each tract
See Table 3 for magnitude and significance of the correlations.

Table 1**Characteristics of Study Participants**

	<i>n</i>	M/F	Age $\pm$ S.D. (Range)	V.I.Q. $\pm$ S.D. (Range)
Young	10	7/3	22.4 $\pm$ 1.65 (21-26)	127 $\pm$ 17 (94-148)
Middle-Age	8	2/6	44.5 $\pm$ 7.93 (32-53)	123 $\pm$ 15 (110-154)
Older	6	2/4	73.7 $\pm$ 5.57 (66-80)	134 $\pm$ 11 (116-146)
Comparison			$\chi^2(2) = 4.13$; $p > .1$	$F(2,21) = 0.92$; $p > .1$

S.D. = standard deviation; V.I.Q. = Verbal IQ;

Table 2**Correlations Between Age and FA**

	Right Hem <i>r</i>	Unadjusted <i>p</i>	Left Hem <i>r</i>	Unadjusted <i>p</i>
IFOF	-0.692 [*]	$p < .001$	-0.798 [*]	$p < .001$
UF	-0.606 [*]	$p = .001$	-0.647 [*]	$p < .001$
SLF	-0.726 [*]	$p < .001$	-0.606 [*]	$p = .001$
ILF	-0.443	$p = .015$	-0.453	$p = .013$
Cingulum	-0.329	$p = .058$	-0.604 [*]	$p = .001$
CST	-0.081	$p > .1$	-0.116	$p > .1$
CC⁺	-0.750 [*]	$p < .001$		

^{*} indicates correlations reaching significance after controlling for multiple comparisons. Hem = hemisphere;

⁺ corpus callosum was not divided into left and right hemisphere components.

Table 3
Correlations between FA and TMT Part B Completion Time

	Right Hem <i>r</i>	Unadjusted <i>p</i>	Left Hem <i>r</i>	Unadjusted <i>p</i>
IFOF	-0.742 [*]	<i>p</i> < .001	-0.742 [*]	<i>p</i> < .001
UF	-0.696 [*]	<i>p</i> < .001	-0.592 [*]	<i>p</i> = .001
SLF	-0.704 [*]	<i>p</i> < .001	-0.538 [*]	<i>p</i> = .003
ILF	-0.519 [*]	<i>p</i> = .005	-0.385	<i>p</i> = .032
Cingulum	-0.445	<i>p</i> = .015	-0.463	<i>p</i> = .011
CST	-0.173	<i>p</i> = .080	-0.036	<i>p</i> > .1
CC⁺	-0.651	<i>p</i> < .001		

* indicates correlations reaching significance after controlling for multiple comparisons. Hem = hemisphere;

⁺ corpus callosum was not divided into left and right hemisphere components.

Table 4

Proportion of variance in TMT Part B performance explained by age alone, or by age when entered after average FA of tracts that showed significant correlations with TMT Part B performance

Model	Change in R^2 with Age	Unadjusted p
Age alone	0.398*	$p = .001$
Age after R IFOF	0.026	$p > .1$
Age after L IFOF	0.004	$p > .1$
Age after R UNC	0.069	$p = .086$
Age after L UNC	0.105	$p = .057$
Age after R SLF	0.030	$p > .1$
Age after L SLF	0.147	$p = .029$
Age after R ILF	0.200	$p = .010$
Age after CC	0.046	$p > .1$