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White Matter Integrity And Age Related Differences In Reaction Time Components

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DEDICATION

This work is dedicated to my family for their love, support, and help**.**

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CHAPTER 1

INTRODUCTION

Specific Aims

Aging is associated with decline in selected cognitive functions. To reveal the mechanism of age-related cognitive decline is a long-standing goal of cognitive aging researchers. Since the mid-nineteenth century, reaction (or response) time (RT) has been regarded as a potentially powerful means of assessing mental processes (Brebner & Welford, 1980; Donders, 1868 / 1969; Welford, 1987). Research on this topic has been thought as a way to understand the mechanism of age-related cognitive declines both because age-related slowing is a most reliable psychological aging marker, and because speed of processing is consistently related to higher-order cognitive performance (Vernon, 1987).

In spite of age-related slowing being well documented, little is known about its specific neural mechanism. As diffuse axonal injury shows stronger association with response slowing than focal injury did (Felmingham, Baguley, & Green, 2004), many researchers have focused on the age-related differences in integrity of the cerebral white matter and their associations with speed of processing (Deary et al., 2006; Kennedy & Raz, 2009; Burgmans et al., 2012; Madden et al., 2009; Vernooij et al., 2009). However, the findings vary with regards to specific associations between speed and microstructural differences in particular white matter regions or tracts. Because multiple factors determine RT (Salthouse, 2000), decomposing RT into

meaningful sub-processes may clarify the specific relationship between age-related deterioration of white matter integrity and age-related slowing.

Many approaches have been used to identify and examine the components of RT. However, traditional methods such as Donders' subtractive method (Donders, 1969) and Sternberg's additive-factor method (Sternberg, 1969b) suffer from serious limitations because they are based on mean or median of RT on correct responses only and do not take into account the issue of speed-accuracy trade-off. The advancement of mathematical modeling of RT made it possible to overcome these problems. Ratcliff's diffusion model (Ratcliff & McKoon, 2008) is one of the few successful models in accounting for all aspects of RT data and decomposing them into meaningful mental processes.

Therefore, the purpose of this study was to investigate the neuroanatomical substrates of RT components derived from the Ratcliff diffusion model. Specifically, I investigated the relationship between age related difference in microstructural integrity of white matter fibers and three RT components: rate of information acquisition, response conservativeness and speed of non-decision processes.

Literature Review

Age-related slowing

Speed of information processing is fundamental to cognitive processes. According to Salthouse (2000), at least six different variables have been used to assess processing speed: decision speed, perceptual speed, psychomotor speed, RT, psychophysical speed, and time

course of internal responses. RT, one of the most commonly used processing speed measures (Salthouse, 1992, 2000), is operationally defined as the interval between the onset of the stimulus presentation and the initiation of the response (Pachella, 1974). Both sensory-motor and high-order cognitive elements are involved in reaction time process.

Reduced speed of behavior is one of the most reliable psychological markers of aging (Birren & Fisher, 1991). Age-related decline in speed is observed in everyday activities, as well as in laboratory tasks (Myerson, Hale, Wagstaff, Poon, & Smith, 1990). One of the earliest studies demonstrating age-related slowing in simple RT test was by Koga and Morant from Galton's Anthropometric Laboratory in 1923 (Hicks & Birren, 1970). Age-related reduction in processing speed spreads from simple tasks to complex behaviors (Birren, Woods, & Williams, 1980), affecting a wide variety of processes across various cognitive systems, including digit-symbol substitution, visual search, lexical decision, mental rotation, memory search, and speech discrimination (Verhaeghen & Cerella, 2008). The associations between age and various speed-related variables are quite strong, with estimated effect size of r=-0.52 for associations involving perceptual speed and RT (weighted-average Pearson correlation; Salthouse, 2000; Verhaeghen & Salthouse, 1997). Age-related slowing is evident even when the influence of health status is controlled (Myerson et al., 1990).

Cross-sectional comparisons of people from different age groups suggest that processing speed increases during childhood and declines throughout middle and old age in a manner that the duration of the process could be described by a U shaped function of age (Cerella & Hale, 1994). It is possible that age-related slowing follows a nonlinear trajectory with the reduction of

speed accelerating during the older age (Kail & Salthouse, 1994; Salthouse & Kail, 1983). For example, Wilkinson and Allison examined simple reaction time of 5325 participants and reported that RT increased gradually from age 20 to 65, with the most precipitous increase occurring after age 50 (Wilkinson & Allison, 1989). Longitudinal studies confirmed the decline in processing speed with advanced age. In the Baltimore Longitudinal Study of Aging (BLSA), Fozard et al. examined auditory RT at baseline and follow-ups (three to five times over four or eight years) in a sample of 1,265 community volunteers that spanned a wide age range. They found that RT started to increase at approximately age 20 and showed continuous increase over four or eight years (Fozard, Vercruyssen, Reynolds, Hancock, & Quilter, 1994). Schaie reported that the decline in perceptual speed with age was found in both cross-sectional and longitudinal studies; however, cross-sectional study tended to underestimate the magnitude of the decline (Schaie, 1989). Based on findings from 26 studies on simple reaction time tasks, Birren, Woods, and Williams estimated that RT slowed by 20% between the age of 20 and 60 (Birren et al., 1980). Welford estimated in a cross-sectional study that choice RT increased 1.5 ms with each year of adult life (Welford, 1977).

Although older adults are slower than younger adults on almost all tasks, the slowness is greater for some tasks (e.g. mental rotation) than for others (e.g. simple and choice reaction time) (Myerson et al., 1990). Age-related slowing increases with advanced task difficulty (Cerella, Poon, & Williams, 1980; Salthouse, 1996). Based on a Brinley-plots analysis of 18 reaction time studies with various types of tasks, Cerella et al. (1980) found that the magnitude of age difference in RT increased linearly with the difficulty of the task. Findings from Baltimore

longitudinal study suggested that RT increased with task complexity, with a rate of about 0.5 ms per year for simple RT and 1.6 ms per year for choice RT (Fozard et al., 1994). Cerella and colleagues (Cerella, 1985; 1980) identified two levels of deficits associated with age. Sensory motor tasks evidenced a little slowing while tasks involving higher order mental processing exhibited a more severe slowing. Therefore, the extent of age-related slowing observed in any single task depends on the proportion of sensory-motor and central processes of the given task (Birren & Fisher, 1995).

Despite age-related speed reduction being widely reported, there is no consensus about the mechanisms of the phenomenon. Two broad alternatives have been proposed to characterize the nature of age-related slowing (Salthouse & Somberg, 1982). The 'general slowing hypothesis' (or Birren Hypothesis) originally advocated by James Birren posits that the age-related slowing is due to speed reduction in the central nervous system activities, which causes nearly all processes to slow. The slowing is universal and all processes evidence equivalent slowing (Birren, Woods, & Williams, 1980; Cerella et al., 1980; Salthouse & Somberg, 1982). The alternative 'domain or task specific hypothesis' states that slowing does not affect every mental process in the same manner; instead, each mental process slows at different rate (Kail & Salthouse, 1994). At the beginning, the general slowing hypothesis took the extreme position and insisted that all processes were equally slowed. There was debate among the proponents of these two alternative hypotheses (Cerella, 1991; Fisk, Fisher, & Rogers, 1992). With accumulation of evidence, the consensus emerged that both general and task specific factors are associated with

age-related behavior slowing (Birren & Fisher, 1995; Lima, Hale, & Myerson, 1991; Salthouse, 2000).

Relationship between processing speed and cognitive functions

Age differences in processing speed are consistently related to higher-order cognitive performance (Vernon, 1987). For instance, several studies reported that processing speed was a principal candidate for explaining age-related cognitive differences (Hartley, 2006; Salthouse, 1996, 2000). Results with multivariate analysis suggested that the effect of age on measures of processing speed was not unique, but instead was shared with other cognitive variables (Salthouse, 2000), and adjustment for the measures of perceptual speed greatly reduced the age-related variance in measures of fluid cognition and memory (Hertzog, 1989; Salthouse, 1992, 1993). Verhaeghen and Salthouse (1997) conducted a meta-analysis on the interrelationship between age and various cognitive functions. They found that measures of speed showed the largest correlation with age, and that information processing speed accounted for a substantial amount of the age-related variance in working memory, general fluid intelligence, and episodic memory.

Salthouse (1996) proposed a processing-speed theory to explain the observed relationship between processing speed and high-order cognitive functions. This theory has two assumptions. The first is that performance in fluid aspects of cognitive tasks is limited by general processing constraints. The other assumption is that processing speed is a critical constraint associated with advanced age. Slow processing speed and cognitive performance are linked through two distinct mechanisms. The limited time mechanism states that fewer operations can be completed in a

given amount of time if the speed in processing operations is slow. The other mechanism is the simultaneity mechanism, which refers to the idea that products of early operation may be lost before the later processing is completed. However, little is known about how slowness in processing speed and poor cognitive performance are related through these or other possible mechanisms.

Neural substrates of slowing in processing speed

Early evidence from clinical studies suggested that processing speed was a sensitive index of the integrity of the nervous system. For instance, psychomotor speed was found to be able to reliably distinguish normal individuals from those with various psychopathological conditions (Hicks & Birren, 1970). On simple RT tasks, patients with hemispheric brain disease responded more slowly than did the age-matched control patients. Moreover, the detrimental effect of brain disease on speed of processing could be exaggerated by aging. While younger patients with various brain diseases were 24 ms slower on simple visual RT task than were younger control participants, the differences became 94 ms between older patients with brain disease and older control participants (Benton, 1977). A meta-analysis of 41 studies on brain trauma indicated that processing speed measured by simple or choice RT tests was significantly impaired in participants following severe traumatic brain injury (Mathias, 2007). Prolonged RT was found following ischemic stroke and brain trauma even after recovery (Light, 1980).

White matter

The findings from traumatic brain injury and multiple sclerosis (MS) linked slowed processing to diffuse damage of white matter pathways. It is plausible that reduction in

processing speed stems from degraded neural transmission along the damaged axons. Felmingham, et al. (2004) found that participants with predominant diffuse axonal injury were more impaired on processing speed tasks than were mixed-injury and healthy controls. Niogi et al. (2008) further examined the lesions involved in mild diffuse axonal injury (DAI) and found that microstructural white matter differences detected by diffusion tensor imaging were associated with slow reaction time on a simple cognitive task. Slowed information processing was also observed in patients with multiple sclerosis, a condition known for its characteristic diffuse loss of myelin and axonal damage (Demaree, DeLuca, Gaudino, & Diamond, 1999; Rao, St. Aubin-Faubert, & Leo, 1989).

Evidence from aging brain studies suggested that age-related reduction in white matter integrity may contribute to decline in information processing speed (Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Madden, Bennett, & Song, 2009). White matter hyperintensity (WMH) burden was associated with declines in processing speed in healthy adults (Gunning-Dixon & Raz, 2000; Schmidt et al., 1993; Ylikoski et al., 1993). For instance, Schmidt et al. (1993) examined cognitive correlates of WMH in 150 middle aged and older participants free of neuropsychiatric or general disease. They found that participants with WMH performed worse than those without WMH on all cognitive tests, particularly on tasks measuring processing speed. Findings from a longitudinal study also demonstrated that progression of periventricular WMH burden over three years was associated with the decline in mental processing speed (Van Den Heuvel et al., 2006).

Diffusion tensor imaging (DTI). DTI is an MRI method assessing the magnitude and direction of water diffusion within tissues. It provides information about the microstructural integrity of white matter in vivo because the diffusion of water molecules is more constrained for intact than degraded white matter fibers (Concha, Gross, Wheatley, & Beaulieu, 2006). Although water molecules in white matter are present in both extracellular and intracellular compartments, extracellular space is thought to be the main avenue of the water diffusion detected by DTI (Sullivan & Pfefferbaum, 2006).

DTI is more sensitive to subtle alteration in white matter structure than WMH or white matter volume is. Studies with DTI revealed microstructural disruption in normal- appearing white matter on conventional MRI (Moseley, 2002; O'Sullivan, Summers, et al., 2001). There was significant age difference in fractional anisotropy even after controlling for WMH and white matter volume (Burgmans et al., 2010). In addition, DTI measures had been shown to have additional contribution in predicting cognitive performance (Vernooij et al., 2009), and were more sensitive in predicting age-related cognitive decline than WMH and white matter volume or brain volume (Burgmans et al., 2011; Charlton, Schiavone, Barrick, Morris, & Markus, 2010).

Mean diffusivity (MD, also called mean apparent diffusion coefficient, or ADC) and fractional anisotropy (FA) are the two most frequently used DTI summary measures. MD represents the rate of water diffusion within a voxel, independent of the directionality. It can be calculated as the average of the ADC across the three axes of the diffusion tensor. Higher MD reflects greater diffusivity, lower impediment of diffusion and, by inference, lower microstructural tissue integrity. FA is a scalar measure of anisotropy which reflects the degree of

directionality of water diffusion. Values for FA vary between 0 and 1 (e.g. FA is close to 0 in ventricular CSF and approach 1.0 in highly ordered myelinated fiber regions, such as the splenium of the corpus callosum). Greater values correspond to higher directionality of diffusion. FA was interpreted as an index of the integrity of microstructure including myelination and microtubule and microfiber condition etc. (Pfefferbaum et al., 2000). Developmental studies using DTI found that FA increased with advancing child age and suggested that FA was related to maturational increase in myelination (see Moseley, 2002 for a review). However, other factors, unrelated to myelin, such as the placement and organization of axonal membranes, were thought to play a significant role in the determination of diffusion anisotropy as well (Mädler, Drabycz, Kolinda, Whittall, & MacKay, 2008; Paus, 2010).

While decreased FA and increased MD are frequently associated with advancing age, the associations vary across brain regions. O'Sullivan and colleagues (2001) reported that there were more FA decrease and MD increase in anterior than in posterior white matter, with middle white matter evidencing intermediate influence of age. Head et al. (2004) observed greater age- related difference in anterior than in posterior corpus callosum and in frontal white matter than in temporal, parietal and occipital white matter. Findings from several studies using quantitative fiber tracking also confirmed an anterior-posterior gradient of FA decline or diffusivity increase with advancing age (Davis et al., 2009; Madden, Bennett, et al., 2009; Sullivan, Adalsteinsson, & Pfefferbaum, 2006; Sullivan, Rohlfing, & Pfefferbaum, 2010b). Such cross-sectional finding had been replicated by a longitudinal study on corpus callosum as well (Sullivan, Rohlfing, & Pfefferbaum, 2010a). In addition, a superior-to-inferior gradient of decreased FA and increased

diffusivity was also reported (Sullivan et al., 2010b; Zahr, Rohlfing, Pfefferbaum, & Sullivan, 2009). Another study examined age-related changes in diffusion parameters between association, callosal, and projection fibers and found that greatest age-related differences in FA in association fibers (Stadlbauer, Salomonowitz, Strunk, Hammen, & Ganslandt, 2008). Although the specific change in white matter microstructure underlying these diffusion parameters is unclear, the evidenced age difference in microstructure white matter is in accord with "(phylogenetically and ontogenetically) last in, first out" differential aging pattern observed in the macroscopic brain structures (Raz, 2000).

Directional diffusivity is the rate of diffusion (eigenvalue of the diffusion tensor) along the individual eigenvectors (or axes) of the diffusion tensor. Axial diffusivity (DA or longitudinal diffusivity) refers to the diffusion along the primary axis of the diffusion ellipsoid, whereas radial diffusivity (DR or transverse diffusivity) is the diffusivities in the two minor axes perpendicular to the primary axis and is defined by the average of the two eigenvalues. Results from animal models of demyelination and nerve injury suggested that myelin-specific damage tended to increase DR without affecting DA, whereas axonal damage decreased DA (Kim et al., 2006; Song et al., 2002). However, findings regarding age-related differences in directional diffusivity were not uniform. Several studies reported significant age-related increases in DR, but not DA (Bhagat & Beaulieu, 2004; Davis et al., 2009; Madden, Spaniol, et al., 2009; Zhang et al., 2010), while age-related increase in both DA and DR had been revealed by other studies (Sullivan et al., 2010b; Vernooij et al., 2008; Zahr et al., 2009). The discrepancy probably stems from methodological differences in these various studies, as well as the diverse underlying

processes accompanying aging. Several processes can cause decrease in DA, such as debris from axonal damage, microphage infiltration or deterioration of microtubular transport system that can hinder diffusion along the axon (Budde, Xie, Cross, & Song, 2009; Burzynska et al., 2010). On the other hand, normal aging is associated with decrease in tissue organization, increases in extra-axonal fluid, as well as other changes in the extracellular space surrounding axons, which may contribute to increase in DA (Meier-Ruge, Ulrich, Bruhlmann, & Meier, 1992; Zahr et al., 2009).

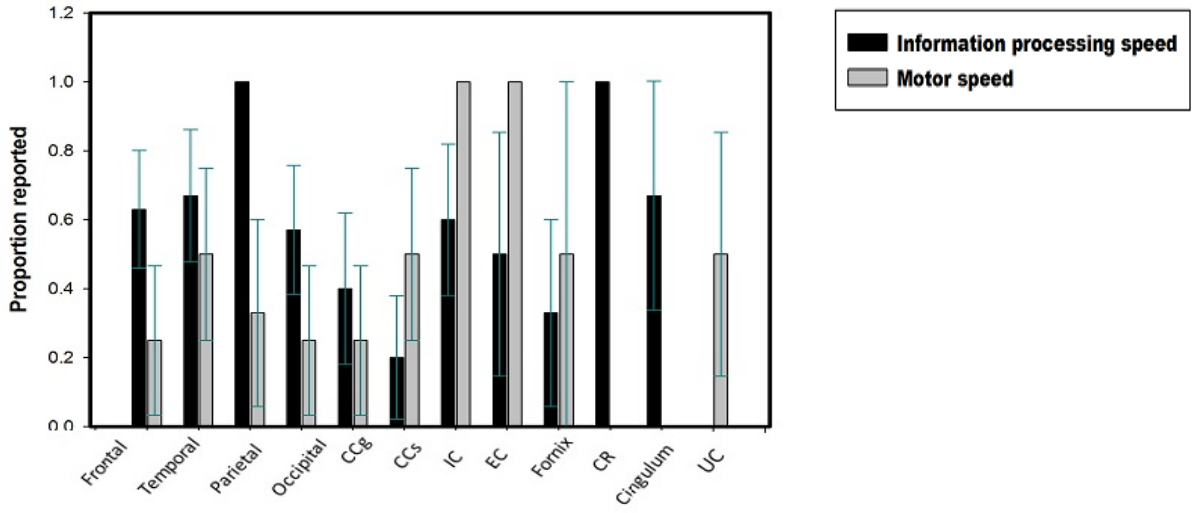
Results from DTI studies suggested that age-related deterioration in the integrity of white matter microstructure was associated with declined performance on various processing speed tests (Madden, Bennett, et al., 2009). For instance, Deary et al. (2006) reported that in older adults, greater FA in normal-appearing centrum semiovale was associated with faster simple and choice RT. In a large population-based sample of the Rotterdam Scan Study, Vernooij et al. (2009) found that low FA and high MD in white matter lesions or normal-appearing white matter were related to slow processing and motor speed. However, only the association with processing speed remained after statistical control of white matter atrophy and lesions. Findings regarding the connection between the reductions in processing speed of older adults and the integrity of white matter in particular brain regions or circuits are diverse. Table 1 shows the results with significant correlations between one or more DTI indices in particular white matter areas and processing speed measures from 11 published papers.

Table 1. Summary of findings showing significant association between DTI parameters in particular white matter regions and performance on information processing and motor speed tasks

Regions or fibers	**Tasks**	**Papers cited**
Temporal, parietal, and occipital	N-back and Letter and pattern comparison (latent score)	Burgmans et al., 2011
Frontal and parietal	Information processing speed task from AMIPB, Digit symbol, and grooved pegboard (composite score)	Charlton et al., 2006
Frontal and parietal	Choice RT	Grieve et al., 2007
Frontal, parietal, and CC genu	Letter and pattern comparison	Kennedy & Raz, 2009
Anterior limb of the internal capsule and CC splenium	Visual target detection (oddball)	Madden et al., 2004
Fornix, internal and external capsules, frontal forceps, superior longitudinal fasciculus, and CC genu	Digit Symbol	Sullivan et al., 2010b
Anterior and small portion of posterior corona radiate; superior fronto-occipital fasciculus; superior longitudinal fasciculus, internal capsule, posterior cingulum, inferior fronto-occipital fasciculus	Trail Making Test A	Bendlin et al., 2010
Cingulum, inferior longitudinal fasciculus, corona radiata, parietal white matter	Two-digit arithmetic problems solving (composite score)	Sasson et al., 2012
Frontal and temporal	Finger tapping (tapping a circle on the touchscreen)	Grieve et al., 2007
Splenium and parietal pericallosal	Alternated finger tapping	Sullivan et al., 2001
Internal and external capsule	Fine finger movement	Sullivan et al., 2010b
Inferior longitudinal fasciculus	Finger tapping and Grooved pegboard (factor score)	Voineskos et al., 2012
Genu, splenium, fornix, and uncinate fasciculus	Grooved pegboard, CANTAB:Motor, CANTAB:Big/LittleCircle (composite score)	Zahr et al., 2009

Note: AMIPB: Adult Memory and Information Processing Battery

Figure 1. Proportion of studies reporting significant associations between DTI indices in specific brain regions with information processing speed and motor speed



Abbreviation: CCg: genu of corpus callosum; CCs: splenium of corpus callosum; IC: internal capsule; EC: external capsule; CR: corona radiate; UC: uncinate fasciculus. The bars are standard errors.

The results suggest that microstructural integrity of white matter in various brain regions or tracts play a role in performing different speed tasks. The involvement of particular regions or fibers in speeded performance seems task dependent. Figure 1 shows the proportion of relevant studies reporting white matter regions involved in tasks for information processing speed and motor speed. For the purpose of reducing the number of classifications, white matter tracts are labeled by the regions they pass through or connect. Specifically, superior fronto-occipital fasciculus is translated into frontal and occipital white matter; superior longitudinal fasciculus is translated into frontal, parietal, occipital, and temporal white matter; inferior fronto-occipital fasciculus is translated into frontal, temporal and occipital white matter; inferior longitudinal fasciculus is translated into temporal and occipital white matter. Although there is no clear

distinction between the associations of particular brain regions with the speed of two different activities, Figure 1 provides some support for the notion that white matter connecting high-order association cortices is more likely involved in information processing speed than in motor speed. A recent study supports for this idea. The study revealed that reduced white matter integrity in the genu and body of the corpus callosum, superior longitudinal fasciculus, and inferior fronto-occipital fasciculus was related to the slowing of cognitive processing (Kerchner et al., 2012). However, this study suffers from several limitations. First, only middle-aged and older adults (aged 55 to 87) were included in the study; therefore, the magnitude of age-related differences might have been underestimated due to a restriction of the age range. Second and more importantly, although the authors tried to design a refined 'cognitive processing speed' measure by minimizing motor processing demands, they cannot separate 'cognitive processing speed' from the other components. Because multiple processes are involved in performing a speed task, separating RT into sub-processes might be a better way in teasing apart the complex relationships between processing speed and integrity of white matter across brain regions or fibers.

A survey of RT decomposition methods

Identification and isolation of information processing stages is a long-standing goal in experimental psychology (Salthouse, 1981). Various methods have been used to decompose RT into sub-processes. These methods can be divided into two broad categories: the central tendency based methods and the methods with distributional analysis beyond central tendency.

Methods based on central tendency

Subtractive method. A pioneering work of isolating the components of processing in speeded mental tasks was conducted by Donders (1868) who proposed an influential subtractive method (Welford, 1980). According to Donders, there are successive processes or stages between perceiving a stimulus and generating a response, and the beginning of each stage is followed by the ending of the previous one. Thus, if one administers two tasks with the second task including all the stages of the first one and an additional inserted stage, the duration of inserted stage can be acquired by subtracting the mean reaction time for the two different tasks (Donders, 1969; Sternberg, 1969a).

Donders' subtractive method rests on two strong assumptions. One assumes that component processes are strictly successive so that the overall reaction time is the sum of the durations of the components. The other assumption is that stages of processing are inserted or deleted in a purely additive/subtractive fashion from one to the other reaction time tasks (Meyer, Osman, Irwin, & Yantis, 1988). The subtraction method had been criticized mainly on the grounds that its major assumptions could be untenable. First, there is little evidence that the durations of stage are stochastically independent. Second, introspective data suggested that when a stage was inserted into a task, the other stage might have been altered as well (Sternberg, 1969b). Thus, Donders' stages of processing may be mutually dependent and not strictly serial.

Sternberg's additive-factor method. Sternberg's additive-factor method is an alternative way to study the stages of information processing without postulating insertion or deletion of stages. The general idea of the additive-factor method is as follows. Suppose a, b, and c are successive stages of processing between stimulus presentation and response execution; and E, F,

and G are three factors manipulated to influence the duration of stages, such that factor E influences only the stage a, factor F influences only stage b, and factor G influences both stages b and c. If two factors affect two different stages (e.g., E and F), their effects on mean duration are additive. If two factors influence the same stage (e.g., F and G), their effects would not be additive and there would be an interaction between the two factors (Sternberg, 1969a). By checking whether there is an additive or interactive effect among factors, one can identify the existence of separate processing stages. However, this method also relies on the assumption that there is no temporal overlap between stages and this assumption has been challenged by other investigations indicating the involvement of parallel rather than serial processing (see Meyer et al., 1988 for a review; Miller, 1982; Neisser, 1963; Neisser, Novick, & Lazar, 1963). In addition, this method does not provide measurements of stage duration.

Other investigators decompose reaction time into pre-motor and motor time by simultaneously recording reaction time and electromyogram (EMG) which measures the electrical activity of muscles. The pre-motor time is the duration between the presentations of the stimulus and the appearance of the first increased muscle firing, whereas the motor time is the period between the change in action potential and the finger-lift response (Botwinick & Thompson, 1966; Weiss, 1965). However, because this method cannot isolate central cognitive processes, its usefulness in cognitive aging research is limited.

Limitations of methods based on central tendency

All methods discussed in the previous section are based on the estimation of central tendency, but such approaches are limited by the shape of a typical RT distribution. First, a

typical RT distribution is almost always skewed, and the mean is not a representative measure of its central tendency. Although data transformation may reduce skewness or lessen the impact of outliers, it can cause problems in the interpretation of time-dependent processes (Whelan, 2008). More importantly, data transformation can conceal valuable information because for RT, the skew is not just a nuisance; it reflects a meaningful aspect of the data. For instance, several studies have shown that the RT-cognition association depends on the position of RT trials in the RT distribution. The correlations of RT with intelligence and working memory increased from the fastest to the slowest responses, and the slowest response (worst performance) was the best predictor of high-order cognitive functions (Coyle, 2003; Larson & Alderton, 1990). Another study fitted the ex-Gaussian distribution (a convolution of a normal and an exponential distribution) to RT data and examined the relationship between three ex-Gaussian parameters and cognitive performance. The result showed that among these three parameters, parameter Γ which carries information about slowed response and is related to the skew and variability of the RT distribution, was the only strong predictor of performance on working memory and reasoning tasks (Schmiedek, Oberauer, Wilhelm, Süß, & Wittmann, 2007). That slowed responses play a more important role in predicting cognitive functioning had also been confirmed by another study using both quintile analysis and ex-Gaussian distribution analysis (Unsworth, Redick, Lakey, & Young, 2010). Use of the median can only reduce the impact of the extreme values, while other inherent problems associated with using central tendency remain (Heathcote, Popiel, & Mewhort, 1991). A second and extremely important point to consider is that focusing only on central tendency ignores the variability, which is an important property of the data. This issue is

particular relevant in cognitive aging as intra-individual variability in RT increases with age and is associated with cognitive performance (Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000; Nesselroade & Salthouse, 2004) as well as brain integrity (Lövdén et al., 2013). In sum, RT distributions might carry important information about the response behavior (Whelan, 2008), and examining the mean RT alone can be misleading (Heathcote et al., 1991).

Early distributional analysis beyond central tendency

Worst performance analysis (or band analysis). Larson and Alderton (Larson & Alderton, 1990) found that the slowest RTs were the strongest predictor of general intelligence. This finding is regarded as the worst performance rule and the relevant method is called the worst performance analysis. The worst performance analysis involves dividing rank-ordered RTs into RT bands and calculating mean or median RTs within each band. The correlation between the mean or median RT of each band and performance (measures) on various cognitive ability tests are then computed. Although separating RT bands gives fine grained estimates of RT data, this analysis is hampered by low reliability unless the number of trials in each band is large enough which is unlikely in most studies. In addition, the separation of the distribution into RT bands is arbitrary, which makes it impossible to connect band RTs with meaningful cognitive processes.

Ex-Gaussian distributions. Another way to obtain distribution information of RT data is to specify a particular probability distribution that best fit the data and then to estimate parameter values of the distribution. Different mathematical models have been used to comprehensively characterize the entire distribution of the response time (e.g. gamma, lognormal, Wald, Weibull

and ex-Gaussian distributions) (Luce, 1986; Ratcliff & Murdock, 1976). The ex-Gaussian function is one of the most commonly used models and has been demonstrated to yield a good fit with empirical data from a range of choice RT paradigms (Heathcote et al., 1991; Hohle, 1965).

The ex-Gaussian distribution has a positively skewed unimodal shape and represents the additive combination of exponential and Gaussian (normal) distributions. The ex-Gaussian function has three parameters: μ, σ, and τ. μ and σ are estimates of the mean and standard deviation of a Gaussian distribution while τ is an estimate of both the mean and standard deviation of the exponential distribution (Heathcote et al., 1991). Ratcliff and Murdock (1976) tested three common mathematical models with response time data from memory recognition tasks. They found that Ex-Gaussian distribution fitted data better than did the gamma and lognormal models. In addition, they proposed that the ex-Gaussian distribution provided an excellent summary for the properties of RT distributions after applying the model to the data from four experiments, because the parameters reflect the important properties of RT distributions.

The ex-Gaussian distribution was once thought to reflect two distinctive processes. According to Hohle (1965), the exponentially distributed RT component is RT for decision, whereas the Gaussian RT portion represents motor RT. However, the rationale of Hohle's interpretation had been questioned (Luce, 1986) and this interpretation was not supported by empirical data from a recent study (Matzke & Wagenmakers, 2009).

Limitations of traditional methods

All methods listed above are based on RTs of correct responses without taking into account the speed-accuracy trade-off issue. Based on a wide variety of tasks with various manipulations of speed and accuracy, Pew (1969) found that there was a negative correlation between speed and accuracy as evidenced by a linear line on a plot of log odds over reaction time. Therefore, the precise quantitative comparison is impossible without knowing the relationship between reaction time and error rate (Welford, 1980). In addition, although both young and older adults trade accuracy for speed, older adults tend to emphasize accuracy more than younger adults (Salthouse, 1979). Therefore, it is necessary to consider the speed-accuracy relationship when comparing RTs, especially in samples of participants with a wide age range.

Sequential sampling models and Ratcliff diffusion model

Substantial effort has been devoted to quantitative modeling of decision processes for the past century. Among the models proposed to account for the data generated by binary decision tasks, sequential sampling models are the most successful in predicting the relationship between speed and accuracy, and RT distribution (Ratcliff & Smith, 2004; Smith & Vickers, 1988). Sequential sampling models, originally developed in the context of simple perceptual identification tasks, are stochastic/statistical decision models. The basic assumption of sequential sampling models is that, after stimulus onset, an individual *sequentially* extracts and accumulates information from the stimulus and/or its mental representations until a criterion amount of evidence is obtained (Otter et al., 2008; Ratcliff & Smith, 2004). Both the rate of information accumulation and the amount of information required for a response determine the performance (response probabilities and time). Within the same sequential sampling framework, models may

differ in the ways and means of evidence accumulation, and the rules set for accumulation cessation. Evidence can be accumulated continuously, at discrete intervals, equally spaced or randomly distributed within the time intervals. With an absolute stopping rule, the amount of evidence must reach a specific criterion value for one or the other alternative response. A relative stopping rule requires that the evidence for one of the response alternatives must exceed the other by a criterion amount. Random walk and recruitment models represent two main classes of successful sequential sampling models. In random walk models, the information in favor of each response is accumulated until the evidence favoring one over the other exceeds a critical value. In recruitment models (or race models), information in favor of each response is accrued in parallel, until a criterion is reached (Smith & Ratcliff, 2004).

The diffusion model is the continuous version of the simple random walk model. The diffusion model assumes that a noisy process that accumulates evidence over time makes binary decisions. Accumulation of information begins from a starting point and continues until sufficient amount of evidence reaches either a positive or negative response boundary. The diffusion model can be derived from the simple random walk by making the time steps arbitrarily small.

The Ornstein-Uhlenbeck model (OU model) is a variant of the diffusion model. However, unlike the Ratcliff diffusion model, the actual information accumulated in the OU model depends on two opposite forces: an evidence accumulation and a decay that moves the accumulating process back to the starting point. The rate of accumulation of evidence is constant, while the decay increases linearly with the amount of information accumulated (Smith, 1995).

The accumulator model and the Poisson counter model are two successors of the recruitment model. Ratcliff and Smith (2004) evaluated the four most developed sequential sampling models for two choice decisions: the Wiener diffusion, the OU diffusion, accumulator, and Poisson counter models. After fitting all the models with RT distributions and accuracy data, they found that both the accumulator model and the Poisson counter model could not predict observed faster error responses. Although the OU model accounted for the RT distribution and error RTs in a similar way as the Wiener diffusion model, it did not fit the empirical data well when the decay was large. The model fitted best when the decay parameter approached zero, where the OU model was identical to the Wiener diffusion model. The Ratcliff diffusion model is also a widely tested model (Ratcliff & McKoon, 2008).

Figure 2 shows a hypothetical diffusion process and the main parameters of the diffusion model. On the vertical axis, 0 and a, are two response boundaries. The distance between the boundaries is called *boundary separation* (a). It pertains to the evidence required to make a response and is an estimate of response conservativeness (also called response caution or response criterion). Wider boundary separation leads to slower but more accurate responses, whereas narrow boundary separation leads to faster but less accurate responses. The *Starting point* (z) measures the *a priori* bias of a participant for one of two alternative responses. The process is more likely to reach the boundary closer to the starting point. In the case that there is no prior bias, z lies in the middle of two boundaries. The *Drift rate* (v) is the mean rate of information accumulation, indicating the average amount of evidence that an individual extracts from the stimulus. The drift rate reflects either task difficulty or perceptual sensitivity.

Higher drift rate leads to faster and more accurate responses. Drift rates vary around the mean and within trial *variability in drift rate* (s) is a scaling parameter. *Non-decision time* (T_{er}) includes time for everything except decision (e.g. time for encoding and motor processes).

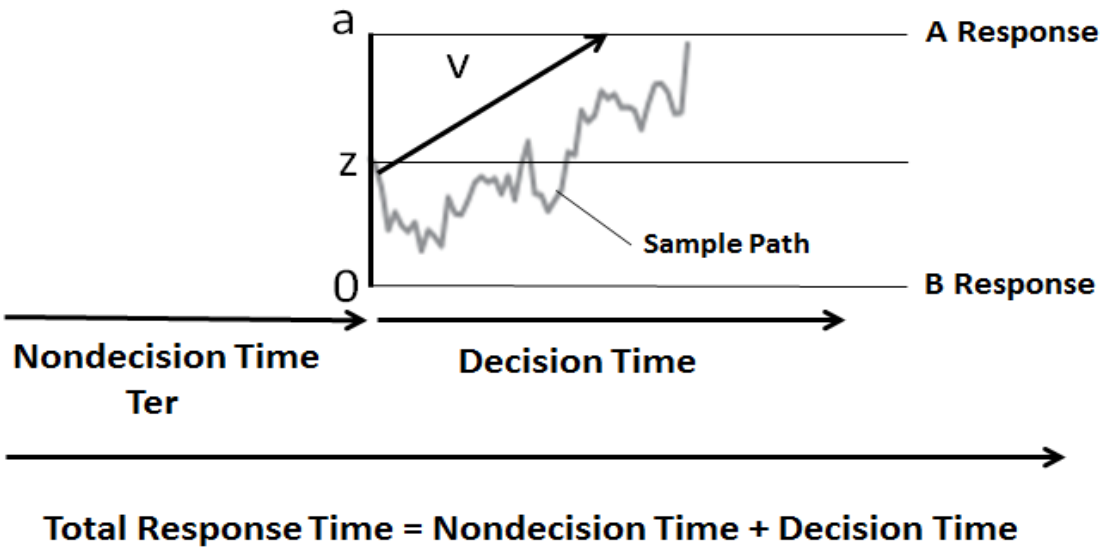


Figure 2. A schematic illustration of the diffusion model. The process starts at point z and continues until it reaches the lower threshold at 0 or the upper threshold at a. The arrow represents the average drift rate v. The sample path gives an example of one process that reaches the upper threshold with mean drift rate v which varies within the trial.

The Ratcliff diffusion model is defined by the four main parameters: drift rate (v), boundary separation (a), stating point (z), and non-decision time (T_{er}) (Ratcliff & McKoon, 2008). Thus, the diffusion model enables decomposition of RT and accuracy measures into parameters reflecting non-decision and decision processes, and further separation of the latter into speed of evidence accumulation and response criterion. The interpretations of the parameters of the diffusion model have been validated empirically (Voss, Rothermund, & Voss, 2004).

The results from fitting the diffusion model to 18 data sets showed that drift rate was consistently correlated with response accuracy. There was a stable association between boundary separation and mean RT. The non-decision component was correlated with mean RT in most of the studies. There were no significant correlations between drift rate and mean RT (Ratcliff & McKoon, 2008). In other words, response accuracy is mainly a function of the quality of accumulated evidence, and RT is mainly a function of response conservativeness and, to some extent, non-decision components of processing (Ratcliff, Thapar, & McKoon, 2006).

Schmiedek and colleagues (2007) investigated the relationship between parameters of diffusion model and several domains of cognitive functions including psychometric speed, reasoning, and working memory tasks in younger adults. The results using the EZ diffusion model analysis revealed that both drift rate and response conservativeness were significantly correlated to the performance on speed, reasoning, and working memory tasks. Drift rate was the strongest positive predictors of cognitive performance. More recently, Ratcliff, Thapar, and McKoon reported that larger drift rate was associated with higher IQ (Ratcliff, Thapar, & McKoon, 2010).

Studies with Ratcliff diffusion model analyses reported that older adults adopted more conservative criteria than young adults; and that older adults had longer non-decision time (Ratcliff, 2008b; Ratcliff, Thapar, & McKoon, 2001). Ratcliff and colleagues applied the diffusion model to data from a number of tasks and found that the quality of the information on which decisions are based (e.g., drift rate) was not significantly lower for the older than for the

younger adults in most tasks they studied. The slowdown of older adults was mainly due to their response conservativeness (Ratcliff & McKoon, 2008; Ratcliff et al., 2006).

Very few studies have investigated neural correlates of diffusion model parameters. Two studies examined the association between event-related potential (ERP) components and diffusion model parameters, but findings were inconsistent. Philiastides, Ratcliff, and Sajda (2006) used a single-trial analysis of electroencephalography (EEG) to examine the correlation between two ERP components, 170 ms (early) and 300 ms (late) and diffusion model parameters on a simple categorization task. They reported that the late component, which is believed to reflect decision-making processes strongly correlated with the drift rate. Martin, Huxlin, and Kavcic (2010) assessed relationship between several components of visual evoked potentials (VEPs) and elements of the decision process on a visual motion discrimination task. Using the EZ (simplified) diffusion model analysis, they found that both the drift rate and the non-decision time, but not boundary separation, were predicted by three VEP latency components representing stages of processing from early perceptual, motion-specific processing, to decision-making and response processes. Giving that the drift rate is deemed to reflect decision processes, the discrepancy may stem from using a simplified instead of a full diffusion model. The EZ model's failing in providing precise estimates of the parameters may be due to the fact that the EZ model only uses accuracy rate, mean and variance of RT for correct response, without taking into account error RTs and the shapes of the RT distributions for both correct and error responses. According to Ratcliff (2008a; Ratcliff & McKoon, 2008), the shapes of the RT distributions

provide particularly strong constraints on whether and how the diffusion model can account for empirical data.

Another study examined the correlation between the parameters of Ratcliff diffusion model and regional brain activation assessed by functional MRI (fMRI). The results showed that the drift rate was related to activity in the inferior parietal lobe, whereas the response criterion was associated with striatal activity (Kühn et al., 2011). Madden and colleagues (2009) examined the relationship between white matter integrity in specific tracts within selected brain regions (fronto-parietal network) and two RT components derived from EZ diffusion model. In a small sample of extreme age groups (20 older and 20 younger adults), they found that FA in the central part of the genu and in the right parietal region of the splenium was positively associated with drift rate, but not non-decision time.

Rationale of the Proposed Study and Hypotheses

Findings from previous studies suggest that separating RT into sub-processes might be useful in understanding the neuroanatomical mechanism associated with age-related slowing. The diffusion model has proved to be one of the few successful models in decomposing RT and accuracy data in a way that may reflect meaningful mental processes. To date, only one study examined the associations between white matter integrity and drift rate and non-decision time (Madden, Spaniol, et al., 2009). However, this study has several limitations. First, the simplified version of the diffusion model (EZ) was used to estimate diffusion parameters. Because the EZ model is derived only for exploration purposes; it did not use the entirety of the RT data, and thus could not provide meaningful estimates of parameter values (Ratcliff, 2008a). Secondly,

only extreme age groups (young and old adults) were compared. Therefore, age-related differences had not been investigated across the adult life span. Thirdly, limited pathways in the fronto-parietal network have been studied but the neuroanatomical substrates of response conservativeness have not yet been examined. Finally, the study did not separate WMH out from normally appearing white matter, thus the influence of these breaches of integrity that are associated with age-related slowing (Gunning-Dixon & Rz, 2000) could have affected the results.

In this study, I planned to address the listed limitations. First, I applied the full diffusion model to decompose RT into three components: drift rate, boundary separation, and non-decision time. Second, I computed DTI indices from total white matter and normal-appearing white matter, and examined them separately to gauge the influence of the WMH burden on the relationship between white matter integrity and cognitive processing. I examined the following white matter pathways: the superior longitudinal fasciculus, the uncinate fasciculus, the genu and splenium of the corpus callosum, and the anterior and posterior limb of the internal capsule. My selection was based on the published results of several investigations suggesting the frequent involvement of these fibers in perceptual or motor speed tasks (Bucur et al., 2008; Kennedy & Raz, 2009; Sullivan et al., 2001; Sullivan et al., 2010b; Zahr et al., 2009) and the evaluation of the findings presented in Fig. 1 above. I modeled the relationships between RT parameters and white matter integrity with a path analysis framework. Path analysis has advantages of taking into consideration of mutual influence among the predictors and assessing the unique contribution of predictors to criterions. All these innovations were implemented in a data set

collected on a relatively large sample of healthy adults with a wide age range. I expected that age-related differences in two decision components of RT (drift rate and response conservativeness) would show higher correlations with white matter integrity in anterior than posterior regions, and in association rather than projection fibers. In contrast, age-related differences in non-decision time would show greater associations with white matter integrity in posterior than anterior regions, projection than association fibers.

Hypotheses

1) It was hypothesized that older adults would have a wider boundary separation and longer non-decision times than younger adults, and that older adults would have lower drift rates than younger adults, replicating previous findings in the literature (Ratcliff et al., 2006).

2) It was hypothesized that there would be an age-related reduction in FA and an increase in diffusivity (MD, DA, and DR), similar to that found in white matter microstructure and aging literature (Madden et al., 2012). Age-related difference in DTI measures of white matter integrity would be more pronounced in whole white matter than in normal-appearing white matter, because WMH burden increases with age and there were correlations between DTI indices (FA and MD) with both WMH volume and intensity (Zhan et al., 2008).

3) It was hypothesized that age-related decrease in drift rate would be more likely associated with age-related reductions in microstructural integrity of white matter in the superior longitudinal fasciculus and the genu of the corpus callosum. This prediction was based on the previous finding that frontoparietal networks were implicated in stimulus accumulation process (Philiastides et al., 2006), and white matter integrity in anterior and superior regions contributed

to perceptual speed (Bucur et al., 2008; Grieve, Williams, Paul, Clark, & Gordon, 2007; Kennedy & Raz, 2009; Turken et al., 2008). It was also hypothesized that stronger association would be found for DTI indices measured from whole white matter than for those measured from normal-appearing white matter on the superior longitudinal fasciculus, because the prevalence of WMH is relatively lower in the corpus callosum than in central semiovale (Barkhof & Scheltens, 2002), and the severity of WMH was associated with processing speed (Gunning-Dixon & Raz, 2000).

4) It was hypothesized that age-related increases in response conservativeness would be more likely related to age-related deterioration in microstructural integrity of the uncinate fasciculus, the superior longitudinal fasciculus, and the anterior limb of the internal capsule. The uncinate fasciculus and superior longitudinal fasciculus might be involved in response conservativeness because DTI parameters of these tracts were associated with performance on tasks assessing executive functioning in older adults (Davis et al., 2009; Sasson, Doniger, Pasternak, Tarrasch, & Assaf, 2012). Although the internal capsule belongs to projection fiber system, medial portion of anterior limb of the internal capsule carries pathways (anterior thalamic radiation) between the thalamus and prefrontal cortex, and microstructural integrity of this tract was involved in executive processes (Mamah et al., 2010). Previous findings suggested that frontal-striatum network was implicated in cognitive control (Liston et al., 2006), and the latter had been shown to play a role in response conservativeness (Dutilh et al., 2012; Saunders & Jentzsch, 2012). In addition, cortico-striatal network was reported to play a role in decision making (Bogacz & Gurney, 2007). It was also hypothesized that stronger association would be

found for DTI indices measured from whole white matter than those measured from normal-appearing white matter on the uncinate fasciculus and the superior longitudinal fasciculus, because of a relatively higher prevalence of WMH in the central semiovale and a lower prevalence of WMH in the internal capsule (Duering et al., 2011).

5) It was hypothesized that age-related increases in non-decision time would be more likely associated with age-related reductions in microstructural integrity of white matter in the splenium of the corpus callosum, and the anterior and posterior limb of the internal capsule. This hypothesis was based on the reports that white matter integrity in the posterior region was associated with sensory-motor responses (Sullivan et al., 2001), and the integrity of the internal capsule was associated with motor performance (Sullivan et al., 2010b).

CHAPTER 2

METHOD

Participants

Participants were healthy community volunteers from the Metro Detroit area. They were recruited through advertisements in the local media and screened via a telephone interview and health questionnaire. Participants were ineligible if they reported history of cardiovascular, neurological, or psychiatric conditions, head trauma with loss of consciousness for more than 5 min, treatment for drug and alcohol problems, or a habit of taking more than three alcoholic drinks per day. Those with either diabetes or thyroid problems were also excluded from the study, as were those taking any anxiolytics, antidepressants or anti-seizure medication. None of the participants resided in a hospital or an assisted-living facility. All participants had corrected visual acuity of 20/50 or better (Optec 2000 apparatus; Stereo Optical, Chicago, IL) (ICO, 1984) without color blindness, and hearing of 40 dB or better for frequencies of 500–4,000 Hz (MA27 audiometer; Maico, Eden Prairie, MN) (WHO, 1991). All of the participants were native English speakers, with a minimum of a high school education (or a GED diploma), and consistent right-handers based on Edinburgh Handedness Questionnaire (Oldfield, 1971). To screen for dementia and depression, the Mini-Mental State Examination (MMSE: Folstein, Folstein, & McHugh, 1975), with a cut-off of 26 (O'Connor et al., 1989) and a geriatric depression questionnaire from the Center for Epidemiologic Studies—Depression scale (CES-D; Radloff, 1977), with a cut-off of 15 (Burns, Lawlor, & Craig, 2002) were used. All participants provided written informed

consent in accord with the guidelines of Wayne State University human investigations committee.

Reaction Time Task and Diffusion Model Analysis

A two-choice RT task, the letter discrimination task (Thapar, Ratcliff, & McKoon, 2003) was administered. In this task, stimuli were presented on a PC computer and responses were collected on a response box with seven buttons on the top. Participants were seated in front of a 19-in. liquid crystal display (LCD) computer monitor in a quiet room. They were asked to sit comfortably and lean back on the chair. The height of the monitor was adjusted so that the midpoint of the monitor was at the subject's eye level. The distance from the middle of the screen to the outer corner of participants' eye was 60 cm. Participants were required to maintain their positions after the distance had been established. The experimenter was present in the room throughout the testing to ensure compliance with the instructions.

In the letter discrimination task (Thapar, Ratcliff, & McKoon, 2003), two letters were displayed, one on the left and the other on the right edge of the screen. The letters remained on the screen throughout the block. In the middle of the screen, a white cross (courier new bold, size 40) appeared for 500 ms, and then the target letter was displayed for six variable durations (13, 26, 39, 52, 66, and 80ms), followed by a mask. The task was to identify the target letter and decide whether it was the same as the letter on the left or the letter on the right edge of the screen. Responses were collected on a response box. Participants received feedback when they responded too quickly or too slowly. This task was administered in two sessions. Each session

took about 36 minutes, and was composed of six experimental blocks, preceded by two practice blocks. There were 108 trials in each experimental block. Each block lasted approximately 4 minutes, and participants were required to take brief breaks (about 1 minute) between blocks. The total number of trials across both sessions was 1296 with 216 trials for each stimulus duration condition. The stimuli were letter pairs P/R, O/Q, I/J, F/E, C/G, and V/W. All trials of a block used the same letter pair. Because the order of the letter pairs was different between two sessions, the order of the sessions was counterbalanced across participants.

The two-choice RT data was analyzed with DMAT (Diffusion Model Analysis Toolbox) (Vandekerckhove & Tuerlinckx, 2008). Before fitting the diffusion model, RT date were checked to exclude extreme values using cutoff (>=200ms and <1799 ms). Because outliers share of even 5% can increase estimation biases dramatically (Vandekerckhove & Tuerlinckx, 2007), a combination of exponentially weighted moving average (EWMA) and mixture model methods was applied to deal with the remaining outliers. EWMA control method was used for filtering out fast guesses by detecting shifts in performance, whereas the mixed model method is able to deal with variety of contaminates (e.g. delayed startup) by representing them in the model. Parameters were calculated separately for each participant. Starting point was fixed in the middle between the two response boundaries because there was no a priori bias towards either boundary. Only drift rates were allowed to vary, while other parameters were assumed to be invariant across experimental conditions. This is because only the drift rate which reflects the quality of information obtained from the stimulus is affected by the experimental manipulation employed in the present study (varying in stimulus duration) (Thapar et al., 2003; Voss et al.,

2004). All indicators gleaned from the RT data (RTs for both correct and error response, accuracy, and correct and error RT distributions) from the task were used to generate the parameters. There is one measure of boundary separation and non-decision time, but six measures of drift rate corresponding to the six durations of letter presentation.

The diffusion models were fitted to the RT data on 107 normotensive participants. The full model (hypothesis based model) fitted RT data well and had better fit than the reduced model (all parameters were fixed across conditions) for all but six participants. The three of these six participants had worse fitted full model compared to the reduced model. Among these three participants, two performed at chance level and another one was diagnosed with depression, the fact not known during the recruitment stage. Another participant had to be removed because of psychoactive medication use. The other two participants failed to fit the full model. One had the largest number of missing responses (266 trials) and lowest error rate (error rate <4% overall). Another one had almost half of the data contaminated. All these six cases were dropped from further analysis. Additional four participants had lower rate of used data identified by EWMA method (less than 90%). Two of them had over 100 missing responses. All of them had relatively higher number of 'less than 200' fast response (8, 12, 24, 26 respectively compared to average of 4.4). According to Ratcliff, subjects with over 5% or 10% fast guesses are candidates for elimination from the experiment (Ratcliff & Tuerlinckx, , 2002). Four participants had no MRI scan due to either being claustrophobic or having metallic implants. Three other participants who had MRI scan were dropped from the study due to MRI findings or medications. Thus, 90 participants were included in the final sample. The dropped participants did not differ from the

remaining sample on age, education, sex ratio, and ethnic origin. The total sample with complete data consists of 90 healthy normotensive adults, 18 to 82 years of age. Sample demographic information is presented in Table 2.

Table 2. Descriptive statistics of demographic variables

	N	**Age**	**Education**	**MMSE**	**Systolic BP**	**Diastolic BP**
Total	90	47.39±16.87	15.28±2.05	28.69±1.07	120.74±13.91	76.08±8.08
Women	60	47.6±16.41	15.22±2.28	28.8±0.99	120.02±13.34	75.14±7.08
Men	30	46.97±18.04	15.4±1.52	28.47±1.20	122.19±15.13	77.96±9.63
t		.162	-.453	1.318	-.667	-1.425
p		.872	.652	.193	.508	.161

Because very higher accuracy rate in easier conditions 4, 5, and 6 affected the fit of the diffusion model, only drift rate from the first three conditions was analyzed.

MRI Protocol and Data Processing

MRI protocol

Imaging was performed on a 3T MRI system (Siemens MAGNETOM Verio^{TM} , Erlangen, Germany) with a 12-channel RF coil. Magnetization-prepared rapid gradient echo (MPRAGE) T1-weighted images was acquired in the coronal plane, with the following acquisition parameters: TR = 1680 ms, TE = 3.51 ms, TI = 900 ms, FOV = 256×256 mm^2, slice thickness = 1.34 mm, matrix size = 384×384, number of slices = 176. The duration of this sequence acquisition was 5:41 min. Diffusion tensor images (DTI) was acquired in the axial plane with a single shot echo-planar imaging (EPI) sequence. The parameters were as follows:

GRAPPA acceleration factor 2, TR=12000 ms, TE=124 ms, 20 diffusion directions, 2 averages, 50 slices, slice thickness=2mm, FOV=256×256 mm^2, voxel size=1.3×1.3×2 mm^3, b=1000 s/mm^2. Acquisition duration was 9:02 min. All MR scans were examined for signs of space-occupying lesions and all participants were free of pathological findings.

Diffusion tensor imaging processing

Data preprocessing. Diffusion weighted data was analyzed using FDT FMRIB Software Library (FSL) package (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Motion artifacts and eddy current distortions was corrected by Eddy Current Correction of FDT (FMRIB's Diffusion Toolbox), which aligns each diffusion-weighted image to the b0 image. The gradient orientations were rotated accordingly as well. The eddy-current-corrected volume was then be split and averaged to produce a single volume containing one b=0 and 20 gradient directions. The first averaged volume that did not have gradient applied (i.e. b=0) was used to generate a binary brain mask with the Brain Extraction Tool (BET). DTIFIT was used to fit a diffusion tensor model at each voxel included in the brain mask and generate the diffusion maps (e.g. FA, MD). To take into account the influence of WMH, an additional brain mask (WMH-free brain mask) excluding WMH and cerebrospinal fluid (CSF) was created with the following steps. First, FMRIB's automated segmentation tool (Fast) was used to segment Bo image into four separate classes: CSF, WMH, gray and white matter. Secondly, fslmaths command was used to create a WMH-free brain mask by combining segmented gray and white matter images and binarizing the combined image. This WMH-free brain mask was then used to refit the diffusion tensor and generate the diffusion maps.

Tract-Based Spatial Statistics (TBSS). TBSS analysis of FA image was conducted following the processes described by Smith et al. (2006). First, individual FA image was non-linearly aligned to the FMRIB58_FA template. Next, transformed FA images were averaged and thinned to create a skeletonized mean FA image. The mean FA skeleton was thresholded at 0.2 to exclude voxels containing gray matter or CSF. Finally, the aligned FA image of each participant was projected onto the skeleton by filling each skeleton voxel with FA values from the nearest relevant tract center, resulting in a skeletonized FA image. Skeletonized diffusivity maps (MD, AD and RD) were generated using spatial transformation parameters obtained in the initial FA analysis. Following these steps, selected skeletonized maps of all four DTI indices in total white matter and normal-appearing white matter were generated. All skeletonized maps were further thresholded such that voxels with FA less than .2 or larger than 1.0 were not included to reduce the noise of DTI data.

White matter tracts were labeled according to ICBM-DTI-81 white-matter labels atlas (Mori, Wakana, Nagae-Poetscher, & van Zijl, 2005), which was generated by mapping DTI data of 81 normal subject to a template image. Because the skeletonized DTI maps and the atlas were both in the same standard space, no additional registration step was required. Fslmaths command was applied to create masks for the individual white matter tracts relevant in this study. DTI parameters of each white matter tract with and without excluding WMH for all participants were extracted using fslstats command.

Due to limited number of slices, there was incomplete coverage of the temporal lobe for most participants. So, DTI indices from the uncinate fasciculus were eliminated from all the analysis.

CHAPTER 3

RESULTS

Raw data were used only for descriptive statistics and scatterplot. Before statistical analyses, all RT and MRI data were checked for outliers and violations of normality. If deviation from normality and significant outliers were identified, the data were log-transformed or winsorized. After the described data conditioning, all variables were either normally distributed or not significantly skewed. To avoid scaling discrepancy, all variables were z-transformed before structural equation modeling (SEM) analyses. To reduce the number of variables in SEM models, drift rates from the three conditions were standardized and averaged to yield a single composite score (v). DTI indices of white matter tracts from both hemispheres were also averaged to form a composite score. To minimize rounding errors, all measures of MD, DA and DR were multiplied by a factor of 1000.

Age-relate Differences in Drift Rate, Response Conservativeness, and Non-Decision Time

The descriptive statistics and zero order age correlations of accuracy and response time across six conditions were presented in Table 3. As displayed there, older age was associated with decreased response accuracy and increased response time for all conditions.

Response conservativeness and non-decision time increased with age, while drift rate decreased with age. There were correlations between drift rate and accuracy across all conditions and between drift rate and RT for all but the one with the longest duration. Response

conservativeness was associated with RT, whereas non-decision time was associated with accuracy and RT.

Table 3. Descriptive statistics for accuracy and reaction time measures across conditions

	Accuracy				Reaction time			
Condition	**Mean**	**SD**	**CV**	**r_{age}**	**Mean**	**SD**	**CV**	**r_{age}**
D 13	0.67	0.10	0.14	**-.59**	526.28	81.05	0.15	**.65**
D 26	0.78	0.12	0.15	**-.55**	505.77	77.41	0.15	**.62**
D 39	0.88	0.08	0.10	**-.53**	479.33	69.59	0.15	**.65**
D 52	0.92	0.07	0.08	**-.53**	465.00	66.26	0.14	**.64**
D 66	0.94	0.06	0.06	**-.47**	456.62	64.67	0.14	**.62**
D 80	0.94	0.06	0.06	**-.41**	461.95	63.57	0.14	**.63**
Mean	0.85	0.07	0.09	**-.57**	479.02	67.58	0.14	**.65**

Note: D: duration of stimulus presentation; CV: coefficient of variation; **r_{age}**: correlation between age and mean; significant results are in bold.

Comparison of correlations between each RT component and either accuracy or response time with Steiger's Z (Steiger, 1980) revealed that the association between drift rate and accuracy was stronger than was the association between drift rate and RT. Response conservativeness and non-decision time, on the other hand, were associated mainly with RT. The descriptive information of RT components and the correlations with age, accuracy and RT were presented in Table 4 and 5 respectively.

Table 4. Descriptive statistics for three RT components

	Drift Rate			Response Conservativeness			Non-decision time		
Condition	**Mean**	**SD**	**CV**	**Mean**	**SD**	**CV**	**Mean**	**SD**	**CV**
D 13	0.17	0.11	0.66	0.087	0.019	0.21	0.39	0.054	0.14
D 26	0.34	0.19	0.56						
D 39	0.60	0.30	0.51						
D 52	0.83	0.44	0.54						
D 66	1.01	0.64	0.63						
D 80	0.99	0.65	0.66						

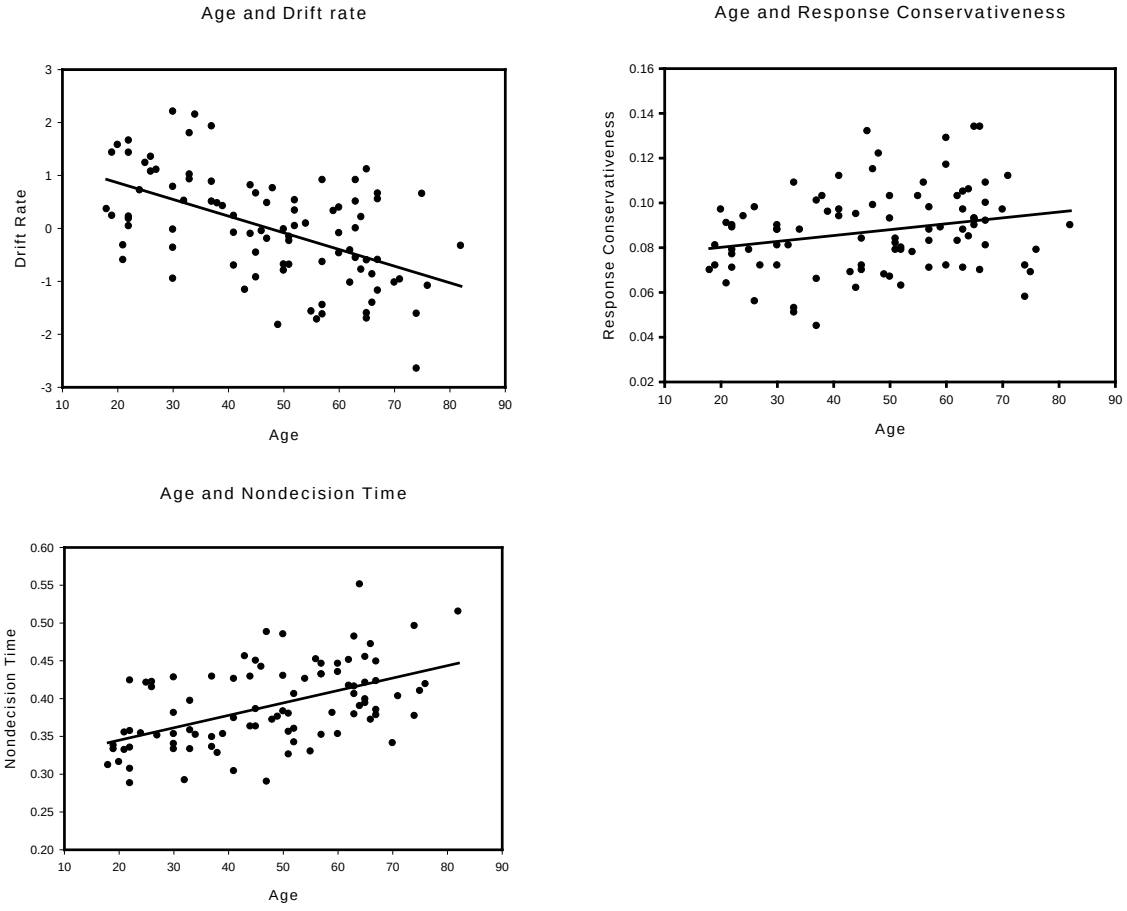
Table 5. Correlation between RT components and age, accuracy and response time

RT components		r_{age}	$r_{accuracy}$	r_{RT}	**Steiger's Z**	**p**
Drift Rate	D 13	**-.54**	**.82**	**-.41**	**5.46**	**<.01**
	D 26	**-.50**	**.81**	**-.47**	**4.93**	**<.01**
	D 39	**-.46**	**.71**	**-.39**	**3.90**	**<.01**
	D 52	**-.40**	**.58**	**-.26**	**3.31**	**<.01**
	D 66	**-.31**	**.45**	**-.24**	**2.09**	**<.05**
	D 80	**-.25**	**.43**	-.18	**2.21**	**<.05**
Response Conservativeness		**.24**	-.06	**.47**	**-4.24**	**<.01**
Non-decision Time		**.52**	**-.37**	**.83**	**-6.63**	**<.01**

General linear model (GLM) was used to investigate age-relate differences on drift rate, response conservativeness, and non-decision time separately. In these models, each RT component was dependent variable, while age and sex were independent variables. The possible

interactions between age and sex were tested. There were significant main effects of age on drift rate: $F(1, 87) = 34.31$, $p < .001$; on response conservativeness: $F(1, 87) = 5.32$, $p < .05$; and on non-decision time: $F(1, 87) = 31.57$, $p < .001$. Neither Age × sex interaction nor the main effect of sex was significant. The results suggested that advanced age was associated with decreased drift rate, increased response conservativeness and prolonged non-decision time (shown in figure 3).

Figure 3. Association between age and RT components



To replicate Ratcliff's finding of IQ association with drift rate, IQ score from the Culture Fair Intelligence Test (CFIT) was added as a predictor to the GLM. No main or moderating effects of IQ on response conservativeness and drift rate were found {F (1, 85) =.02, p=.88; F (1, 85) =.03, p=.87 respectively}, although zero-order correlations between IQ with drift rate from the first two conditions and with the composite score of drift rate were significant ($p<.05$). The main effect of IQ on non-decision time was marginally significant: F (1, 85) =3.86, p=.053. Higher IQ was associated with shorter non-decision time ($p<.001$).

Age-related Differences in DTI Indices (FA, MD, AD, and RD)

Separate GLMs were applied to examine the effects of age on each index of white matter integrity in normal and whole white matter. In each model, individual DTI index (e.g. FA) was a dependent variable. Age and sex were independent variables, and white matter tracts served as the repeated measure factor. All non-significant interactions between age and sex were dropped from the final models.

In normal-appearing white matter

FA and age. The descriptive statistics and zero order age correlations of FA across white matter tracts were presented in table 6.

Table 6. Descriptive statistics and age correlations of FA in normal-appearing white matter across white matter tracts

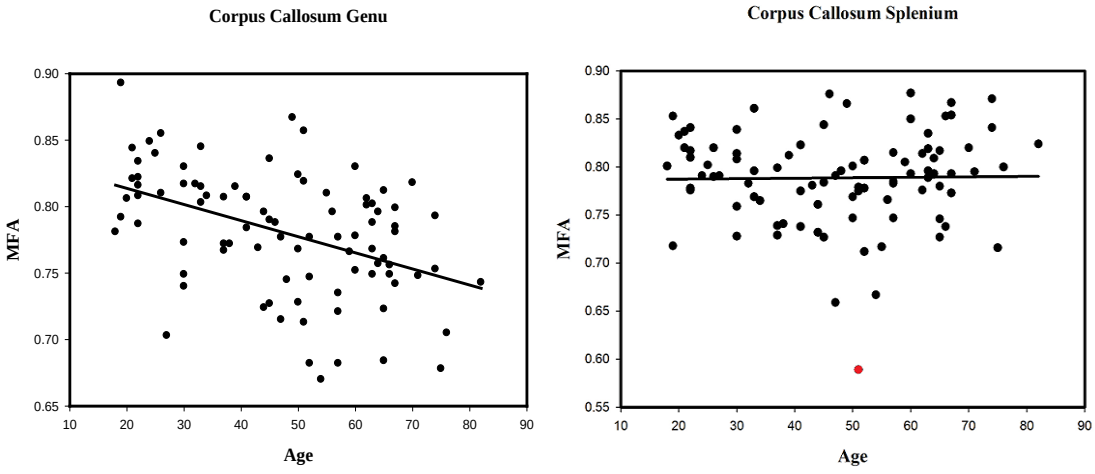
ROI	Mean	SD	CV	r_{age}	R^2 (linear)	R^2 (Quadratic)	F	p
CCg	0.78	0.05	0.06	**-0.44**	.20	.20	.55	ns
CCs	0.79	0.05	0.06	0.02	0	—	—	—
ALIC	0.66	0.05	0.08	**-0.21**	.05	.06	1.75	ns
PLIC	0.67	0.08	0.12	**0.38**	.14	.14	.02	ns
SLF	0.56	0.05	0.09	-0.19	.03	—	—	—
ACR	0.53	0.06	0.11	**-0.51**	.26	.26	.002	ns
SCR	0.46	0.07	0.15	-0.02	0	—	—	—
PCR	0.42	0.07	0.18	0.11	.01	—	—	—
EC	0.45	0.04	0.09	**-0.24**	.058	.06	.23	ns
PTR	0.52	0.08	0.16	**-0.39**	.15	.24	9.91	<.01
RIC	0.62	0.04	0.07	-0.20	.039	—	—	—

Note. CCg: the genu of the corpus callosum; CCs: the splenium of the corpus callosum; ALIC: the anterior limb of the internal capsule; PLIC: the posterior limb of the internal capsule; SLF: the superior longitudinal fasciculus; ACR: the anterior corona radiata; SCR: the superior corona radiata; PCR: the posterior corona radiata; EC: the external capsule; PTR: the posterior thalamic radiation; RIC: the retrolenticular part of the internal capsule; Significant linear age correlations are bolded; F test tests the significance of R square change with addition of polynomial term; —: not applicable.

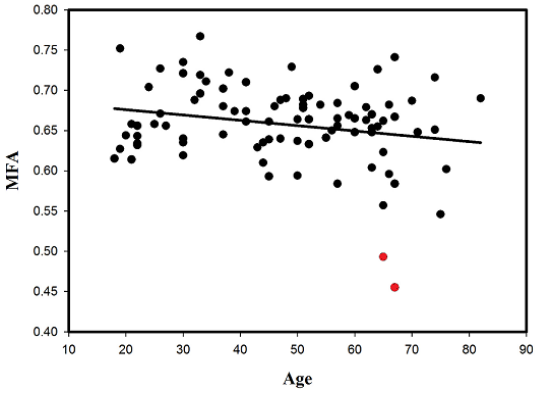
The GLM analysis revealed a significant main effect of age, $F(1, 86) = 4.21$, $p < .05$, indicating that advanced age was associated with decreased FA across the examined white matter tracts. Neither the main effect of sex nor age × sex interaction was significant. There was a significant tract × age interaction, $F(10, 860) = 16.04$, $p < .001$, suggesting that the magnitude of age differences varied across the examined white matter tracts. Specifically, age-related reduction in FA was observed in the genu of the corpus callosum: $F(1, 86) = 23.76$, $p < .001$; the anterior limb of the internal capsule: $F(1, 86) = 5.30$, $p < .05$; $F(1, 86) = 16.12$, $p < .001$; the anterior corona

radiata: F (1, 86) =33.87, p<.001; the external capsule: F (1, 86) =8.02, p<.01; and the posterior thalamic radiation: F (1, 86) =15.98, p<.001. However, age-related increase in FA was found in the posterior limb of the internal capsule. There was no age-related differences in FA of the splenium: F (1, 86) =.14, p= .71; the superior longitudinal fasciculus: F (1, 86) =3.23, p=.08; the superior corona radiata: F (1, 86) =.004, p= .95; the posterior corona radiata: F (1, 86) =.99, p= .32; and the retrolenticular part of the internal capsule: F (1, 86) =3.62, p=.06. There was an age-related anterior-posterior gradient decrease in FA in the corpus callosum, the internal capsule, and the corona radiata as evidenced by age-related reduction in FA in the genu but not the splenium of the corpus callosum, in the anterior limb but not the posterior limb of the internal capsule, and in the anterior but not the posterior corona radiata. The scatterplots of age and FA association across white matter tracts were presented in Figure 4. Outliers undergoing treatment before statistical analysis were marked red and this applied to all the scatterplots in this paper.

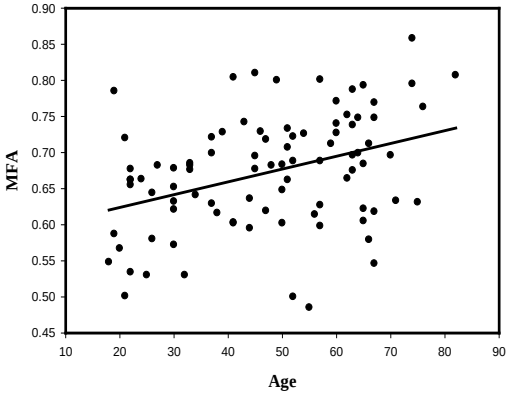
Figure 4. Association between age and FA in normal-appearing white matter



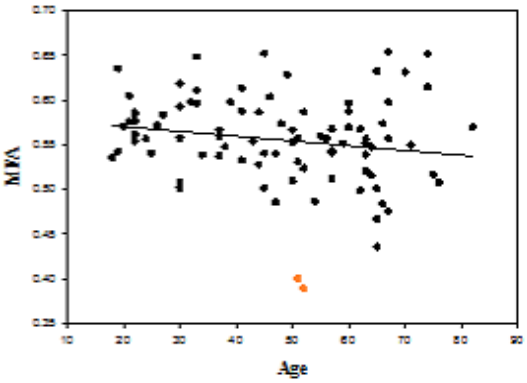
Anterior Limb of the Internal Capsule



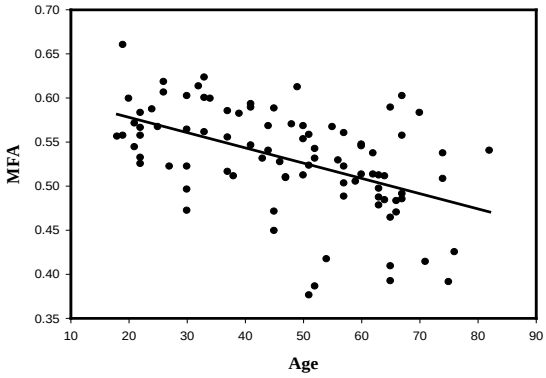
Posterior Limb of the Internal Capsule



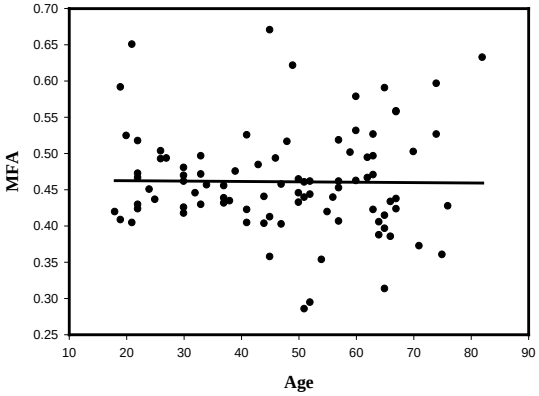
Superior Longitudinal Fasciculus



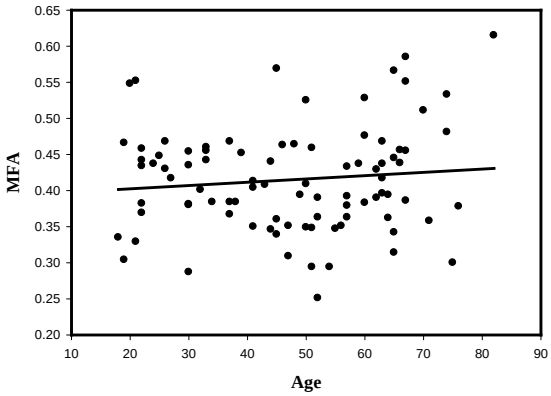
Anterior Corona Radiata

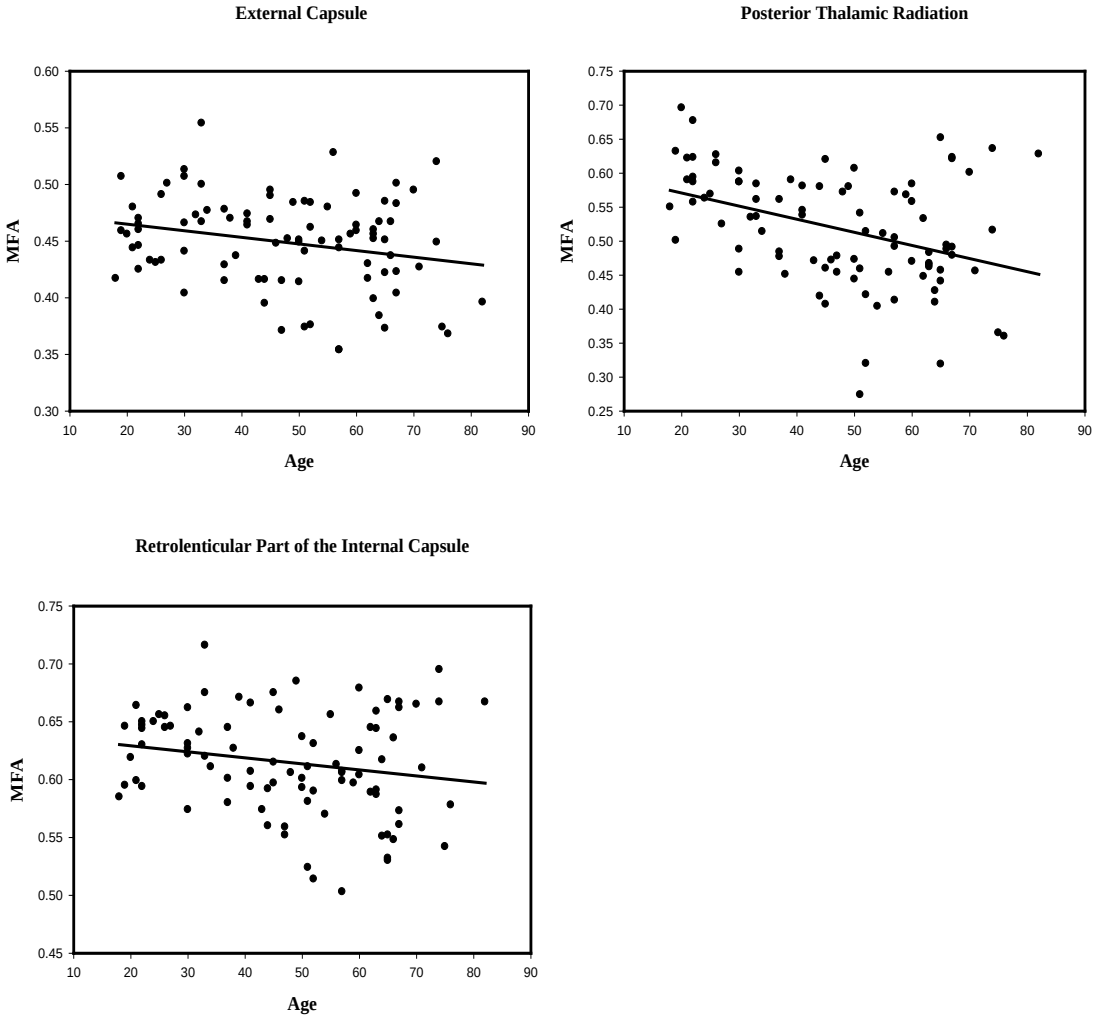


Superior Corona Radiata



Posterior Corona Radiata





The nonlinear trend was tested by adding a second order polynomial term into the regression model and comparing the R square change. The analysis revealed nonlinear trajectory of age and FA in the posterior thalamic radiation. However, linear term explained more variance than nonlinear term did (see Table 6).

There was a significant tract × sex × age interaction, $F(10, 860) = 2.57$, $p < .01$. Separate analysis for men and women revealed that the effect of age on FA in the external capsule was significant in men: $F(1, 28) = 7.16$, $p < .05$, but not in women: $F(1, 58) = .40$, $p = .53$.

MD and age. The descriptive statistics and zero order age correlations of MD across white matter tracts were presented in table 7.

The GLM analysis demonstrated a significant main effect of age, $F(1, 86) = 6.08$, $p < .05$, suggesting that advanced age was associated with higher MD across the examined white matter tracts. There was a significant sex × age interaction, $F(1, 86) = 4.39$, $p < .05$, indicating that the overall effect of age on MD was significant only in men: $F(1, 28) = 7.16$, $p < .05$; but not in women: $F(1, 58) = .10$, $p = .75$. Significant tract × age interaction, $F(10, 860) = 4.14$, $p < .001$, indicated that age exacted differential effects across these white matter tracts. Specifically, age-related increase in MD was observed in the genu of the corpus callosum: $F(1, 86) = 18.27$, $p < .001$; the posterior limb of the internal capsule: $F(1, 86) = 8.30$, $p < .01$; the anterior corona radiata: $F(1, 86) = 4.38$, $p < .05$; the superior corona radiata: $F(1, 86) = 9.94$, $p < .01$; and the posterior corona radiata: $F(1, 86) = 7.20$, $p < .01$. But there was no age-related MD difference in the splenium of the corpus callosum: $F(1, 86) = 2.56$, $p = .11$; the anterior limb of the internal capsule: $F(1, 86) = 1.72$, $p = .19$; the superior longitudinal fasciculus: $F(1, 86) = 2.52$, $p = .12$; the external capsule: $F(1, 86) = 2.06$, $p = .16$; the posterior thalamic radiation: $F(1, 86) = 1.54$, $p = .22$; and the retrolenticular part of the internal capsule: $F(1, 86) = 1.51$, $p = .22$. The results also suggested an age-related anterior-posterior gradient increase in MD in the corpus callosum by demonstrating an age-related increase in MD in the genu but not the splenium of the corpus

callosum. The scatterplots of age and MD association in normal appearing white matter tracts were shown in Figure 5. The analysis of nonlinear trend revealed nonlinear trajectory of age and MD in the genu of the corpus callosum, the posterior limb of the internal capsule, and the superior and posterior corona radiata, but linear term explained more variance than nonlinear term did in the genu of the corpus callosum (see Table 7).

Table 7. Descriptive statistics and age correlations of MD in normal-appearing white matter across white matter tracts

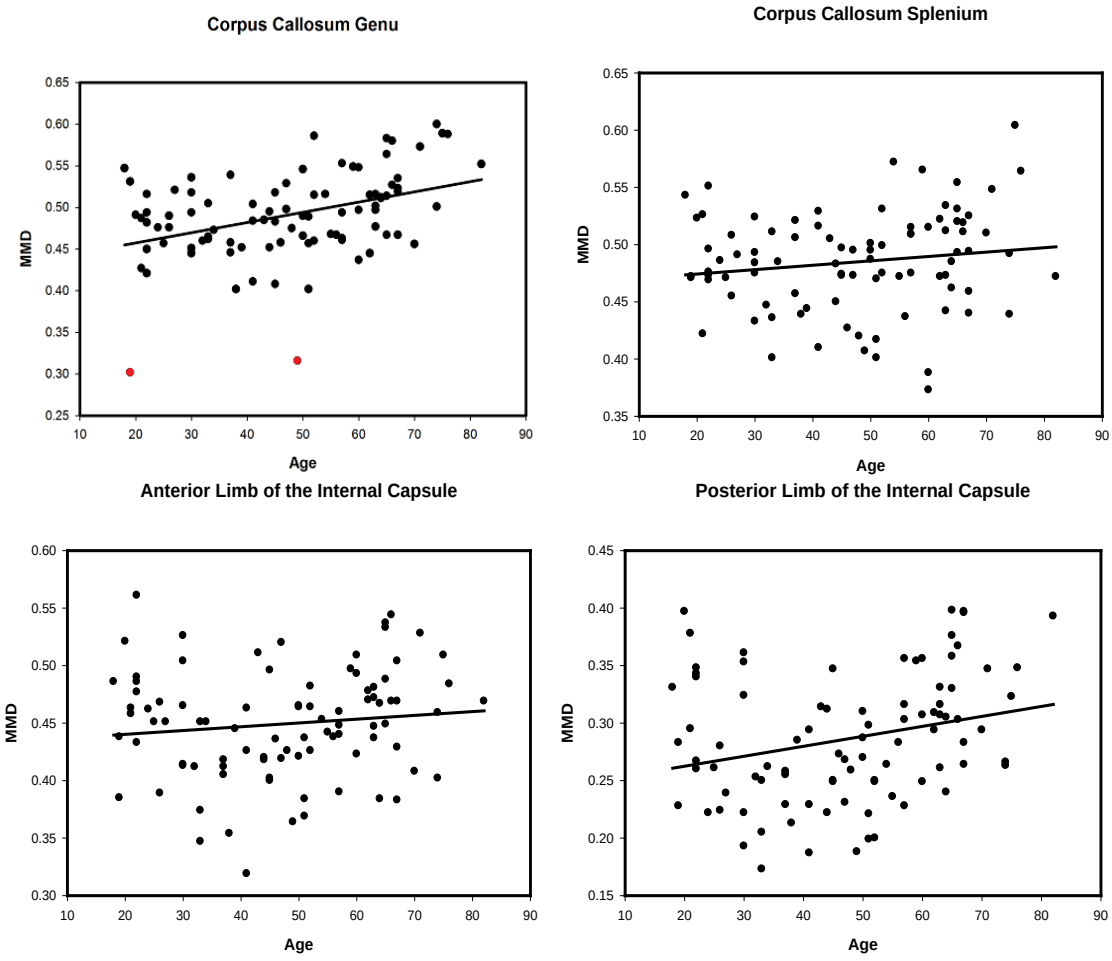
ROI	Mean	SD	CV	r_{age}	R^2 (linear)	R^2 (Quadratic)	F	p
CCg	0.49	0.05	0.11	**0.41**	.17	.26	11.07	<.01
CCs	0.49	0.04	0.09	0.15	.022	—	—	—
ALIC	0.45	0.05	0.11	0.12	.014	—	—	—
PLIC	0.29	0.06	0.20	**0.26**	.068	.23	18.76	<.001
SLF	0.52	0.05	0.09	0.09	.008	—	—	—
ACR	0.54	0.05	0.09	0.17	.03	—	—	—
SCR	0.39	0.07	0.18	**0.28**	.076	.26	22.30	<.001
PCR	0.46	0.09	0.20	**0.22**	.048	.19	14.88	<.001
EC	0.45	0.05	0.11	0.13	.016	—	—	—
PTR	0.53	0.07	0.13	-0.17	.029	—	—	—
RIC	0.55	0.05	0.09	0.10	.009	—	—	—

Note. CCg: the genu of the corpus callosum; CCs: the splenium of the corpus callosum; ALIC: the anterior limb of the internal capsule; PLIC: the posterior limb of the internal capsule; SLF: the superior longitudinal fasciculus; ACR: the anterior corona radiata; SCR: the superior corona radiata; PCR: the posterior corona radiata; EC: the external capsule; PTR: the posterior thalamic radiation; RIC: the retrolenticular part of the internal capsule; Significant linear age correlations are bolded; F test tests the significance of R square change with addition of polynomial term; —: not applicable.

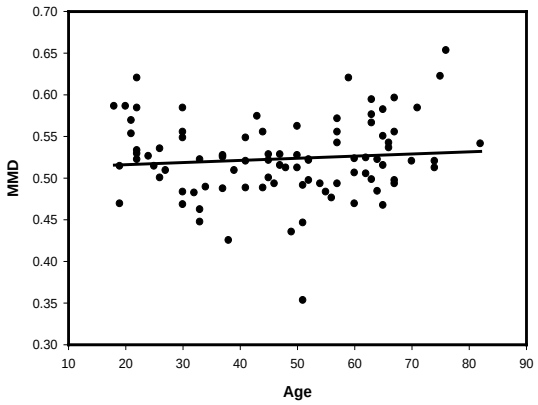
There was a significant tract × sex interaction, $F(10, 860) = 2.12$, $p < .05$, suggesting that MD is higher in women than in men in the anterior limb of the internal capsule: $F(1, 86) = 9.69$,

p<.01; the posterior limb of the internal capsule: F (1, 86) =7.44, p<.01; and the retrolenticular part of the internal capsule: F (1, 86) =5.49, p<.05.

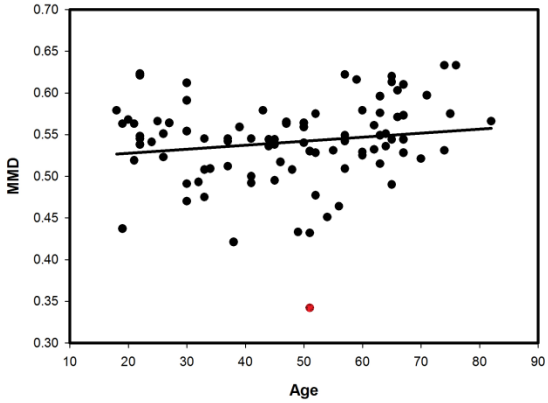
Figure 5. Association between age and MD in normal-appearing white matter



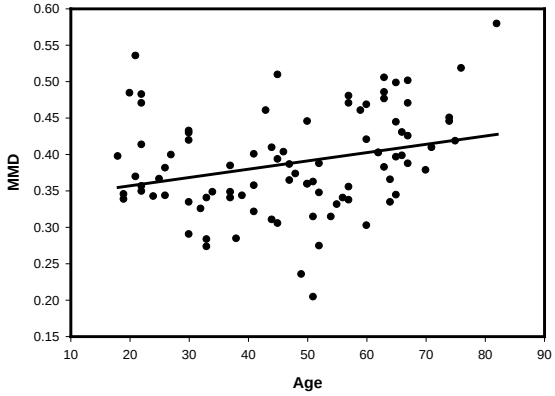
Superior Longitudinal Fasciculus



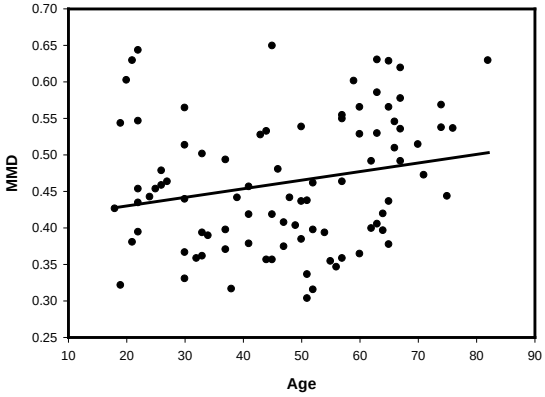
Anterior Corona Radiata



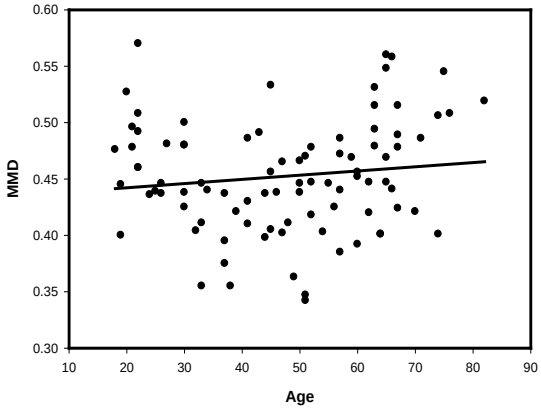
Superior Corona Radiata



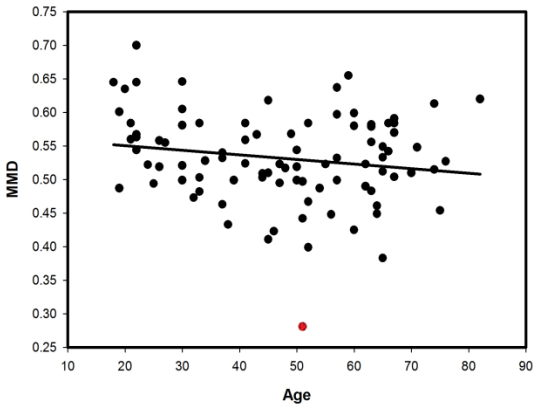
Posterior Corona Radiata

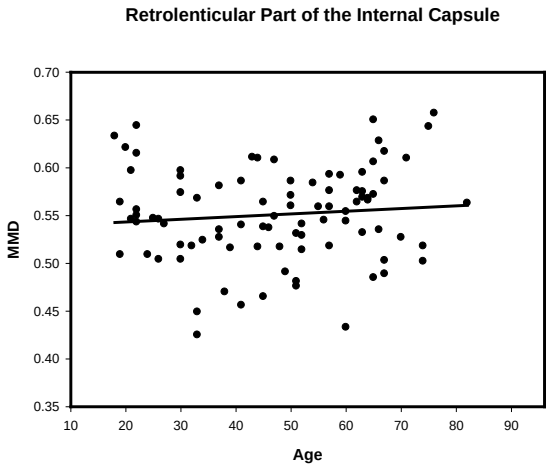


External Capsule



Posterior Thalamic Radiation





DA and age. Table 8 displayed the descriptive statistics and zero order age correlations of DA across white matter tracts.

No main effect of either age or sex and no age × sex interaction were revealed by GLM analysis. There was a significant tract × age interaction, $F(10, 860) = 5.32$, $p < .001$, indicating that the effect of age differed across white matter tracts examined. Specifically, age-related increase in DA was observed in the genu of the corpus callosum: $F(1, 86) = 5.48$, $p < .05$; the posterior limb of the internal capsule: $F(1, 86) = 12.33$, $p = .001$; the superior corona radiata: $F(1, 86) = 6.64$, $p < .05$; and the posterior corona radiata: $F(1, 86) = 5.82$, $p < .05$. There was age-related decrease in DA in the posterior thalamic radiation: $F(1, 86) = 6.02$, $p < .05$. But there was no age-related DA difference in the splenium of the corpus callosum: $F(1, 86) = 1.02$, $p = .32$; the anterior limb of the internal capsule: $F(1, 86) = .39$, $p = .54$; the superior longitudinal fasciculus: $F(1, 86) = .51$, $p = .48$; the anterior corona radiata: $F(1, 86) = .32$, $p = .58$; the external capsule: $F(1, 86) = .04$, $p = .85$; and the retrolenticular part of internal capsule: $F(1, 86) = .001$, $p = .97$. There was an

age-related anterior-posterior gradient increase in DA in the corpus callosum as evidenced by an age-related increase in DA in the genu but not the splenium of the corpus callosum. The scatterplots of age and DA association in normal appearing white matter tracts were revealed in Figure 6. The analysis of nonlinear trend revealed nonlinear trajectory of age and DA in several tracts examined (see Table 8).

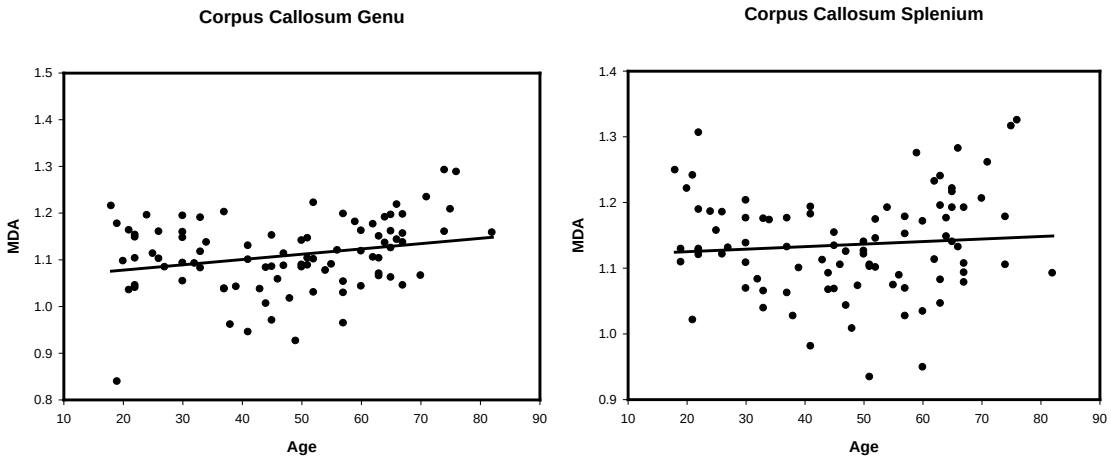
Table 8. Descriptive statistics and age correlations of DA in normal- appearing white matter across white matter tracts

ROI	**Mean**	**SD**	**CV**	**r_{age}**	**R^2 (linear)**	**R^2 (Quadratic)**	**F**	**p**
CCg	1.11	0.08	0.07	**0.25**	.06	.18	12.85	.001
CCs	1.14	0.08	0.07	0.09	.007	—	—	—
ALIC	0.86	0.07	0.08	-0.07	.004	—	—	—
PLIC	0.67	0.09	0.14	**0.30**	.09	.28	23.48	<.001
SLF	0.91	0.07	0.07	0.01	.000	—	—	—
ACR	0.91	0.07	0.07	-0.09	.009	—	—	—
SCR	0.68	0.11	0.17	**0.22**	.048	.24	22.44	<.001
PCR	0.79	0.15	0.19	0.20	.042	—	—	—
EC	0.75	0.07	0.09	0.00	.000	—	—	—
PTR	0.98	0.13	0.14	**-0.28**	.08	.23	16.87	. <.001
RIC	1.00	0.07	0.07	-0.03	.001	—	—	—

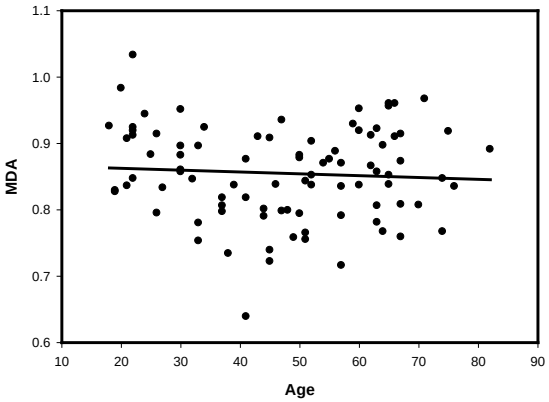
Note. CCg: the genu of the corpus callosum; CCs: the splenium of the corpus callosum; ALIC: the anterior limb of the internal capsule; PLIC: the posterior limb of the internal capsule; SLF: the superior longitudinal fasciculus; ACR: the anterior corona radiata; SCR: the superior corona radiata; PCR: the posterior corona radiata; EC: the external capsule; PTR: the posterior thalamic radiation; RIC: the retrolenticular part of the internal capsule; Significant linear age correlations are bolded; F test tests the significance of R square change with addition of polynomial term. —: not applicable.

Significant tract × sex interaction, F (10, 870) =2.56, p<.01, suggested that DA was higher in women than in men in the anterior limb of the internal capsule: F (1, 86) =7.82, p<.01; the posterior limb of the internal capsule: F (1, 86) =8.71, p<.01; and the retrolenticular part of the internal capsule: F (1, 86) =6.74, p<.05.

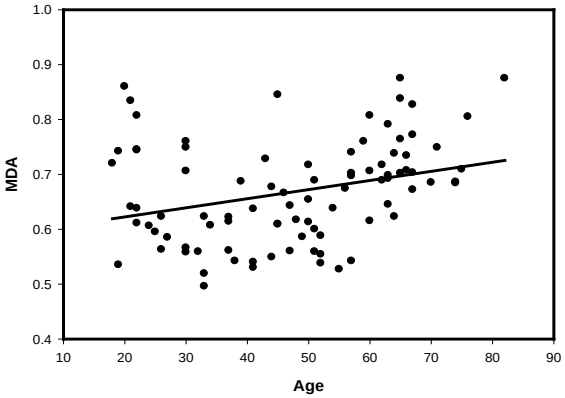
Figure 6. Association between age and DA in normal-appearing white matter



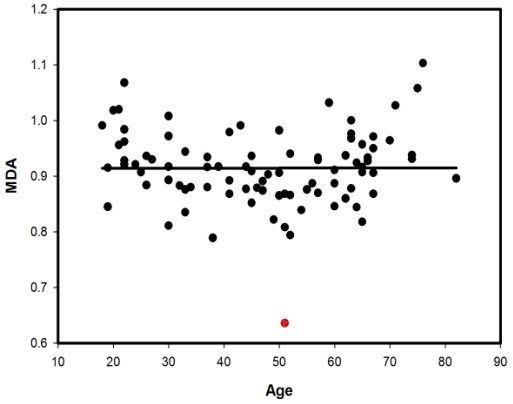
Anterior Limb of the Internal Capsule



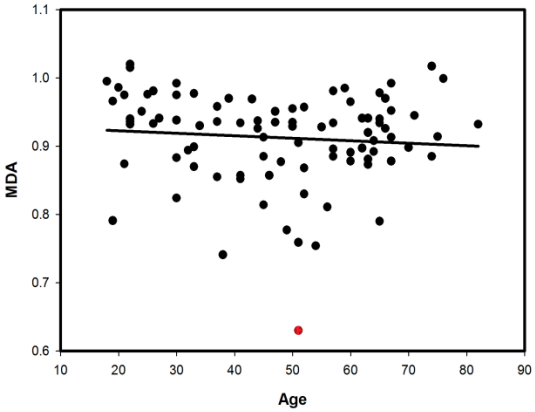
Posterior Limb of the Internal Capsule



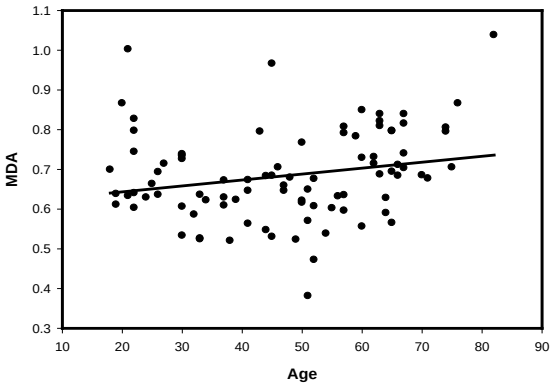
Superior Longitudinal Fasciculus



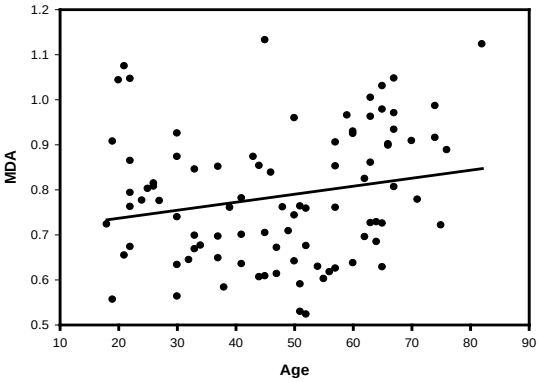
Anterior Corona Radiata

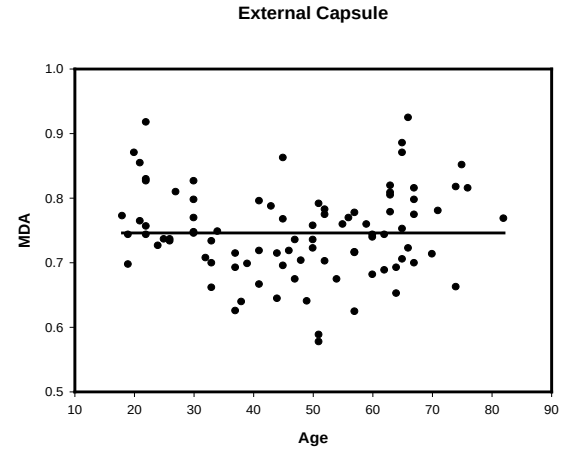


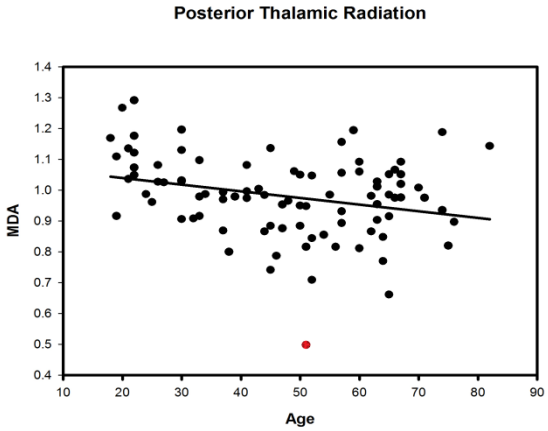
Superior Corona Radiata

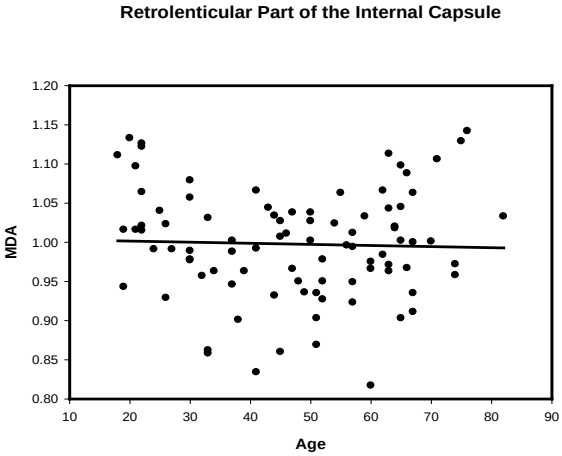


Posterior Corona Radiata









DR and age. Table 9 displayed the descriptive statistics and zero order age correlations of DR across white matter tracts.

The GLM analysis revealed a significant main effect of age, $F(1, 86) = 10.32$, $p < .01$, suggesting that advanced age was associated with higher DR across the white matter tracts examined. The main effect of sex was not significant. There was a significant sex × age

interaction, F (1, 86) =4.54, p<.05, indicating that the overall effect of age on DR was significant only in men: F (1, 28) =9.8, p<.01; but not in women: F (1, 58) =.85, p=.36. There was a significant tract × age interaction, F (10, 860) =2.54, p<.001, indicating that age exacted differential effects across white matter tracts. Specifically, age-related increase in DR was evidenced in the genu of the corpus callosum: F (1, 86) =20.77, p<.001; the anterior limb of the internal capsule: F (1, 86) =7.76, p<.01; the superior longitudinal fasciculus: F (1, 86) =4.92, p<.05; the anterior corona radiata: F (1, 86) =13.79, p<.001; the superior corona radiata: F (1, 86) =13.05, p=.001; the posterior corona radiata: F (1, 86) =8.17, p<.01; the external capsule: F (1, 86) =5.54, p<.05; and the retrolenticular part of the internal capsule: F (1, 86) =4.33, p<.05. But there was no age-related DR difference in the splenium of the corpus callosum: F (1, 86) =2.85, p=.10; the posterior limb of the internal capsule: F (1, 86) =3.48, p= .07; and the posterior thalamic radiation: F (1, 86) =.46, p=.50. There was an anterior-posterior gradient of age-related differences in DR of the corpus callosum and the internal capsule. Advanced age was associated with DR increase in the genu but not the splenium of the corpus callosum, and in the anterior but not the posterior limb of the internal capsule. The scatterplots of age and DR association in normal appearing white matter tracts were displayed in Figure 7.

Table 9. Descriptive statistics and age correlations of DR in normal-appearing white matter across white matter tracts

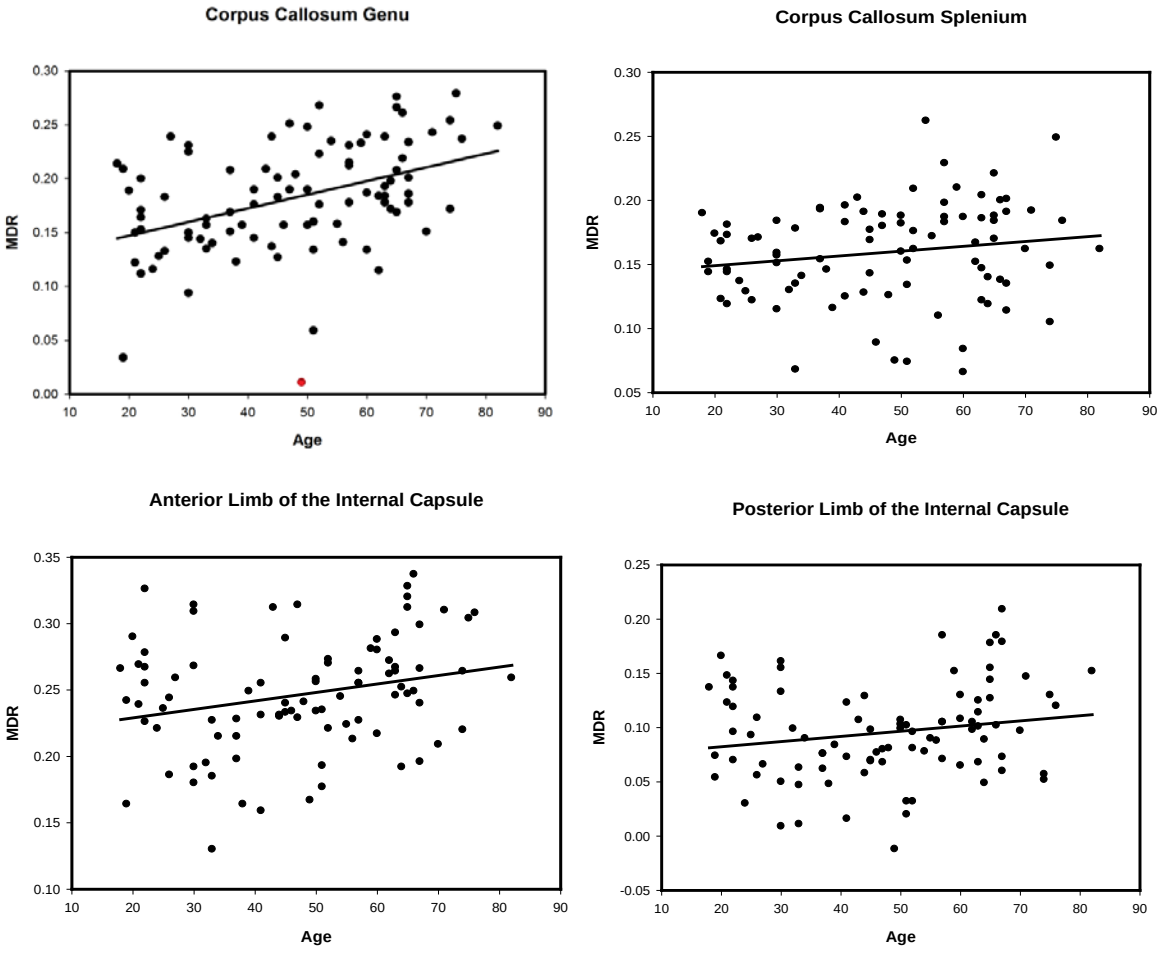
ROI	Mean	SD	CV	r_{age}	R^2 (linear)	R^2 (Quadratic)	F	p
CCg	0.18	0.05	0.28	**0.43**	.19	.20	1.93	ns
CCs	0.16	0.04	0.24	0.17	.028	—	—	—
ALIC	0.25	0.04	0.18	**0.25**	.062	.12	5.32	<.05
PLIC	0.10	0.04	0.46	0.18	.033	—	—	—
SLF	0.33	0.04	0.13	0.16	.024	—	—	—
ACR	0.36	0.05	0.13	**0.32**	.11	.21	12.11	.001
SCR	0.24	0.05	0.21	**0.32**	.10	.25	17.21	<.001
PCR	0.30	0.07	0.22	**0.22**	.05	.16	10.93	.001
EC	0.31	0.04	0.14	**0.22**	.047	.23	20.56	<.001
PTR	0.31	0.04	0.14	0.02	.000	—	—	—
RIC	0.33	0.05	0.14	0.19	.035	—	—	—

Note. CCg: the genu of the corpus callosum; CCs: the splenium of the corpus callosum; ALIC: the anterior limb of the internal capsule; PLIC: the posterior limb of the internal capsule; SLF: the superior longitudinal fasciculus; ACR: the anterior corona radiata; SCR: the superior corona radiata; PCR: the posterior corona radiata; EC: the external capsule; PTR: the posterior thalamic radiation; RIC: the retrolenticular part of the internal capsule; Significant linear age correlations are bolded; F test tests the significance of R square change with addition of polynomial term. —: not applicable.

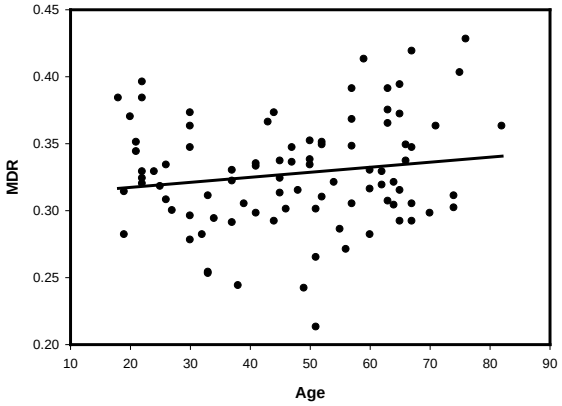
The analysis of nonlinear trend revealed nonlinear trajectory of age and DR in the anterior limb of the internal capsule, the corona radiata (anterior, superior, and posterior), and the external capsule. However, linear term explained more variance in the anterior limb of the internal capsule than nonlinear term did (Table 9).

There was a significant tract × sex interaction, F (10, 860) =1.93, p<.05, suggesting that DR was higher in women than in men in the anterior limb of the internal capsule: F (1, 86) =8.67, p<.01; and the posterior limb of the internal capsule: F (1, 86) =4.60, p<.05.

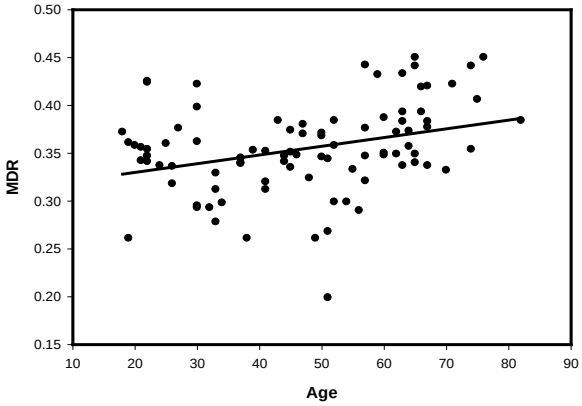
Figure 7. Association between age and DR in normal-appearing white matter



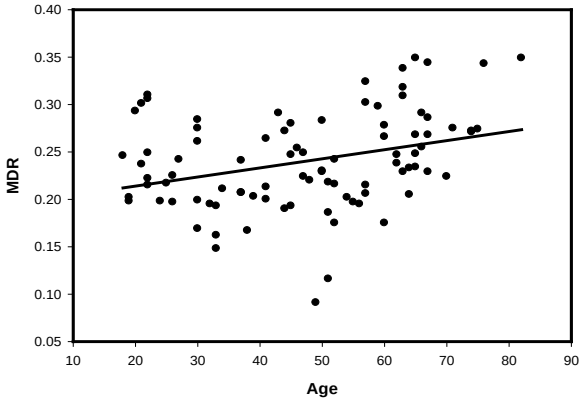
Superior Longitudinal Fasciculus



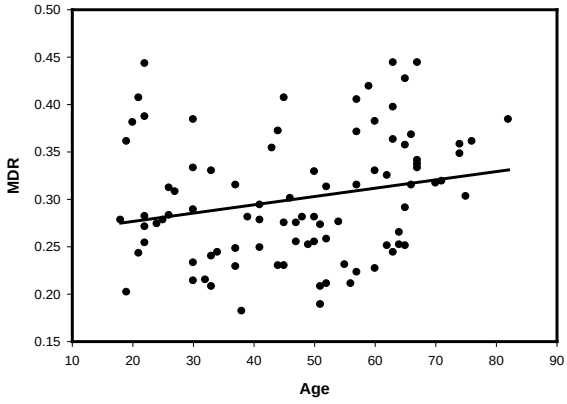
Anterior Corona Radiata



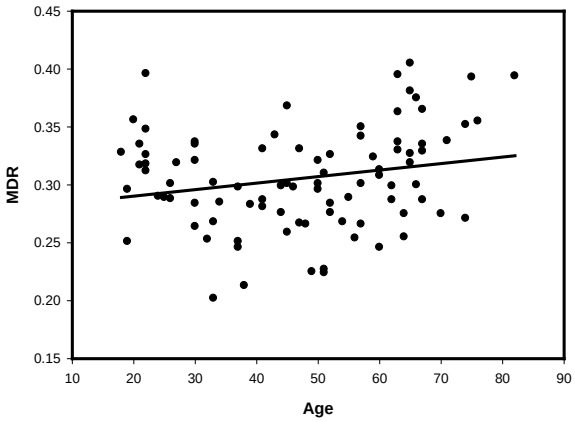
Superior Corona Radiata



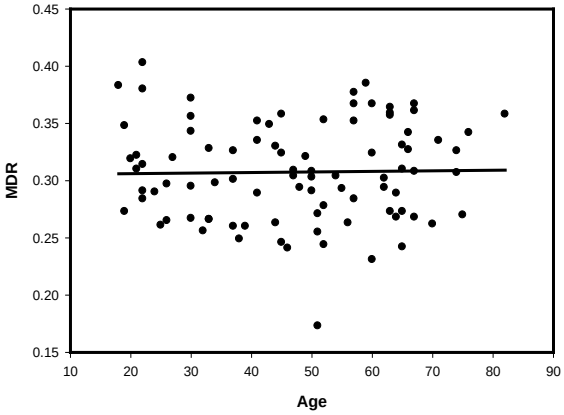
Posterior Corona Radiata

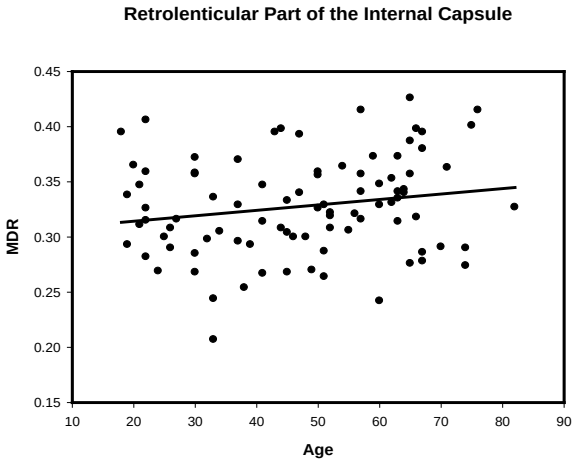


External Capsule



Posterior Thalamic Radiation





In whole white matter

FA and age. Table 10 displayed the descriptive statistics and zero order age correlations of FA across white matter tracts.

The GLM analysis revealed a significant main effect of age, $F(1, 86) = 15.63$, $p < .001$, suggesting that advanced age was associated with lower FA across the examined white matter tracts. The main effect of sex was not significant, but there was a trend toward age × sex interaction ($p = .056$), indicating that the association between age and FA was significant in men: $F(1, 28) = 10.97$, $p < .01$, but marginally significant in women: $F(1, 58) = 3.12$, p=083. There was a significant tract × age interaction, $F(10, 860) = 5.61$, $p < .001$, indicating that the effect of age differed across white matter tracts examined. Specifically, age-related reduction in FA was observed in the genu of the corpus callosum: $F(1, 86) = 24.38$, $p < .001$; the anterior limb of the internal capsule: $F(1, 86) = 14.11$, $p < .001$; the superior longitudinal fasciculus: $F(1, 86) = 5.85$, $p < .05$; the anterior corona radiata: $F(1, 86) = 44.50$, $p < .001$; the superior corona radiata: F (1, 86)

=12.49, p=.001; the external capsule: F (1, 86) =12.88, p=.001; the posterior thalamic radiation: F (1, 86) =18.13, p<.001; and the retrolenticular part of the internal capsule: F (1, 86) =7.34, p<.05. But there was little or no age-related FA reduction in the splenium of the corpus callosum: F (1, 86) =2.88, p= .09; the posterior limb of the internal capsule: F (1, 86) =.22, p= .64; and the posterior corona radiata: F (1, 86) =2.60, p=.11. There was an age-related anterior-posterior gradient in FA decrease in the corpus callosum, the internal capsule, and the corona radiata as evidenced by an age-related decrease in FA in the genu but not the splenium of the corpus callosum, in the anterior limb but not the posterior limb of the internal capsule, and in the anterior but not the posterior corona radiata. The scatterplots of age and FA association in whole white matter tracts were shown in Figure 8.

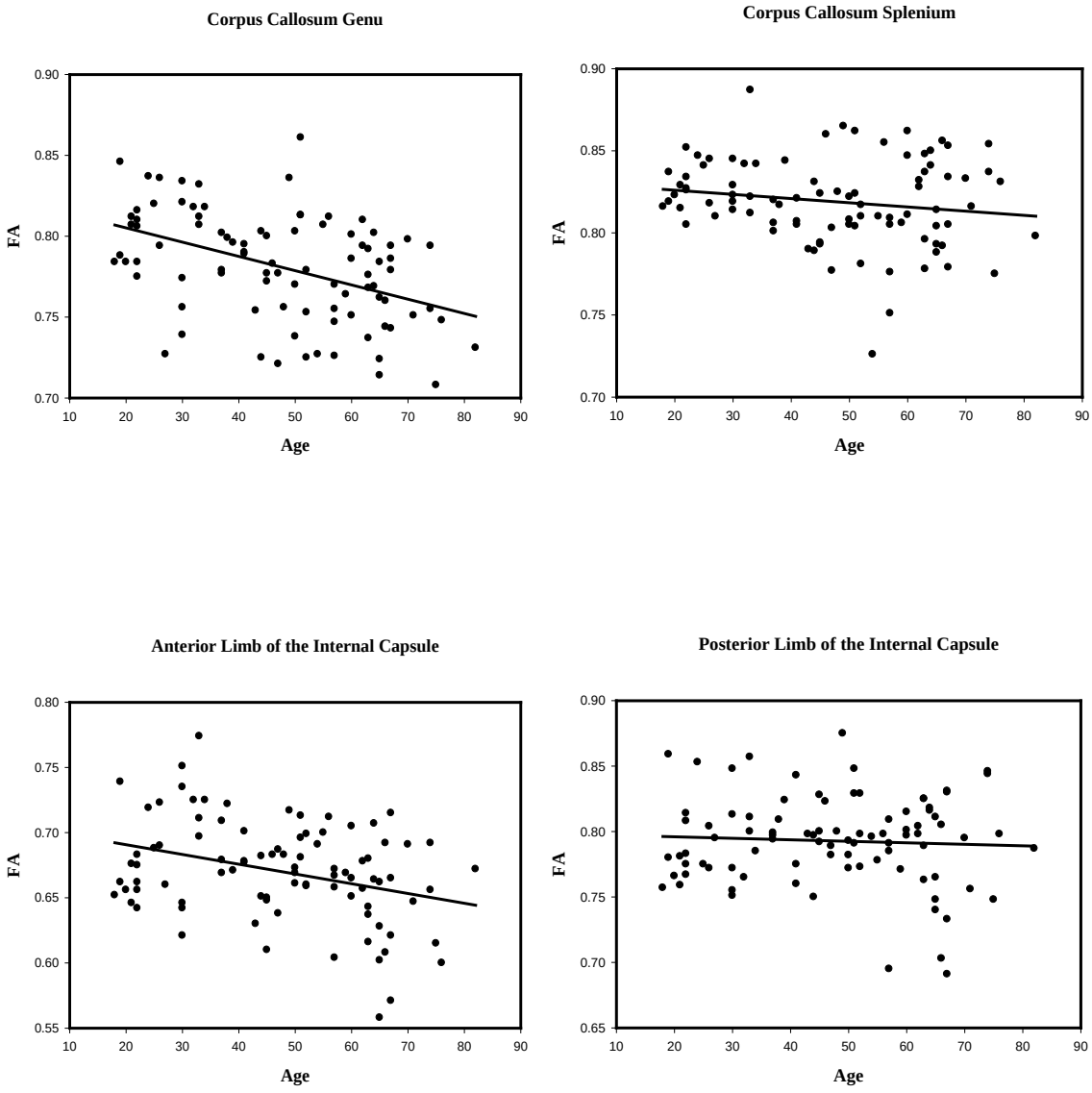
The analysis of nonlinear trend revealed nonlinear trajectory of age and FA in the external capsule. However, linear term explained more variance than nonlinear term did (see Table 10).

Table 10. Descriptive statistics and age correlations of FA in whole white matter across white matter tracts

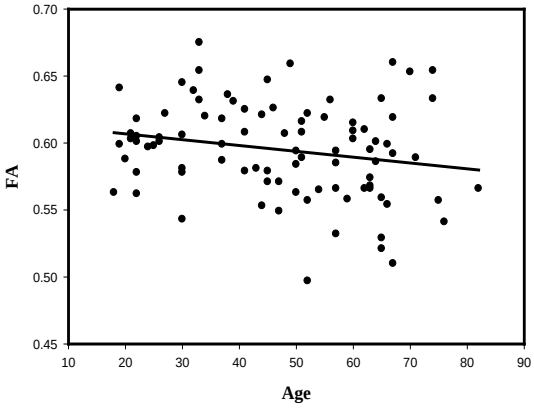
ROI	Mean	SD	CV	r_{age}	R^2 (linear)	R^2 (Quadratic)	F	p
CCg	0.78	0.03	0.04	**-0.45**	0.20	0.20	0.14	ns
CCs	0.82	0.03	0.03	-0.17	0.03	—	—	—
ALIC	0.67	0.04	0.06	**-0.33**	0.11	0.14	2.56	ns
PLIC	0.79	0.03	0.04	-0.06	0.00	—	—	—
SLF	0.60	0.04	0.06	**-0.21**	0.04	0.05	0.14	ns
ACR	0.56	0.04	0.08	**-0.55**	0.30	0.32	3.41	ns
SCR	0.60	0.04	0.06	**-0.34**	0.11	0.11	0.05	ns
PCR	0.55	0.04	0.07	-0.11	0.01	—	—	—
EC	0.52	0.03	0.07	**-0.31**	0.10	0.18	8.11	<.01
PTR	0.63	0.04	0.07	**-0.37**	0.14	0.16	2.02	ns
RIC	0.64	0.04	0.06	**-0.26**	0.07	0.07	0.60	ns

Note. CCg: the genu of the corpus callosum; CCs: the splenium of the corpus callosum; ALIC: the anterior limb of the internal capsule; PLIC: the posterior limb of the internal capsule; SLF: the superior longitudinal fasciculus; ACR: the anterior corona radiata; SCR: the superior corona radiata; PCR: the posterior corona radiata; EC: the external capsule; PTR: the posterior thalamic radiation; RIC: the retrolenticular part of the internal capsule; Significant linear age correlations are bolded; F test tests the significance of R square change with addition of polynomial term. —: not applicable.

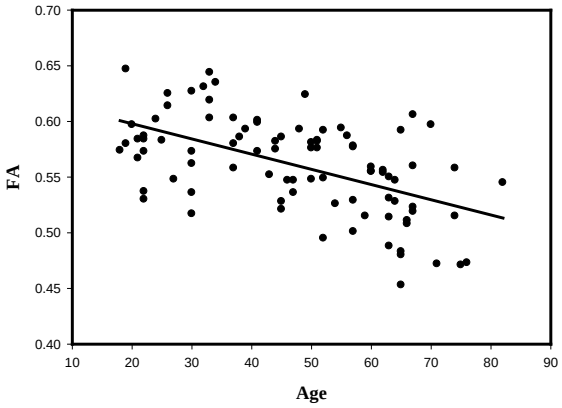
Figure 8. Association between age and FA in whole white matter



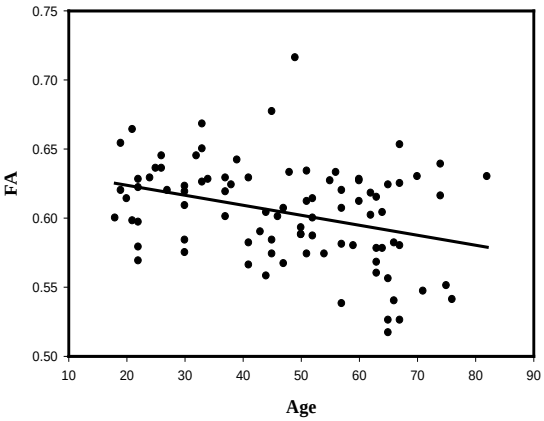
Superior Longitudinal Fasciculus



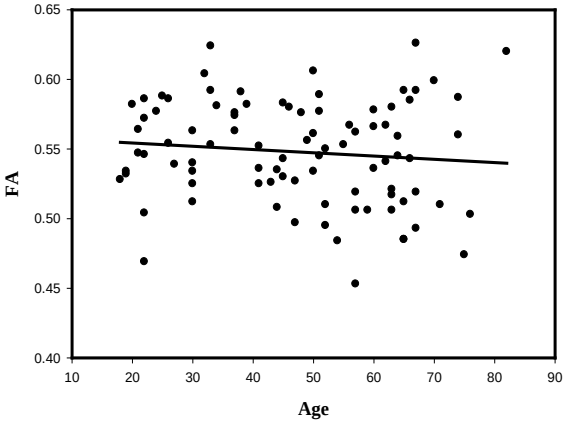
Anterior Corona Radiata



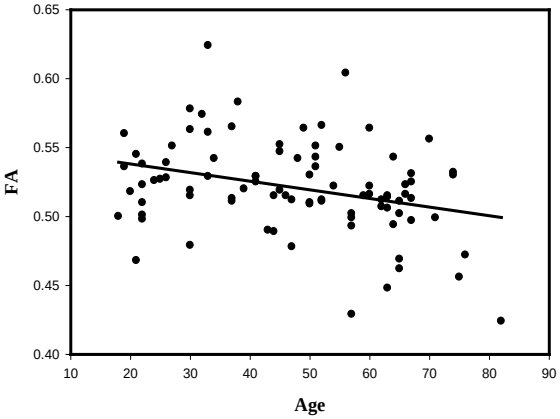
Superior Corona Radiata



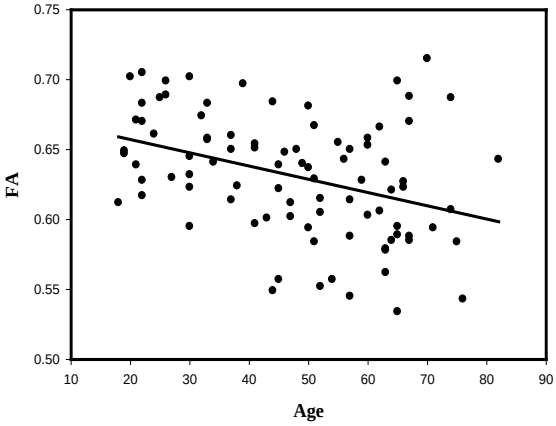
Posterior Corona Radiata



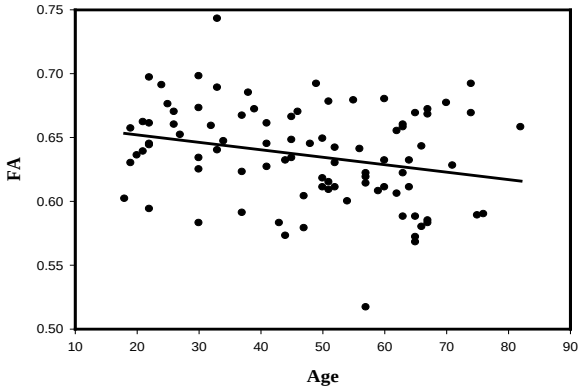
External Capsule



Posterior Thalamic Radiation



Retrolenticular Part of the Internal Capsule:



MD and age. Table 11 displayed the descriptive statistics and zero order age correlations of MD across white matter tracts.

Table 11. Descriptive statistics and age correlations of MD in whole white matter across white matter tracts

ROI	Mean	SD	CV	r_{age}	R^2 (linear)	R^2 (Quadratic)	F	p
CCg	0.54	0.06	0.11	**0.47**	0.22	0.26	4.58	<.05
CCs	0.55	0.05	0.10	0.04	0.00	—	—	—
ALIC	0.51	0.07	0.13	0.12	0.02	—	—	—
PLIC	0.44	0.07	0.16	-0.18	0.03	—	—	—
SLF	0.60	0.05	0.08	**0.24**	0.06	0.08	2.45	ns
ACR	0.61	0.06	0.09	**0.42**	0.17	0.20	2.91	ns
SCR	0.58	0.05	0.09	**0.27**	0.27	0.34	4.05	<.05
PCR	0.70	0.05	0.08	**0.24**	0.06	0.08	2.60	ns
EC	0.63	0.05	0.08	**0.31**	0.09	0.17	8.32	<.01
PTR	0.72	0.06	0.09	**0.38**	0.38	0.38	0.01	ns
RIC	0.60	0.05	0.09	0.16	0.16	—	—	—

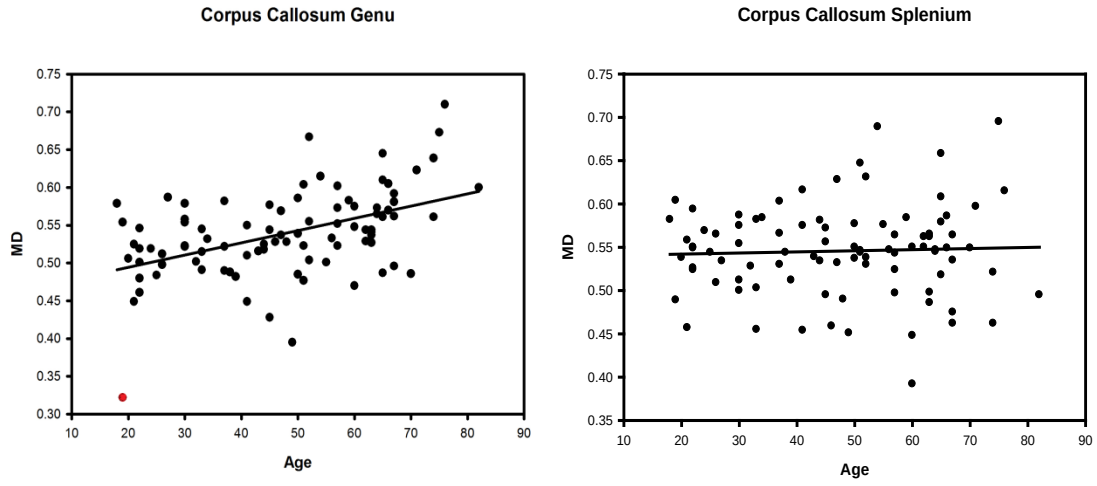
Note. CCg: the genu of the corpus callosum; CCs: the splenium of the corpus callosum; ALIC: the anterior limb of the internal capsule; PLIC: the posterior limb of the internal capsule; SLF: the superior longitudinal fasciculus; ACR: the anterior corona radiata; SCR: the superior corona radiata; PCR: the posterior corona radiata; EC: the external capsule; PTR: the posterior thalamic radiation; RIC: the retrolenticular part of the internal capsule; Significant linear age correlations are bolded; F test tests the significance of R square change with addition of polynomial term. —: not applicable.

The GLM analysis revealed a significant main effect of age, $F(1, 86) = 8.74$, $p < .01$, suggesting that advanced age was associated with higher MD across the examined white matter tracts. Neither the main effect of sex nor an age × sex interaction was significant. There was a significant tract × age interaction, $F(10, 860) = 11.06$, $p < .001$, indicating that age exacted differential effects across these white matter tracts. Specifically, age-related increase in MD was observed in the genu of the corpus callosum: $F(1, 86) = 27.05$, $p < .001$; the superior longitudinal fasciculus: $F(1, 86) = 6.69$, $p < .05$; the anterior corona radiata: $F(1, 86) = 22.51$, $p < .001$; the superior corona radiata: $F(1, 86) = 8.44$, $p < .01$; the posterior corona radiata: $F(1, 86) = 7.79$, $p < .01$; the external capsule: $F(1, 86) = 13.59$, $p < .001$; and the posterior thalamic radiation: $F(1, 86) = 18.20$, $p < .001$. But there was no age-related MD difference in the splenium of the corpus callosum: $F(1, 86) = 0.13$, $p = .72$; the anterior limb of the internal capsule: $F(1, 86) = 1.78$, $p = .19$; the posterior limb of the internal capsule: $F(1, 86) = .2.98$, $p = 0.09$; and the retrolenticular part of the internal capsule: $F(1, 86) = 2.54$, $p = .11$. The comparison of association with age for the anterior and posterior corona radiata showed stronger age association in the anterior than in the posterior corona radiata ($p < .01$). The results suggested an age-related anterior-posterior gradient in MD increase in the corpus callosum and the corona radiata. Age-related increase in MD was evident in the genu but not the splenium of the corpus callosum, and stronger association between age and MD in the anterior than in the posterior corona radiata. The scatterplots of age and MD association in whole white matter tracts were presented in Figure 9.

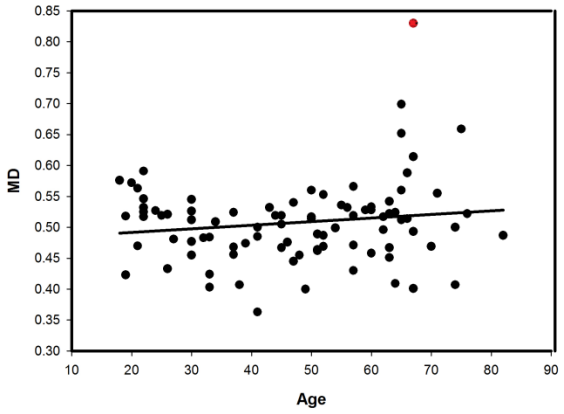
The analysis of nonlinear trend revealed nonlinear trajectory of age and MD in the genu of the corpus callosum, the superior corona radiata, and the external capsule. However, the linear term accounted for more variance than nonlinear term did (see Table 11).

There was a significant tract × sex × age interaction, $F(10, 860) = 2.23$, $p < .05$, indicating that the effect of age on MD was stronger in men than women in the anterior corona radiata: $F(1, 86) = 4.46$, $p < .05$. The effect of age on MD was significant in men, but not in women in the posterior corona radiata: $F(1, 86) = 4.50$, $p < .05$; and the external capsule: $F(1, 86) = 7.26$, $p < .01$. Significant tract × sex interaction, $F(10, 860) = 3.27$, $p < .001$, suggested that MD in the retrolenticular part of the internal capsule was higher in women than in men: $F(1, 86) = 4.31$, $p < .05$.

Figure 9. Association between age and MD in whole white matter

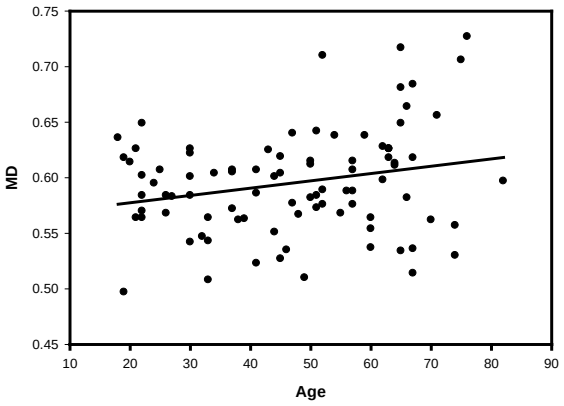


Anterior Limb of the Internal Capsule

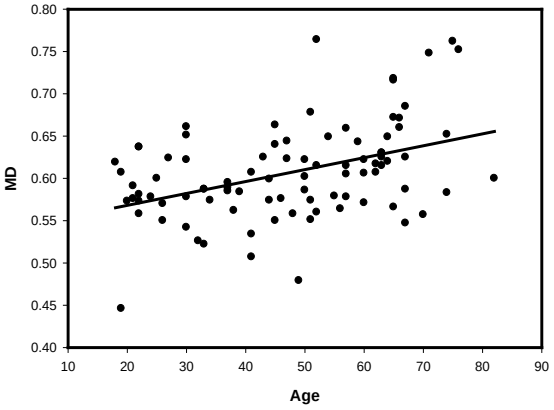


Posterior Limb of the Internal Capsule

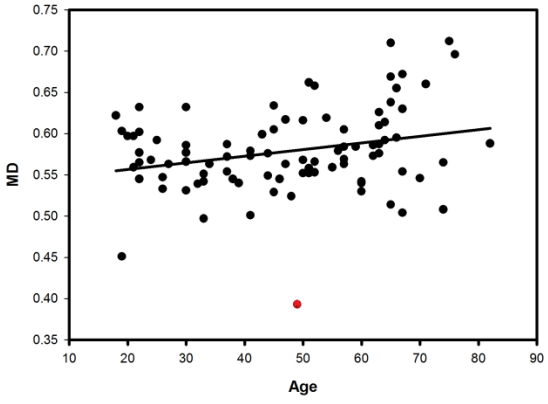
Superior Longitudinal Fasciculus



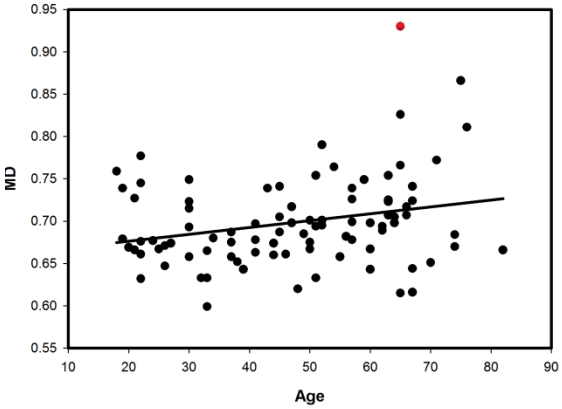
Anterior Corona Radiata

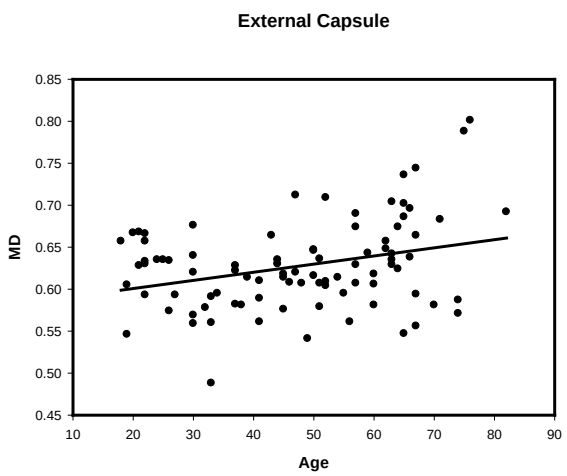


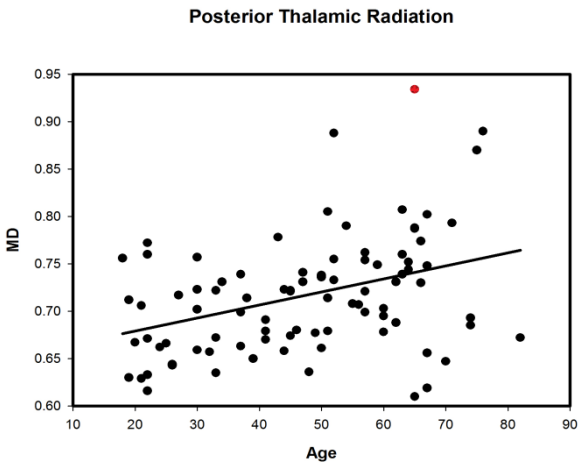
Superior Corona Radiata

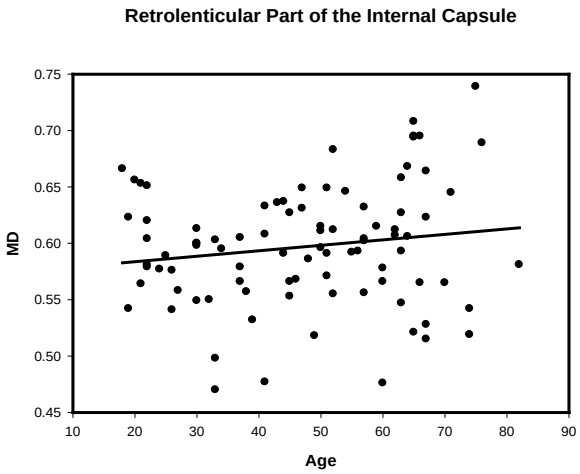


Posterior Corona Radiata









DA and age. Table 12 displayed the descriptive statistics and zero order age correlations of DA across white matter tracts.

Table 12. Descriptive statistics and age correlations of DA in whole white matter across white matter tracts

ROI	Mean	SD	CV	r_{age}	R^2 (linear)	R^2 (Quadratic)	F	p
CCg	1.18	0.09	0.08	**0.33**	0.11	0.16	4.68	<.05
CCs	1.25	0.10	0.08	-0.02	0.00	—	—	—
ALIC	0.94	0.10	0.10	-0.03	0.00	—	—	—
PLIC	0.97	0.11	0.11	**-0.27**	0.07	0.15	7.84	<.01
SLF	1.03	0.06	0.06	0.16	0.03	—	—	—
ACR	1.01	0.07	0.07	**0.23**	0.05	0.07	1.86	ns
SCR	1.01	0.07	0.07	0.15	0.01	—	—	—
PCR	1.16	0.07	0.06	**0.27**	0.07	0.15	7.78	<.01
EC	1.00	0.07	0.07	0.18	0.03	—	—	—
PTR	1.30	0.08	0.06	**0.27**	0.07	0.08	0.608	ns
RIC	1.07	0.08	0.07	0.02	0.00	—	—	—

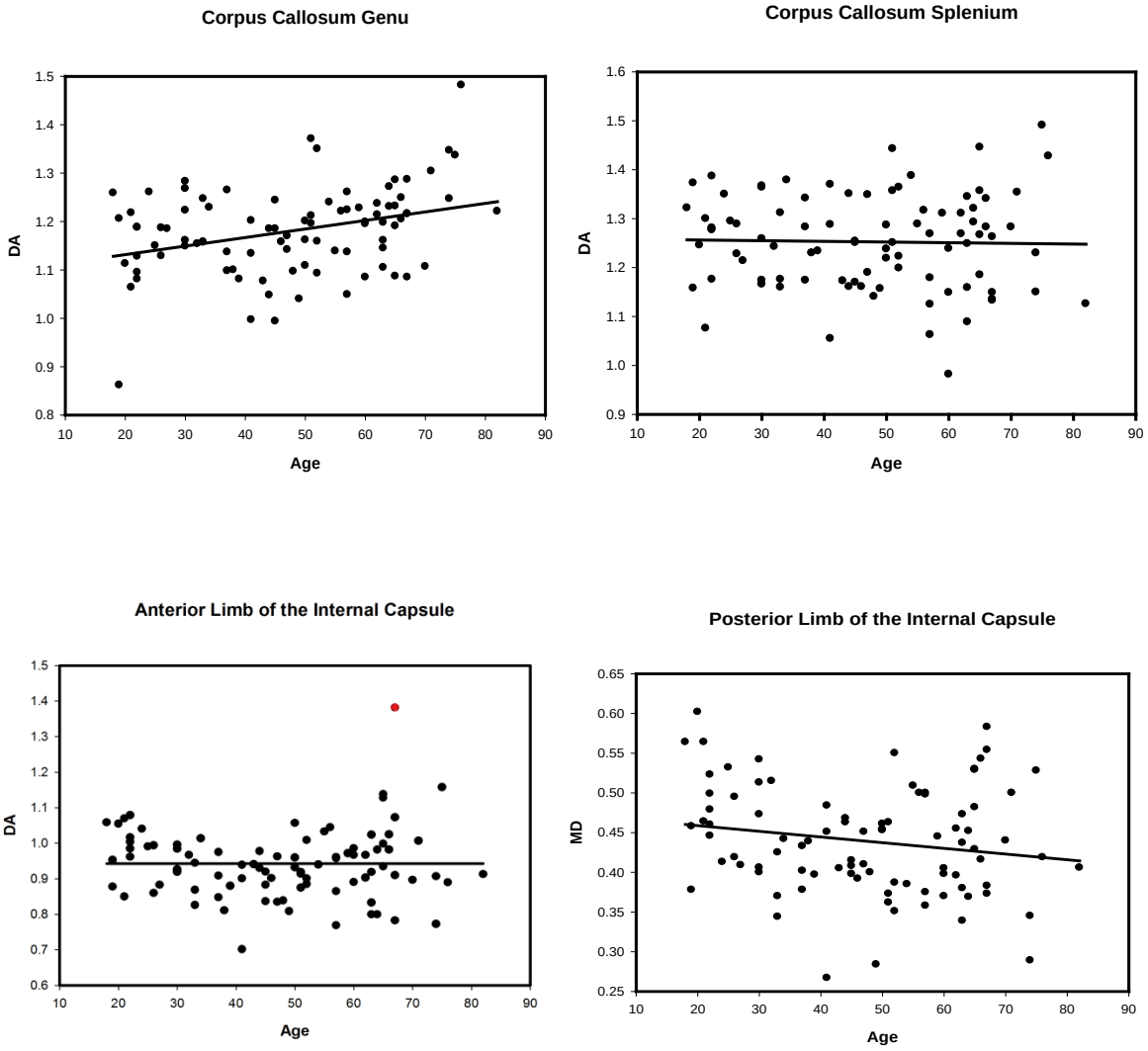
Note. CCg: the genu of the corpus callosum; CCs: the splenium of the corpus callosum; ALIC: the anterior limb of the internal capsule; PLIC: the posterior limb of the internal capsule; SLF: the superior longitudinal fasciculus; ACR: the anterior corona radiata; SCR: the superior corona radiata; PCR: the posterior corona radiata; EC: the external capsule; PTR: the posterior thalamic radiation; RIC: the retrolenticular part of the internal capsule; Significant linear age correlations are bolded; F test tests the significance of R square change with addition of polynomial term. —: not applicable.

GLM analysis revealed that neither main effect of age or sex, nor age × sex interaction was significant. There was a significant tract × age interaction, $F(10, 870) = 7.37$, $p < .001$, indicating that the effect of age differed across white matter tracts examined. Specifically, age-related increase in DA was observed in the genu of the corpus callosum: $F(1, 87) = 10.99$, $p = .001$; the anterior corona radiata: $F(1, 87) = 4.99$, $p < .05$; the posterior corona radiata: $F(1, 87) = 6.95$, $p = .01$; and the posterior thalamic radiation: $F(1, 87) = 7.00$, $p = .01$. There was age-related decrease in DA in the posterior limb of the internal capsule: $F(1, 87) = 7.10$, $p < .01$. However, there was no age-related DA difference in the external capsule: $F(1, 87) = 3.00$, $p = .09$; the

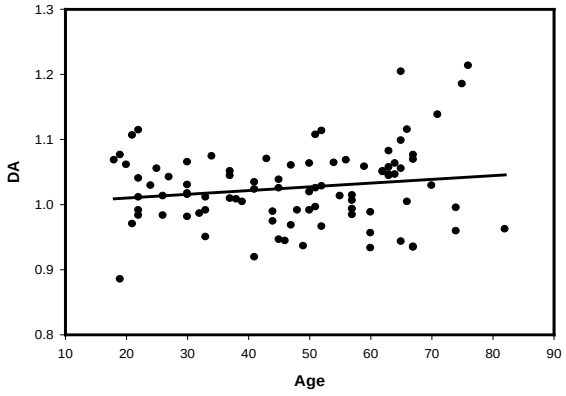
splenium of the corpus callosum: F (1, 87) =.05, p=.82; the anterior limb of the internal capsule: F (1, 87) =.12, p= .73; the superior longitudinal fasciculus: F (1, 87) =2.26, p= .14; the superior corona radiata: F (1, 87) =1.96, p=.17; and the retrolenticular part of the internal capsule: F (1, 87) =.02, p=.89. There was an age-related anterior-posterior gradient of increase in DA in the corpus callosum as evidenced by an age-related increase in DA in the genu but not the splenium of the corpus callosum. The scatterplots of age and DA association in whole white matter tracts were presented in Figure 10. The analysis of nonlinear trend revealed nonlinear trajectory of age and DA in the genu of the corpus callosum, the posterior limb of the internal capsule, and the posterior corona radiata. However, the linear term explained more variance in the genu of the corpus callosum than nonlinear term did (see Table 12).

Significant tract × sex interaction, F (10, 870) =2.56, p<.01, suggested that DA was higher in women than in men in the posterior limb of the internal capsule: F (1, 87) =4.08, p<.05 and the retrolenticular part of the internal capsule: F (1, 87) =4.73, p<.05.

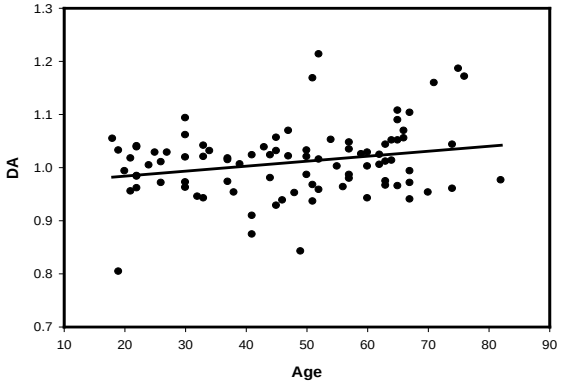
Figure 10. Association between age and DA in whole white matter



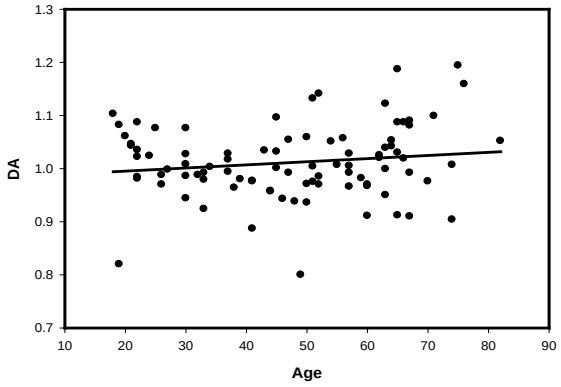
Superior Longitudinal Fasciculus



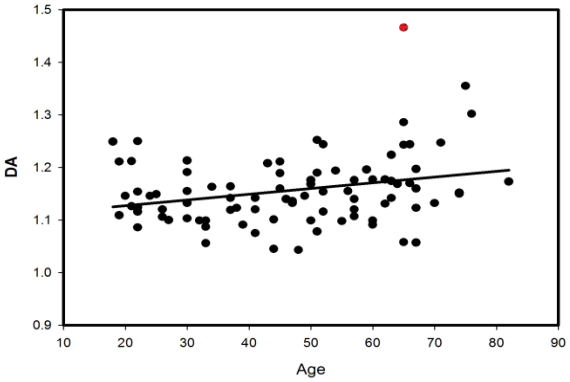
Anterior Corona Radiata



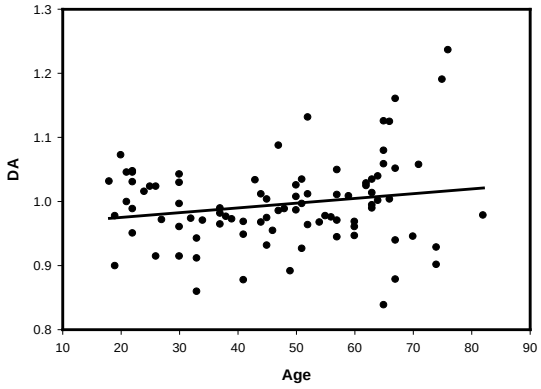
Superior Corona Radiata



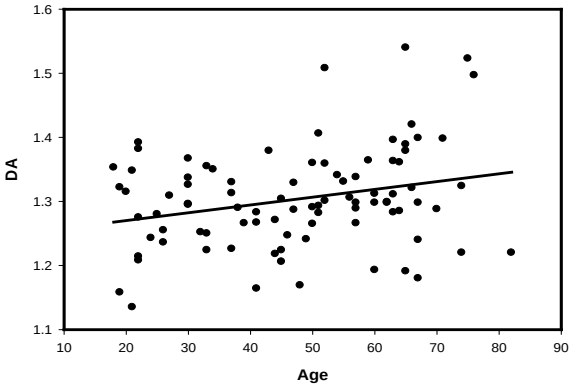
Posterior Corona Radiata

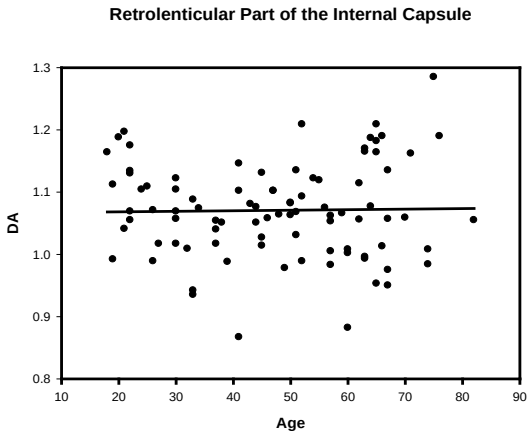


External Capsule



Posterior Thalamic Radiation





DR and age. Table 13 displayed the descriptive statistics and zero order age correlations of DR across white matter tracts.

Table 13. Descriptive statistics and age correlations of DR in whole white matter across white matter tracts

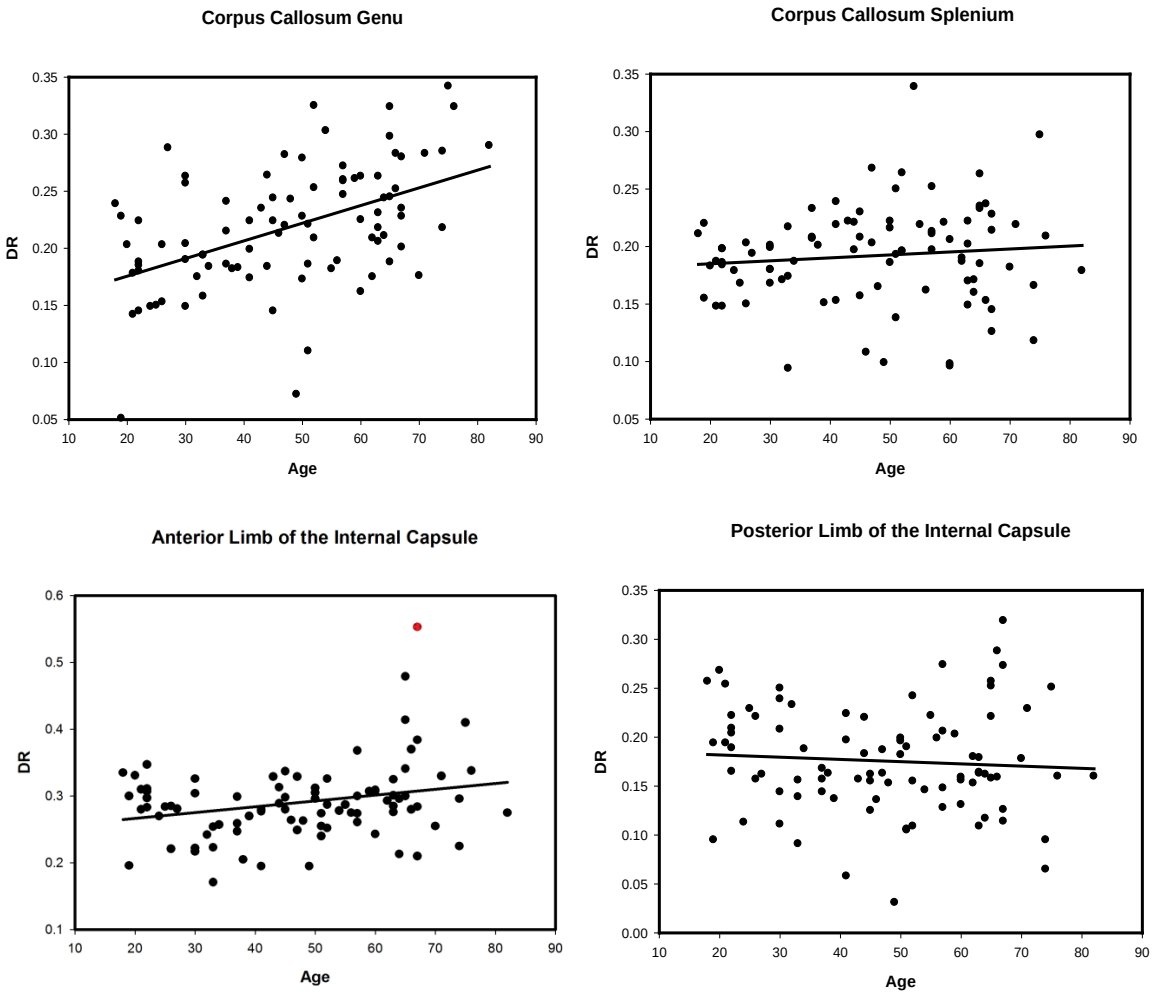
ROI	Mean	SD	CV	r_{age}	R^2 (linear)	R^2 (Quadratic)	F	p
CCg	0.22	0.05	0.25	**0.49**	0.24	0.25	0.88	ns
CCs	0.19	0.04	0.22	0.10	0.01	—	—	—
ALIC	0.29	0.06	0.20	**0.25**	0.06	0.10	3.94	0.05
PLIC	0.18	0.05	0.31	-0.07	0.01	—	—	—
SLF	0.38	0.05	0.12	**0.26**	0.07	0.09	1.53	ns
ACR	0.41	0.06	0.14	**0.50**	0.25	0.27	2.76	ns
SCR	0.36	0.05	0.13	**0.34**	0.12	0.13	1.73	ns
PCR	0.47	0.05	0.11	0.20	0.04	—	—	—
EC	0.44	0.05	0.11	**0.37**	0.14	0.23	10.83	0.001
PTR	0.42	0.06	0.15	**0.40**	0.16	0.16	0.37	ns
RIC	0.36	0.05	0.13	**0.24**	0.06	0.06	0.16	ns

Note. CCg: the genu of the corpus callosum; CCs: the splenium of the corpus callosum; ALIC: the anterior limb of the internal capsule; PLIC: the posterior limb of the internal capsule; SLF: the superior longitudinal fasciculus; ACR: the anterior corona radiata; SCR: the superior corona radiata; PCR: the posterior corona radiata; EC: the external capsule; PTR: the posterior thalamic radiation; RIC: the retrolenticular part of the internal capsule; Significant linear age correlations are bolded; F test tests the significance of R square change with addition of polynomial term. —: not applicable.

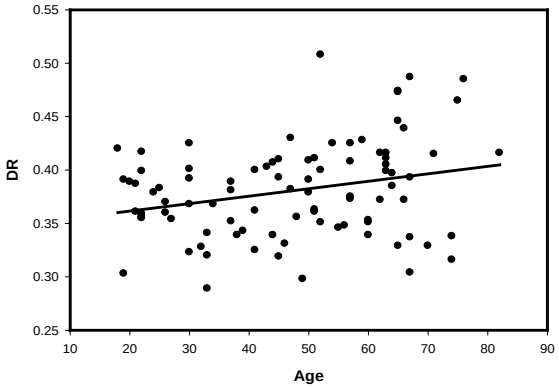
There was a significant main effect of age, $F(1, 86) = 13.73$, $p < .001$, suggesting that advanced age was associated with higher DR across the white matter tracts examined. Neither the main effect of sex nor an age × sex interaction was significant. There was a significant tract × age interaction, $F(10, 860) = 9.11$, $p < .001$, indicating that age exacted differential effects across white matter tracts. Specifically, age-related increase in DR was observed in the genu of the corpus callosum: $F(1, 86) = 29.49$, $p < .001$; the anterior limb of the internal capsule: $F(1, 86) = 7.36$, $p < .01$; the superior longitudinal fasciculus: $F(1, 86) = 8.39$, $p < .01$; the anterior corona radiata: $F(1, 86) = 34.55$, $p < .001$; the superior corona radiata: $F(1, 86) = 13.02$, $p = .001$; the posterior corona radiata: $F(1, 86) = 6.06$, $p < .05$; the external capsule: $F(1, 86) = 19.24$, $p < .001$; the posterior thalamic radiation: $F(1, 86) = 20.71$, $p < .001$, and the retrolenticular part of the internal capsule: $F(1, 86) = 6.23$, $p < .05$. But there was no age-related DR difference in the splenium of the corpus callosum: $F(1, 86) = 0.96$, $p = .33$; and the posterior limb of the internal capsule: $F(1, 86) = .56$, $p = .46$. There was an age-related anterior-posterior gradient in DR increase in the corpus callosum, the internal capsule, and the corona radiata as evidenced by an age-related increase in DR in the genu but not the splenium of the corpus callosum, in the anterior limb but not the posterior limb of the internal capsule, and in the anterior but not the posterior corona radiata. The scatterplots of age and DR association in whole white matter tracts were shown in Figure 11. The analysis of nonlinear trend revealed nonlinear trajectory of age and DR in the anterior limb of the internal capsule and the external capsule. However, the linear term accounted for more variance than nonlinear term did (see Table 13).

There was a significant tract × sex × age interaction, $F(10, 860) = 2.15$, $p < .05$, indicating that the effect of age on DR was stronger in men than women in the anterior corona radiata: $F(1, 86) = 4.90$, $p < .05$. The effect of age on DR was significant in men, but not in women in the posterior corona radiata: $F(1, 86) = 4.87$, $p < .05$; the external capsule: $F(1, 86) = 7.26$, $p < .01$; and the posterior thalamic radiation: $F(1, 86) = 4.33$, $p < .05$. Significant tract × sex interaction, $F(10, 860) = 2.82$, $p < .01$, suggested that DR in the anterior limb of the internal capsule was higher in women than in men: $F(1, 86) = 4.02$, $p < .05$.

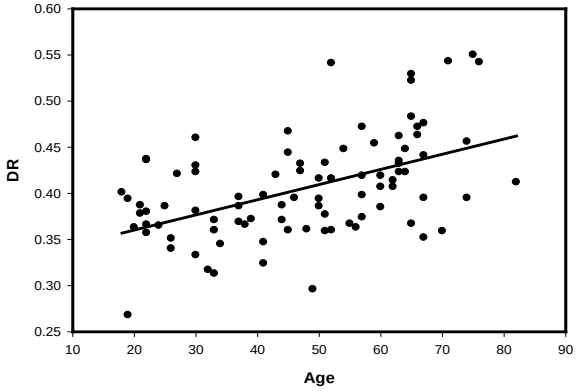
Figure 11. Association between age and DR in whole white matter



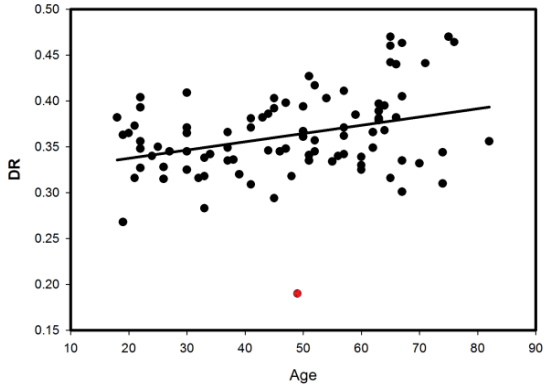
Superior Longitudinal Fasciculus



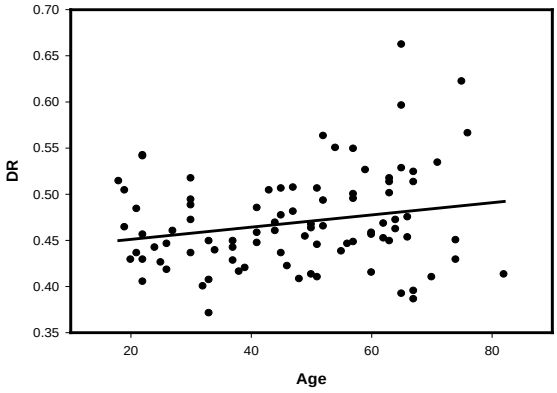
Anterior Corona Radiata



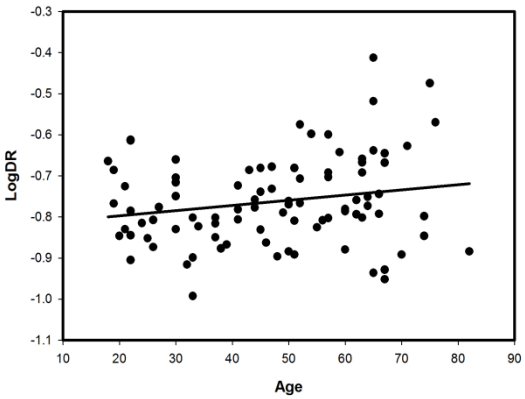
Superior Corona Radiata

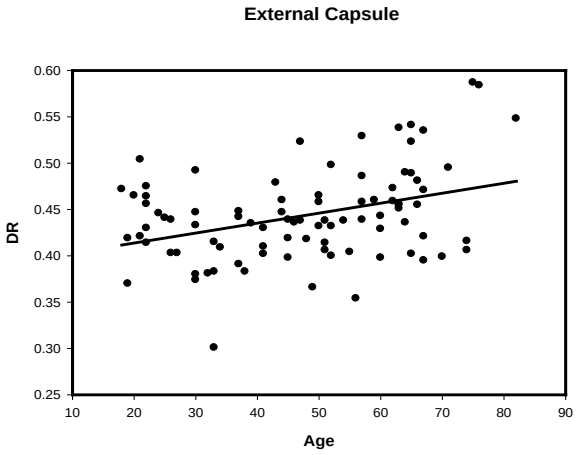


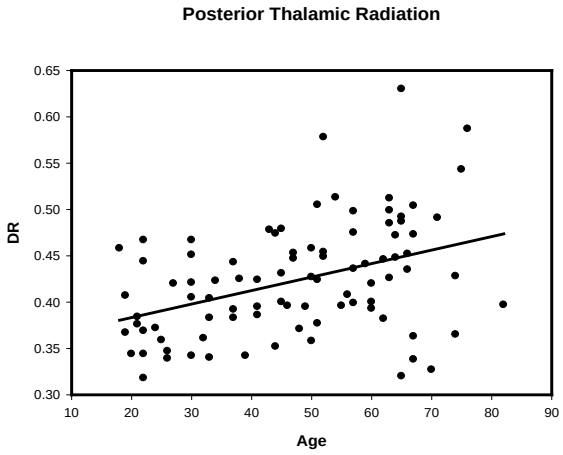
Posterior Corona Radiata

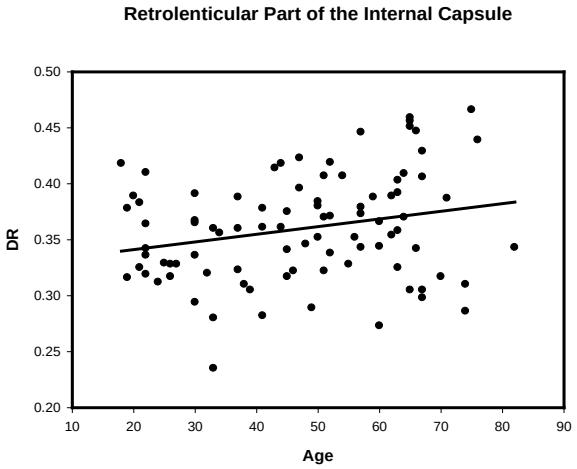


Posterior Corona Radiata









Comparison of age-DTI correlations in normal-appearing and whole white matter

Correlations between age and DTI indices in normal-appearing and whole white matter were compared using Steiger's Z and the results was displayed in table 14 and 15, For FA, age correlation was stronger in the anterior limb of the internal capsule and the superior corona radiata, but weaker in the posterior limb of the internal capsule in whole than in normal-

appearing white matter. For MD, age correlation was stronger in the anterior corona radiata in whole than in normal-appearing white matter (see table 14).

Table 14. Comparison of correlations between age with FA and MD across white matter tracts in normal-appearing and whole white matter

	ROI	r_{ageN}	r_{ageW}	Steiger's Z_1	p_1	Steiger's Z_2	p_2
FA	CCg	**-0.44**	**-0.45**	-.23	ns	.23	ns
	CCs	0.02	-0.17	-1.59	ns	2.01	<.05
	ALIC	**-0.21**	**-0.33**	-2.48	<.05	2.48	<.05
	PLIC	**0.38**	-0.06	3.62	<.01	4.90	<.01
	SLF	-0.19	**-0.21**	-.33	ns	.33	ns
	ACR	**-0.51**	**-0.55**	-.87	ns	.87	ns
	SCR	-0.02	**-0.34**	-3.45	<.01	3.45	<.01
	PCR	0.11	-0.11	0	ns	2.21	<.05
	EC	**-0.24**	**-0.31**	-1.05	ns	1.05	ns
	PTR	**-0.39**	**-0.37**	.31	ns	-.31	ns
	RIC	-0.20	**-0.26**	-1.29	ns	1.29	ns
MD	CCg	**0.41**	**0.47**	-1.28	ns	-1.28	ns
	CCs	0.15	0.04	1.31	ns	1.31	ns
	ALIC	0.12	0.12	0	ns	0	ns
	PLIC	**0.26**	-0.18	.82	ns	4.37	<.01
	SLF	0.09	**0.24**	-1.42	ns	-1.42	ns
	ACR	0.17	**0.42**	-2.52	<.05	-2.52	<.05
	SCR	**0.28**	**0.27**	.08	ns	.08	ns
	PCR	**0.22**	**0.24**	-.14	ns	-.14	ns
	EC	0.13	**0.31**	-1.87	ns	-1.87	ns
	PTR	-0.17	**0.38**	-1.58	ns	-3.48	<.01
	RIC	0.10	0.16	-.97	ns	-.97	ns

Note. CCg: the genu of the corpus callosum; CCs: the splenium of the corpus callosum; ALIC: the anterior limb of the internal capsule; PLIC: the posterior limb of the internal capsule; SLF: the superior longitudinal fasciculus; ACR: the anterior corona radiata; SCR: the superior corona radiata; PCR: the posterior corona radiata; EC: the external capsule; PTR: the posterior thalamic radiation; RIC: the retrolenticular part of the internal capsule; Significant linear age correlations are bolded; r_{ageN}:association with age in normal-appearing white matter; r_{ageW} :association with age in whole white matter. Steiger's Z_1 and p_1 reflects testing the difference in absolute r value regardless of sign; Steiger's Z_2 and p_2 reflects testing the difference in signed r value.

Table 15. Comparison of correlations between age with DA and DR across white matter tracts in normal- appearing and whole white matter

	ROI	r_{ageN}	r_{ageW}	Steiger's Z_1	p_1	Steiger's Z_2	p_2
DA	CCg	**0.25**	**0.33**	-1.53	ns	-1.53	ns
	CCs	0.09	-0.02	.73	ns	1.15	ns
	ALIC	-0.07	-0.03	.53	ns	-.53	ns
	PLIC	**0.30**	**-0.27**	.25	ns	4.50	<.01
	SLF	0.01	0.16	-1.24	ns	-1.24	ns
	ACR	-0.09	**0.23**	-1.11	ns	-2.50	<.05
	SCR	**0.22**	0.15	.50	ns	.50	ns
	PCR	0.20	**0.27**	-.47	ns	-.47	ns
	EC	0.00	0.18	-1.61	ns	-1.61	ns
	PTR	**-0.28**	**0.27**	.08	ns	-3.31	<.01
	RIC	-0.03	0.02	.14	ns	-.68	ns
DR	CCg	**0.43**	**0.49**	-2.0	<.05	-2.0	<.05
	CCs	0.17	0.10	1.41	ns	1.41	ns
	ALIC	**0.25**	**0.25**	0	ns	0	ns
	PLIC	0.18	-0.07	1.77	ns	4.00	<.01
	SLF	0.16	**0.26**	-1.24	ns	-1.24	ns
	ACR	**0.32**	**0.50**	-2.38	<.05	-2.38	<.05
	SCR	**0.32**	**0.34**	-.20	ns	-.20	ns
	PCR	**0.22**	0.20	.15	ns	.15	ns
	EC	**0.22**	**0.37**	-1.87	ns	-1.87	ns
	PTR	0.02	**0.40**	-3.0	<.01	-3.00	<.01
	RIC	0.19	**0.24**	-1.07	ns	-1.07	ns

Note. CCg: the genu of the corpus callosum; CCs: the splenium of the corpus callosum; ALIC: the anterior limb of the internal capsule; PLIC: the posterior limb of the internal capsule; SLF: the superior longitudinal fasciculus; ACR: the anterior corona radiata; SCR: the superior corona radiata; PCR: the posterior corona radiata; EC: the external capsule; PTR: the posterior thalamic radiation; RIC: the retrolenticular part of the internal capsule; Significant linear age correlations are bolded; r_{ageN}: association with age in normal-appearing white matter; r_{ageW} :association with age in whole white matter. Steiger's Z1 and p1 reflects testing the difference in absolute r value regardless of sign; Steiger's Z2 and p2 reflects testing the difference in signed r value.

Although there was no difference in the strength of associations between age and DA in normal-appearing and whole white matter, significant difference in associations with age was

observed in these two types of white matter for several white matter tracts and two of them showed significant increase in positive association with age. For DR, age correlation was stronger in the genu of the corpus callosum, the anterior corona radiata, and the posterior thalamic radiation in whole than in normal-appearing white matter (see table 15). In sum there is an increase in age-related differences in DTI indices from whole rather than from normal-appearing white matter.

Association between DTI Indices and RT Components

Voxel-wise statistical analysis

The voxel-wise cross-subject statistics were computed in thresholded skeletonized DTI maps. Voxel-wise correlations between each DTI index and age, and between DTI indices and RT components with and without controlling for age were computed with 5000 permutations and threshold-free cluster enhancement (TFCE). The p-values corrected for multiple comparisons via Bonferroni adjustment of the nominal $p< 0.05$ were considered significant.

DTI indices and age. The voxel-wise analysis showed that advanced age was associated with decreased FA, increased MD, DA, and DR across a wide variety of white matter tracts in white matter regions with and without WMH (see table 16 for the details).

Table 16. DTI indices showing significant correlation with age across white matter tracts

Tracts		FA	MD	DA	DR	MFA	MMD	MDA	MDR
CCg		—	+	+	+	—	+		
CCb		—	+	+	+	—	+	+	+
CCs		—	+		+	—	+	+	+
SLF	L	—	+		+	—	+	+	+
	R	—	+	+	+	—	+	+	+
ACR	L	—	+	+	+	—	+		
	R	—	+	+	+	—	+		
SCR	L	—	+	+	+	—	+	+	+
	R	—	+	+	+	—	+	+	+
PCR	L	—	+		+		+	+	+
	R	—	+		+	—	+	+	+
ALIC	L	—	+	+	+	—	+	+	
	R	—	+	+	+		+	+	
PLIC	L	—	+				+	+	+
	R					—	+	+	+
RIC	L	—	+		+	—	+		
	R	—	+		+	—	+		
EC	L	—	+	+	+	—	+		
	R	—	+	+	+	—	+		
PTR	L	—	+		+				
	R	—	+		+	—			
CP	L	—	+			—		+	
	R					—		+	
Cing	L	—	+		+		+		
	R	—	+		+				
Fornix		—							
Fornix/ ST	L		+						
	R		+			—			
SS	L	—	+		+	—			
	R	—	+		+	—			
SFOF	L	—	+	+	+	—	+	+	+
	R	—	+	+	+		+		
Tapetum	L								
	R	—	+		+	—			
UF	L		+						
	R								
CST	L		+				+	+	+
	R						+	+	+
MCP							+	+	+

Note: CCg CCb CCs: genu, body, and splenium of the corpus callosum respectively; SLF: superior longitudinal fasciculus; ACR: anterior corona radiata; SCR: superior corona radiata; PCR: posterior corona radiata; ALIC: anterior limb of the internal capsule; PLIC: posterior limb of the internal capsule; RIC: retrolenticular part of the internal capsule; EC: external capsule; PTR: posterior thalamic radiation; CP: cerebral peduncle; Cing: Cingulum; Fornix/ ST: Fornix (cres) / Stria terminalis; SS: sagittal stratum; SFOF: superior fronto-occipital fasciculus; UF: uncinate fasciculus; CST: corticospinal tract; MCP: middle cerebellar peduncle; L: left; R: right; MFA: WMH masked FA; MMD; WMH masked MD; MDA: WMH masked DA; MDR: WMH masked DR; —: negative correlation; +: positive correlation.

DTI indices and drift rate. There were no clusters showing significant correlation between drift rate and any DTI indices in normal-appearing white matter with and without controlling for age. After controlling for age, drift rate was positively associated with mean diffusivity in the right anterior corona radiata; and positively associated with axial diffusivity in the genu and body of the corpus callosum, the corona radiata (anterior and right superior), right anterior limb of the internal capsule, and right external capsule in whole white matter (see table 17).

Table 17. Regional DTI indices showing significant correlation with drift rate after controlling for age

Tracts		FA	MD	DA	DR	MFA	MMD	MDA	MDR
CCg				+					
CCb				+					
ACR	L			+					
	R		+	+					
SCR	L								
	R			+					
ALIC	L								
	R			+					
EC	L								
	R			+					

Note: CCg CCb : genu and body of the corpus callosum respectively; SLF: superior longitudinal fasciculus; ACR: anterior corona radiata; SCR: superior corona radiata; ALIC: anterior limb of the internal capsule; EC: external capsule; L: left; R: right; MFA: WMH masked FA; MMD; WMH masked MD; MDA: WMH masked DA; MDR: WMH masked DR; —: negative correlation; +: positive correlation.

DTI indices and response conservativeness. There were no clusters showing significant correlation between any DTI indices and response conservativeness.

DTI indices and non-decision time. Increased non-decision time was associated with decreased FA, increased MD and DR across a variety of white matter tracts in whole and normal-appearing white matter. In addition, increased non-decision time was associated with

increased DA of various white matter tracts in normal –appearing white matter (see table 18). After controlling for age, non-decision time was positively associated with MD, DA, and DR in normal-appearing white matter only (see table 19).

Table 18. Regional DTI indices showing significant correlation with non-decision time

Tracts		FA	MD	DA	DR	MFA	MMD	MDA	MDR
CCg		—	+		+	—	+		+
CCb		—	+		+	—	+	+	+
CCs		—			+		+	+	+
SLF	L	—			+		+	+	+
	R	—			+		+	+	+
ACR	L	—	+		+	—	+		+
	R	—	+		+	—	+		+
SCR	L	—	+		+		+	+	+
	R	—	+		+		+	+	+
PCR	L	—			+		+	+	+
	R	—			+		+	+	+
ALIC	L	—			+		+	+	+
	R	—	+		+		+	+	+
PLIC	L	—					+	+	+
	R	—			+		+	+	+
RIC	L	—			+		+	+	+
	R	—			+		+	+	+
EC	L	—	+		+		+	+	+
	R	—			+		+		+
PTR	L	—			+				+
	R	—			+		+	+	+
CP	L	—						+	+
	R	—						+	
Cing	L	—			+		+		+
	R	—			+		+		+
Fornix/ ST	L	—			+				+
	R	—			+				+
SS	L	—			+				+
	R	—			+				+
UF	L	—							+
	R								
CST	L						+		+
	R	—					+	+	
MCP							+	+	+
SCP	L	—							
	R						+		

Note: CCg CCb CCs: genu, body, and splenium of the corpus callosum respectively; SLF: superior longitudinal fasciculus; ACR: anterior corona radiata; SCR: superior corona radiata; PCR: posterior corona radiata; ALIC: anterior limb of the internal capsule; PLIC: posterior limb of the internal capsule; RIC: retrolenticular part of the internal capsule; EC: external capsule; PTR: posterior thalamic radiation; CP: cerebral peduncle; Cing: Cingulum; Fornix/ ST: Fornix (cres) / Stria terminalis; SS: sagittal stratum; UF: uncinate fasciculus; CST: corticospinal tract; MCP: middle cerebellar peduncle; SCP: superior cerebellar peduncle; L: left; R: right; MFA: WMH masked FA; MMD; WMH masked MD; MDA: WMH masked DA; MDR: WMH masked DR; —: negative correlation; +: positive correlation.

Table 19. Regional DTI indices showing significant correlation with non-decision time after controlling for age

Tracts		FA	MD	DA	DR	MFA	MMD	MDA	MDR
CCg							+		+
CCb							+	+	+
CCs							+		+
SLF	L						+		+
	R						+	+	+
ACR	L						+		+
	R						+		+
SCR	L						+	+	+
	R						+	+	+
PCR	L						+		+
	R						+		+
ALIC	L								
	R						+		+
PLIC	L						+		+
	R						+		+
RIC	L								
	R						+		
EC	L							+	+
	R								
PTR	L						+		+
	R								+

Note: CCg CCb CCs: genu, body, and splenium of the corpus callosum respectively; SLF: superior longitudinal fasciculous; ACR: anterior corona radiata; SCR: superior corona radiata; PCR: posterior corona radiata; ALIC: anterior limb of the internal capsule; PLIC: posterior limb of the internal capsule; RIC: retrolenticular part of the internal capsule; EC: external capsule; PTR: posterior thalamic radiation; SS: sagittal stratum; L: left; R: right; MFA: WMH masked FA; MMD; WMH masked MD; MDA: WMH masked DA; MDR: WMH masked DR; —: negative correlation; +: positive correlation.

Path analysis

SEM was used to conduct path analyses aimed to assess whether some of the age differences in RT components are associated with individual differences in DTI indices (FA, MD, AD, or RD) of particular white matter tracts. In path models, the flow of variance is

assumed unidirectional with downstream variables predicted by upstream variables. However, it should be noted that path analysis is correlational in nature and that the analysis itself cannot uncover causal relationships among the variables. Recent works have further demonstrated that cross-sectional estimates cannot accurately estimate longitudinal mediation effects in aging and development (Lindenberger, von Oertzen, Ghisletta, & Hertzog, 2011; Maxwell & Cole, 2007). Thus, the term "mediation" or "mediating" in the following path analysis should only be interpreted that individual differences in one variable are associated with individual differences in another variable. SEM was performed using Mplus program (Muthén & Muthén, 2010). Bias-corrected bootstrap approach was used to estimate indirect effects. The advantage of this approach in assessing indirect effects in mediation analysis has been widely recognized (MacKinnon & Fairchild, 2009). Maximum likelihood estimation was used. Model is considered fit if χ^2 is nonsignificant or χ^2/df of less than 2, both comparative fit index (CFI) and Tucker–Lewis Index (TLI) are more than .95, and root mean square error of approximation (RMSEA) is less than .06 (Hu & Bentler, 1999).

The mediation effect of each DTI index was evaluated separately because each of them reflects different property of white matter (Burgmans et al., 2011). Only the white matter tracts and RT components that show significant association with age from previous analysis were included in the SEM analysis. Due to the limited sample size, three sets of models were used for three RT components separately. Each set of analyses started with a full model, in which all paths from upstream to downstream variables were freely estimated. Then, a hypothesis based and statistically grounded target model was constructed by posing restriction on paths untenable

or insignificant. Constrained or unconstrained models were created by eliminating statistically non-significant path and adding paths based on modification indices generated from previous analyses and theoretical perspective. Finally, the goodness of fit among these hierarchical models was compared and a most parsimonious and best fit model was obtained.

Age-related differences in microstructural integrity of white matter might be influenced by individual differences in some aspect of cognition (e.g. IQ) (Chiang et al., 2011), which was not included in estimated models. Therefore, two alternative models (a reversed model and a correlation model) for each set of models were also tested based on the final path model. The model specification was the same as each final model except reversing the path direction between measures of RT components and DTI indices of white matter tracts in the reverse model and replacement of correlation for directional paths in the correlation model.

To incorporate TBSS findings, DTI indices from the following white matter tracts were included: the anterior, superior, and posterior corona radiata; the external capsule; the posterior thalamic radiation, and the retrolenticular part of the internal capsule. I expected that DTI indices in all these tracts would be more likely associated with non-decision time as suggested by TBSS results. In addition, DTI indices in the anterior and superior corona radiata would be more likely associated with drift rate because they continue with similar part of the centrum semiovale, and with response conservativeness due to their connections with the anterior limb of the internal capsule.

In normal-appearing white matter

Drift rate. The first set of model included four subsets that investigate the mediation role of FA, MD, DA, and DR in normal-appearing white matter on age difference in drift rate. For FA, the following white matter tracts were included based on their zero-order correlations with age: the genu of the corpus callosum, the anterior and posterior limb of the internal capsule, the anterior corona radiata, the external capsule, and the posterior thalamic radiation. The initial full model included the following paths: age to all other variables, FA of selected white matter tracts to drift rate. The target model was constrained in the following way based on the previous hypothesis: paths between FA of the anterior and posterior limb of the internal capsule, the external capsule, and the posterior thalamic radiation and drift rate were set to zero (Figure 12: Model MFAv_1). This model fitted the data well: $\chi 2$ was not significant ($\chi 2$=1.48, df=4, p=.83); CFI=1.0; TLI=1.06; RMSEA=.00, and removal of the non-significant paths did not worsen the fit of the reduced model (Figure 12: Model MFAv_2): $\Delta\chi 2$ (2) =1.45, p>.05. As shown in these models, advanced age was associated with decreased FA in the genu of the corpus callosum, the anterior limb of the internal capsule, the anterior corona radiata, the external capsule, and the posterior thalamic radiation; and increased FA in the posterior limb of the internal capsule. Older age was also associated with lower drift rate. However, there was no association between age difference in FA of any selected white matter tract and age-related reduction in drift rate.

For MD, the following tracts were involved: the genu of the corpus callosum, the posterior limb of the internal capsule, the superior and posterior corona radiata. The initial model included the following paths: age to all other variables, MD of selected white matter tracts to drift rate. The target model was constrained based on the previous hypothesis so that paths

between MD of the posterior limb of the internal capsule and the posterior corona radiata and drift rate were set to zero. The fitness of the model was not very well: $\chi 2$ was not significant ($\chi 2$=8.52, df=5, p=.13); CFI=.99; TLI=.96; RMSEA=.09 (Figure 12: Model MMDv_1). The reduced model by removing the non-significant paths fitted the data reasonably well: $\chi 2$ was not significant ($\chi 2$=8.63, df=6, p=.20); CFI=.99; TLI=.98; RMSEA=.07 (Figure 12: Model MMDv_2). As demonstrated in these models, advanced age was associated with increased MD in all the examined white matter tracts. Older age was associated with lower drift rate and increased MD in the genu of the corpus callosum predicted higher drift rate ($p<.05$).

Both the reversed model and correlational model by reversing the direction between MD in the genu of the corpus callosum and drift rate or correlating these two variables did not change the model fit. The directional path from drift rate to MD in the genu of the corpus callosum was significant and there was significant correlation between these two variables (Figure 12: MMDv_3 and MMDv_4). Because all three models fitted the data well, the correlational model (Figure 12: MMDv_4) was preferred in such situation.

IQ was introduced to investigate whether the association between MD of the genu of the corpus callosum and drift rate was due to the influence of this third variable. The model fitted the data well: $\chi 2$ was not significant ($\chi 2$=10.88, df=11, p=.45); CFI=1.00; TLI=1.00; RMSEA=.00. The results showed that advanced age was associated with lower IQ ($p<.001$), but IQ was related to neither MD of the genu of the corpus callosum nor drift rate.

For DA, the involved tracts included the genu of the corpus callosum, the posterior limb of the internal capsule, the superior corona radiata, and the posterior thalamic radiation. The

initial model included the following paths: age to all other variables, DA of selected white matter tracts to drift rate. The model was constrained based on the previous hypothesis so that paths between DA of the posterior limb of the internal capsule and the posterior thalamic radiation and drift rate were set to zero (Figure 12: Model MDAv_1). This model fitted the data well: $\chi 2$ was not significant ($\chi 2$=2.17, df=5, p=.83); CFI=1.0; TLI=1.05; RMSEA=.00. The reduced model by removing the non-significant paths did not show worse fit (Figure 12: Model MDAv_2): $\Delta\chi 2$ (1) =.18, p>.05. As shown in these models, advanced age was associated with increased DA in the genu of the corpus callosum, the posterior limb of the internal capsule, and the superior corona radiata; but decreased DA in the posterior thalamic radiation. Older age was associated with lower drift rate and higher DA in the genu of the corpus callosum tended to predict greater drift rate (p=.051). Both the reversed model and correlational model by reversing the direction between DA in the genu of the corpus callosum and drift rate or correlating these two variables fitted the data equally well: $\chi 2$ was not significant ($\chi 2$=2.35, df=6, p=.89); CFI=1.0; TLI=1.06; RMSEA=.00. The directional path from drift rate to DA in the genu of the corpus callosum was significant and there was significant correlation between these two variables (Figure 12: MDAv_3 and MDAv_4). Therefore, it is safe to conclude that age-related increase in DA in the genu of the corpus callosum was associated with higher drift rate. The potential influence of IQ on the association between DA of the genu of the corpus callosum and drift rate was also tested in a SEM model. The model fitted the data well: $\chi 2$ was not significant ($\chi 2$=9.58, df=12, p=.65); CFI=1.00; TLI=1.02; RMSEA=.00. The results showed that advanced age was associated with

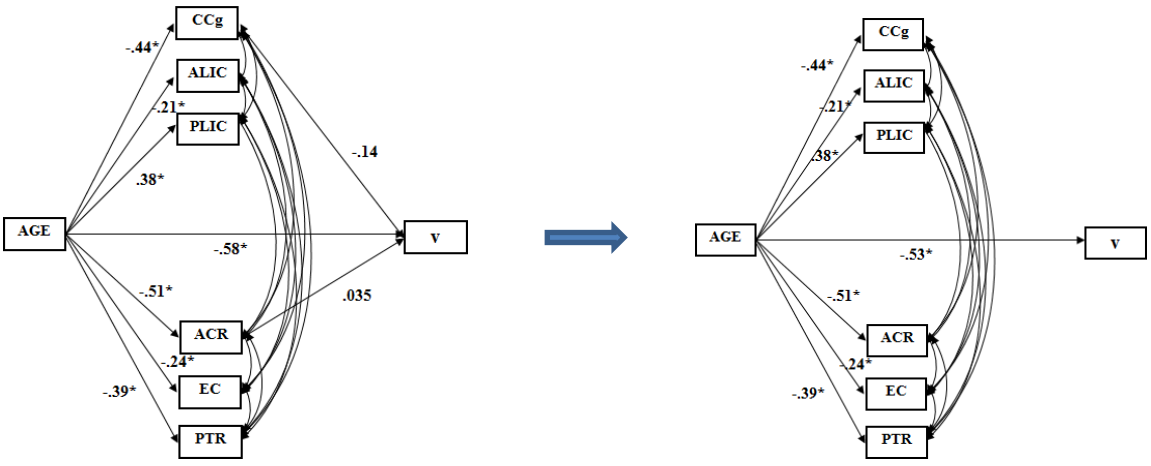
lower IQ ($p<.001$), but there was no association between IQ with either AD of the genu of the corpus callosum or drift rate.

The following tracts were involved for DR: the genu of the corpus callosum; the anterior limb of the internal capsule; the anterior, superior, and posterior corona radiata; and the external capsule. The initial model included the following paths: age to all other variables, DR of these selected white matter tracts to drift rate. Based on the previous hypothesis, the model was constrained so that paths between DR of the anterior limb of the internal capsule, the posterior corona radiata, and the external capsule and drift rate were set to zero (Figure 12: Model MDRv_1). The model fitted the data well: $\chi 2$ was not significant ($\chi 2=3.58$, df=3, $p=.31$); CFI=1.0; TLI=.99; RMSEA=.05. The reduced model by removing the non-significant paths did not show worse fit (Figure 12: Model MDRv_2): $\Delta\chi 2$ (2) =.08, $p>.05$. As demonstrated in these models, advanced age was associated with higher DR in the genu of the corpus callosum; the anterior limb of the internal capsule; the anterior, superior and posterior corona radiata; and the external capsule. Older age was associated with lower drift rate and higher DR in the genu of the corpus callosum predicted larger drift rate ($p<.05$). Both the reversed model and correlational model fitted the data equally well: $\chi 2$ was not significant ($\chi 2=5.13$, df=5, $p=.40$); CFI=1.0; TLI=1.0; RMSEA=.02. However, neither the directional path nor correlation between drift rate and DR in the genu of the corpus callosum was significant (Figure 12: MDRv_3 and MDRv_4). The test of indirect effect between age and drift rate revealed that DR of the genu of the corpus callosum mediated the effect of age on drift rate (standard estimate=.09, $p<.05$, 95% CI= .002-.167). Thus, part of age-related decrease in drift rate was attenuated by age-related increase in

DR in the genu of the corpus callosum. The SEM model testing a potential influence of IQ on the association between DR of the genu of the corpus callosum and drift rate fitted the data well: $\chi 2$ was not significant ($\chi 2$=15.20, df=13, p=.29); CFI=1.00; TLI=.99; RMSEA=.04. The results did not show any association between IQ with either DR of the genu of the corpus callosum or drift rate.

Figure 12. Structural models for the relationships between DTI indices of white matter tracts in normal-appearing white matter and drift rate (v)

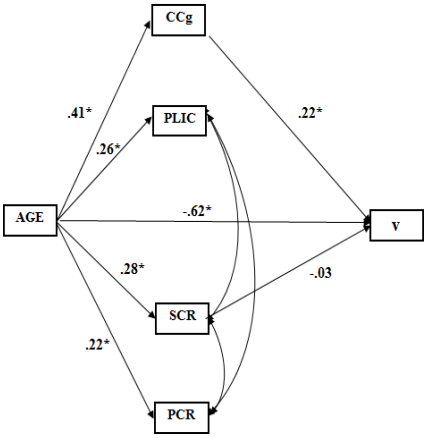
Path model of age, FA in normal-appearing white matter, and drift rate



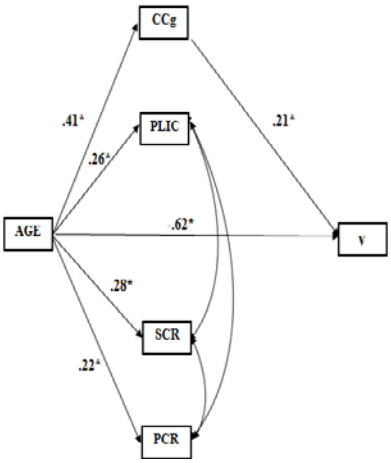
Model MFAv_1 Model MFAv_2

Note: CCg: genu of the corpus callosum; ALIC: anterior limb of the internal capsule; PLIC: posterior limb of the internal capsule; ACR: anterior corona radiata; EC: external capsule; PTR: posterior thalamic radiation.

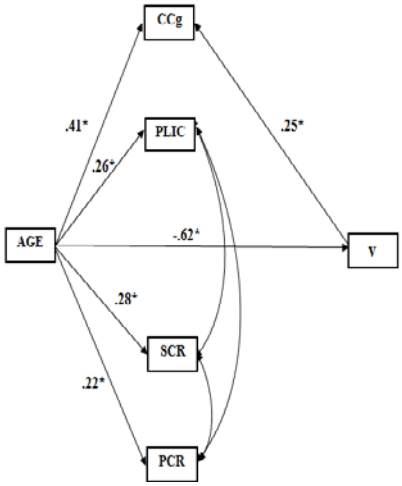
Path model of age, MD in normal-appearing white matter, and drift rate



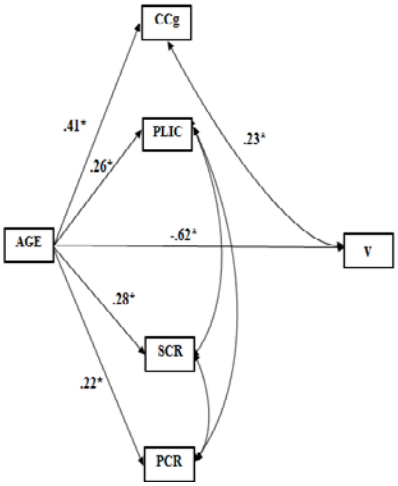
Model MMDv_1



Model MMDv_2



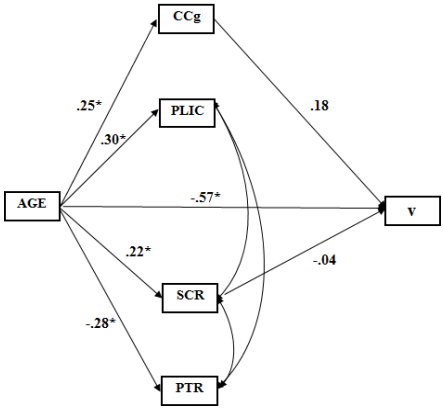
Model MMDv_3



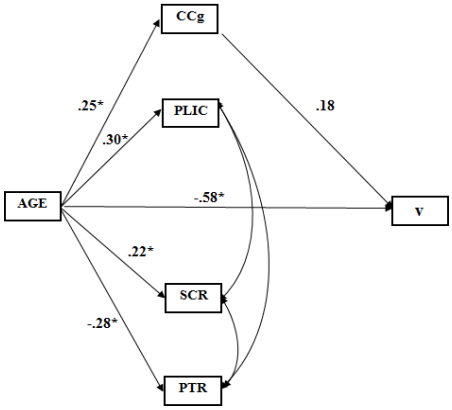
Model MMDv_4

Note: CCg: genu of the corpus callosum; PLIC: posterior limb of the internal capsule; SCR: superior corona radiata; PCR: posterior corona radiata.

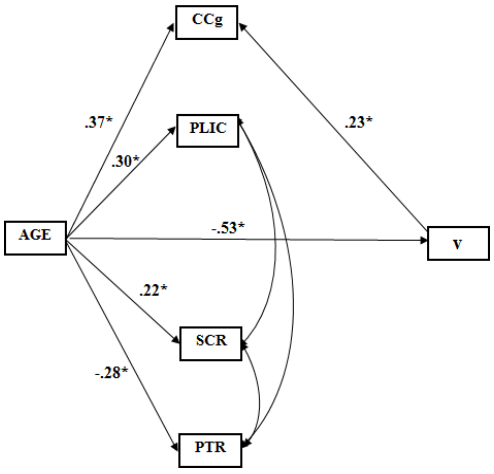
Path model of age, DA in normal-appearing white matter, and drift rate



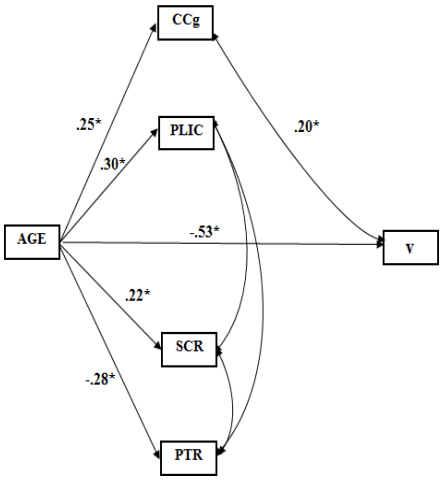
Model MDAv_1



Model MDAv_2



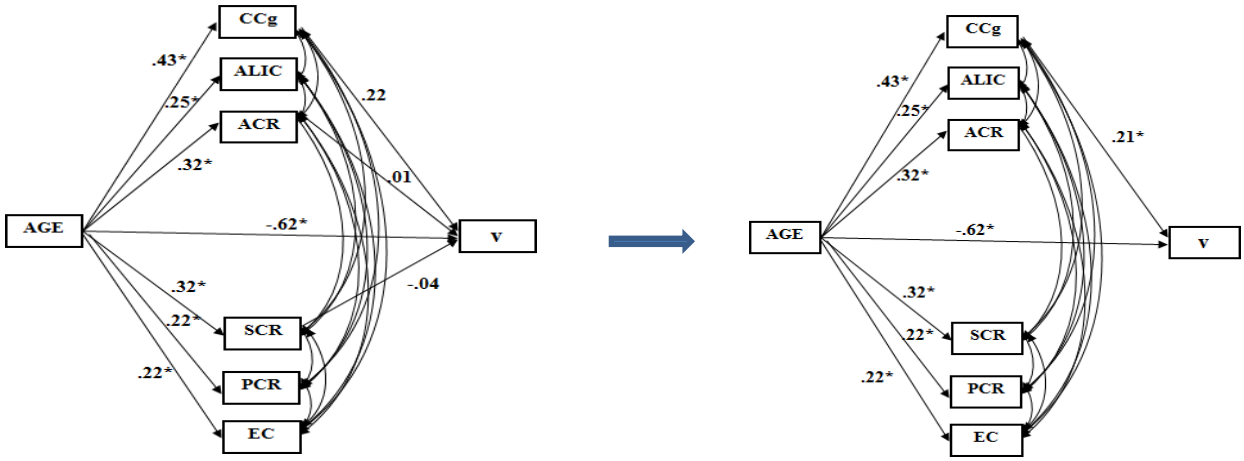
Model MDAv_3



Model MDAv_4

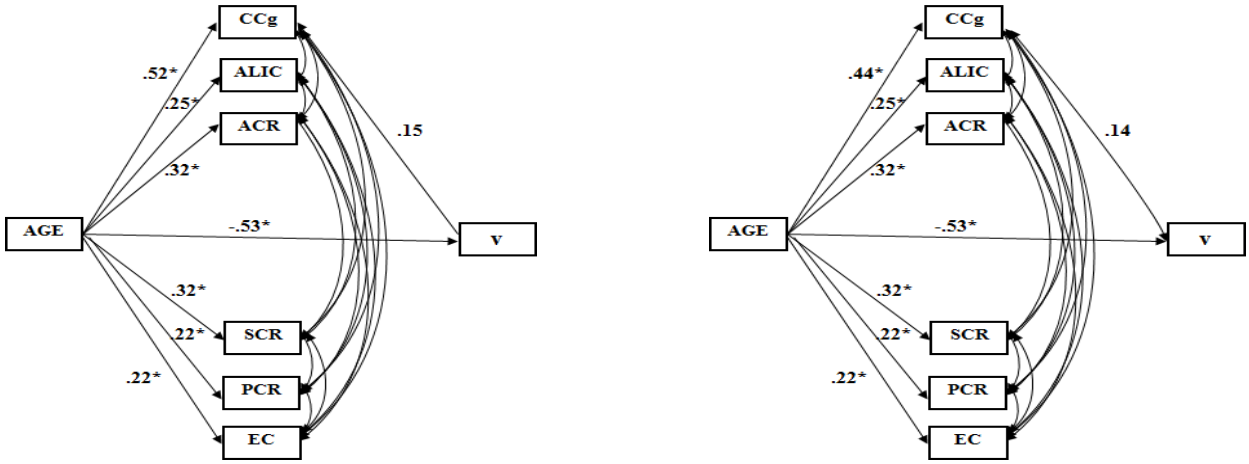
Note: CCg: genu of the corpus callosum; PLIC: posterior limb of the internal capsule; SCR: superior corona radiata; PTR: posterior thalamic radiation.

Path model of age, DR in normal-appearing white matter, and drift rate



Model MDRv_1

Model MDRv_2



Model MDRv_3

Model MDRv_4

Note. CCg: genu of the corpus callosum; ALIC: anterior limb of the internal capsule; ACR: anterior corona radiata; SCR: superior corona radiata; PCR: posterior corona radiata; EC: external capsule.

Response conservativeness. The second set of model included four subsets that investigate the mediation role of FA, MD, DA, and DR on age difference in response conservativeness. As stated previously, white matter tracts with significant zero-order correlations with age were included. The initial model of this set included the paths from age to all other variables and from each DTI index of selected white matter tracts to response conservativeness. For FA, the target model was constrained in a way that paths between FA of the genu of the corpus callosum, the posterior limb of the internal capsule, the external capsule, and the posterior thalamic radiation and response conservativeness were set to zero (Figure 13: Model MFAa_1). This model fitted the data well: $\chi 2$ was not significant ($\chi 2$=3.67, df=4, p=.45); CFI=1.0, TLI=1.01, RMSEA=.00, and removal of the non-significant paths did not worsen the fit of the reduced model (Figure 13: Model MFAa_2): $\Delta\chi 2$ (2) =.29, p>.05. As shown in these models, advanced age was associated with decreased FA in the genu of the corpus callosum, the anterior limb of the internal capsule, the anterior corona radiata, the external capsule, and the posterior thalamic radiation; but increased FA in the posterior limb of the internal capsule. Older age was also associated with higher response conservativeness. However, there was no association between age difference in FA of any tract and age-related increase in response conservativeness.

For MD, the target model was constrained so that paths between MD of the genu of the corpus callosum, the posterior limb of the internal capsule and the posterior corona radiata and response conservativeness were set to zero. This mode did not fit the data well: $\chi 2$ was not

significant ($\chi2$=11.77, df=6, p=.07); CFI=.98; TLI=.94; RMSEA=.10 (Figure 13: Model MMDa_1). The reduced model by removing the non-significant paths fitted the data reasonably well: $\chi2$ was not significant ($\chi2$=11.92, df=7, p=.10); CFI=.98; TLI=.96; RMSEA=.09 (Figure 13: Model MMDa_2). As revealed in these models, advanced age was associated with increased MD in all the examined white matter tracts. Older age was associated with higher response conservativeness. However, there was no association between age difference in MD of selected white matter tracts and response conservativeness.

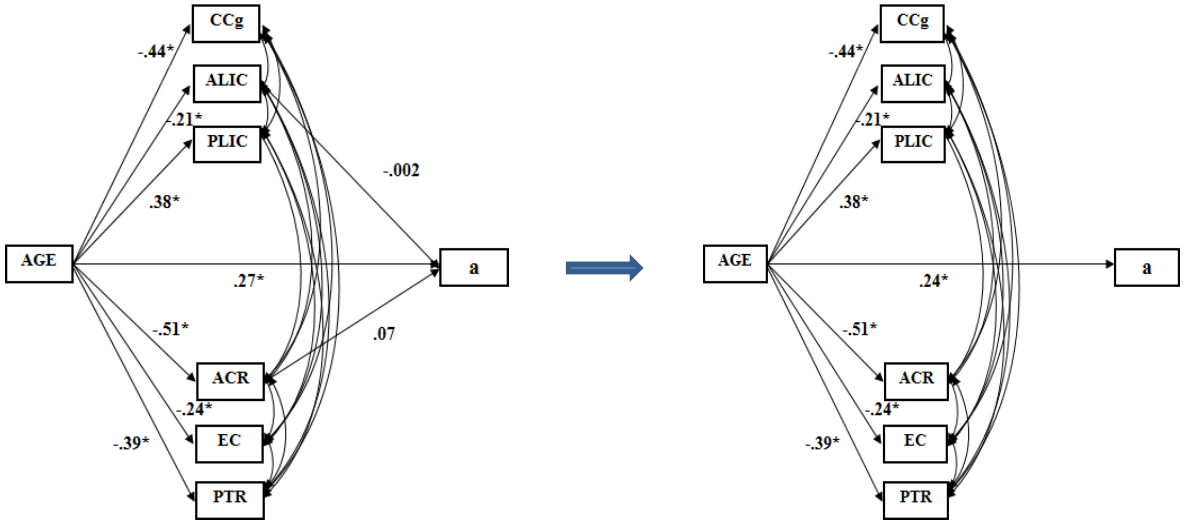
For DA, the target model was constrained in a way that paths between DA of the genu of the corpus callosum, the posterior limb of the internal capsule and the posterior thalamic radiation and response conservativeness were set to zero (Figure 13: Model MDAa_1). This model showed a good fit with the data: $\chi2$ was not significant ($\chi2$=4.91, df=6, p=.56); CFI=1.0; TLI=1.02; RMSEA=.00. The reduced model by removing the non-significant paths did not fit worse (Figure 13: Model MDAa_2): $\Delta\chi2$ (1) =.05, p>.05. As shown in these models, advanced age was associated with increased DA in the genu of the corpus callosum, the posterior limb of the internal capsule, the superior corona radiata, but decreased DA in the posterior thalamic radiation. Older age was associated with lower response conservativeness. However, age difference in DA of selected white matter tracts was not associated with response conservativeness.

The target model for DR was constrained so that paths between DR of the genu of the corpus callosum, the posterior corona radiata, and the external capsule and response conservativeness were set to zero (Figure 13: Model MDRa_1). The model fitted the data well:

$\chi 2$ was not significant ($\chi 2$=2.09, df=3, p=.55); CFI=1.0; TLI=1.02; RMSEA=.00. The reduced model by deleting the non-significant paths did not show worse fit (Figure 13: Model MDRa_2): $\Delta\chi 2$ (3) =2.42, p>.05. As shown in these models, advanced age was associated with higher DR in all the examined tracts. Aging was associated with higher response conservativeness. However, there was no correlation between age difference in DR of any selected white matter tracts and response conservativeness.

Figure 13. Structural models for the relationships between DTI indices of white matter tracts in normal-appearing white matter and response conservativeness (a)

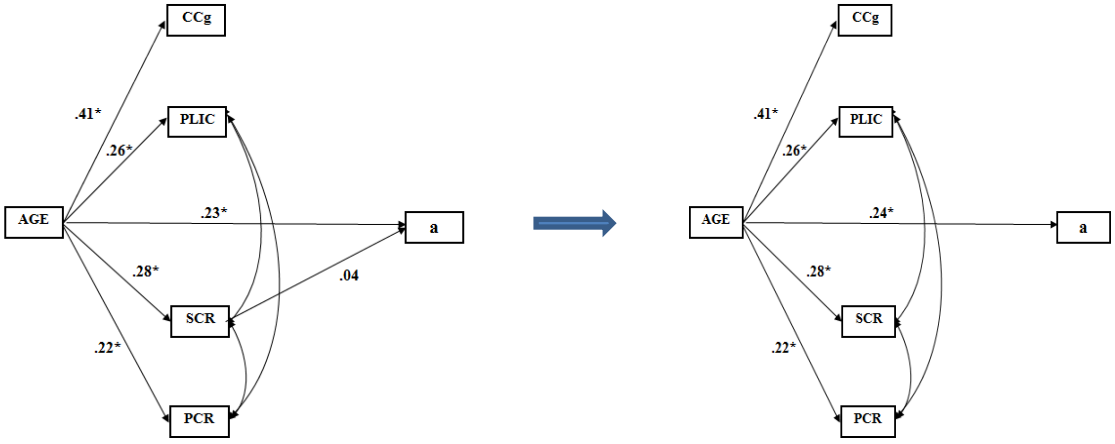
Path model of age, FA in normal-appearing white matter, and response conservativeness



Model MFAa_1 Model MFAa_2

Note: CCg: genu of the corpus callosum; ALIC: anterior limb of the internal capsule; PLIC: posterior limb of the internal capsule; ACR: anterior corona radiata; EC: external capsule; PTR: posterior thalamic radiation.

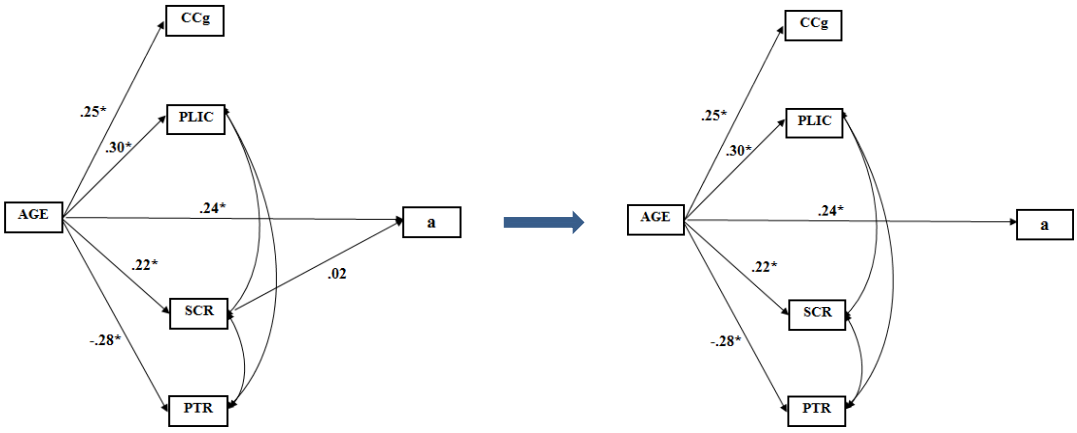
Path model of age, MD in normal-appearing white matter, and response conservativeness



Model MMDa_1 Model MMDa_2

Note: CCg: genu of the corpus callosum; PLIC: posterior limb of the internal capsule; SCR: superior corona radiata; PCR: posterior corona radiata.

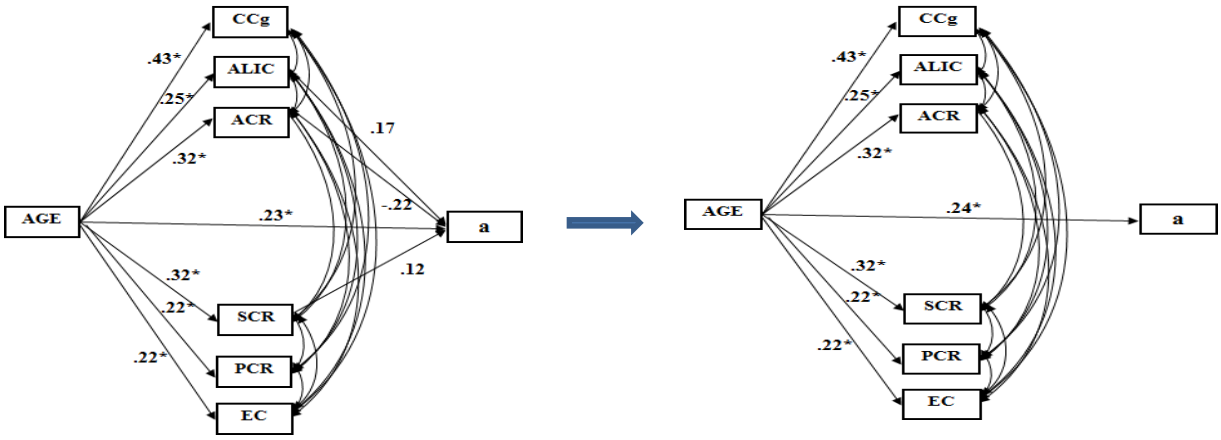
Path model of age, DA in normal-appearing white matter, and response conservativeness



Model MDAa_1 Model MDAa_2

Note: CCg: genu of the corpus callosum; PLIC: posterior limb of the internal capsule; SCR: superior corona radiata; PTR: posterior thalamic radiation.

Path model of age, DR in normal-appearing white matter, and response conservativeness



Model MDRa_1 Model MDRa_2

Note. CCg: genu of the corpus callosum; ALIC: anterior limb of the internal capsule; ACR: anterior corona radiata; SCR: superior corona radiata; PCR: posterior corona radiata; EC: external capsule.

Non-decision time. The third set of model included four subsets that investigate the mediation role of FA, MD, DA, and DR in normal-appearing white matter on age difference in non-decision time. For FA, the target model was constrained in the following way: paths between FA of the genu of the corpus callosum and non-decision time were set to zero (Figure 14: Model MFAter_1). This model fitted the data very well: $\chi 2$ was not significant ($\chi 2$=.02, df=1, p=.90); CFI=1.0; TLI=1.09; RMSEA=.00, and removal of the non-significant paths did not worsen the fit of the reduced model (Figure 14: Model MFAter_2): $\Delta\chi 2$ (5) =6.26, p>.05. As shown in these models, advanced age was associated with decreased FA in all the examined tracts except in the posterior limb of the internal capsule which showed increased FA with age.

Older age was also associated with higher non-decision time. However, there was no correlation between age difference in FA of any selected white matter tracts and non-decision time.

For MD, the target model was constrained so that paths between MD of the genu of the corpus callosum and non-decision time were set to zero. The model fitted the data reasonably well: $\chi 2$ was not significant ($\chi 2$=6.46, df=4, p=.17); CFI=.99; TLI=.96; RMSEA=.08 (Figure 14: Model MMDter_1). The reduced model with dropping the non-significant paths did not fit the data worse (Figure 14: Model MMDter_2): $\Delta\chi 2$ (3) =4.78, p>.05. The results suggested that advanced age was associated with increased MD in all the examined white matter tracts. Older age was associated with longer non-decision time. However, there was no correlation between age difference in MD of any selected white matter tracts and non-decision time. To accommodate TBSS findings, constrains on the paths between non-decision time and MD from the genu of the corpus callosum were relaxed. However, the final results did not change.

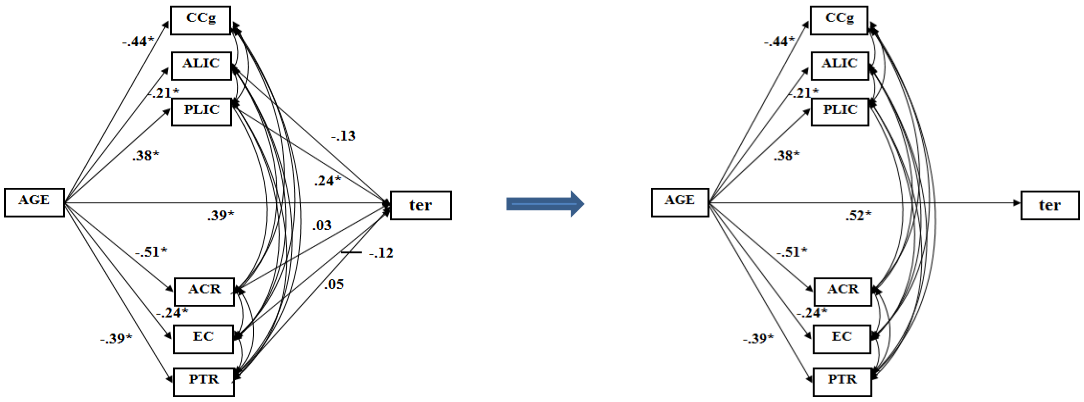
For DA, the target model was constrained based on the previous hypothesis so that paths between DA of the genu of the corpus callosum and non-decision time were set to zero (Figure 14: Model MDAter_1). This model fitted the data well: $\chi 2$ was not significant ($\chi 2$=1.25, df=4, p=.87); CFI=1.0; TLI=1.06; RMSEA=.00. The reduced model with removing the non-significant paths did not show worse fit (Figure 14: Model MDAter_2): $\Delta\chi 2$ (2) =.83, p>.05. As revealed by these models, advanced age was associated with increased DA in the genu of the corpus callosum, the posterior limb of the internal capsule, and the superior corona radiata; but decreased DA in the posterior thalamic radiation. Older age was associated with longer non-decision time and DA in the superior corona radiata was positively associated with non-decision

time ($p<.05$). Both the reversed model and correlational model fitted the data equally well: $\chi 2$ was not significant ($\chi 2=2.28$ df=6, $p=.89$); CFI=1.0; TLI=1.06; RMSEA=.00. However, neither the directional path nor correlation between DA in the superior corona radiata and non-decision time was significant (Figure 12: MDAter_3 and MDAter_4). The test of indirect effect between age and non-decision time revealed that there is no significant indirect effect between age and non-decision time through DA of the superior corona radiata ($p=.14$, 95% CI= -.013-.09). Thus, although increased DA in the superior corona radiata was related to age-related decrease in non-decision time, DA of the superior corona radiata did not mediate the effect of age on non-decision time.

For DR, the model was constrained so that paths between DR of the genu of the corpus callosum and non-decision time were set to zero (Figure 14: Model MDRter_1). The model fitted the data well: $\chi 2$ was not significant ($\chi 2=.001$, df=1, $p=.97$); CFI=1.0; TLI=1.06; RMSEA=.00. The reduced model by removing the non-significant paths did not show worse fit (Figure 14: Model MDRter_2): $\Delta\chi 2$ (5) =8.15, $p>.05$. As demonstrated in these models, advanced age was associated with higher DR in all examined tracts. Older age was associated with longer non-decision time. However, age difference in DR of selected white matter tracts was not associated with non-decision time. Similarly, to incorporate TBSS findings, constrains on the paths between non-decision time and DR from the genu of the corpus callosum were relaxed. However, the final results stayed the same.

Figure 14. Structural models for the relationships between DTI indices of white matter tracts in normal-appearing white matter and non-decision time (ter)

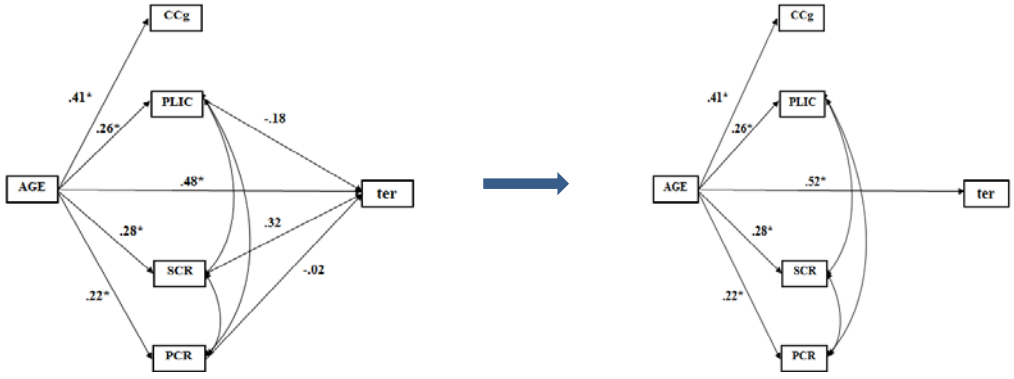
Path model of age, FA in normal-appearing white matter, and non-decision time



Model MFAter_1 Model MFAter_2

Note: CCg: genu of the corpus callosum; ALIC: anterior limb of the internal capsule; PLIC: posterior limb of the internal capsule; ACR: anterior corona radiata; EC: external capsule; PTR: posterior thalamic radiation.

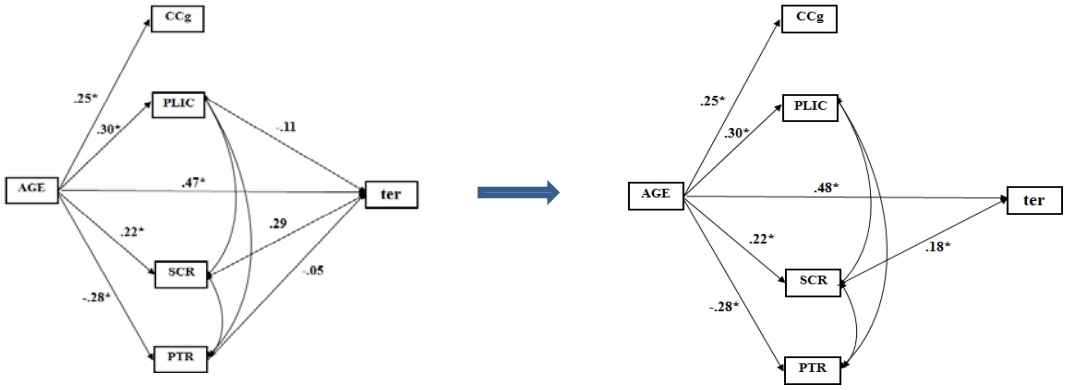
Path model of age, MD in normal-appearing white matter, and non-decision time



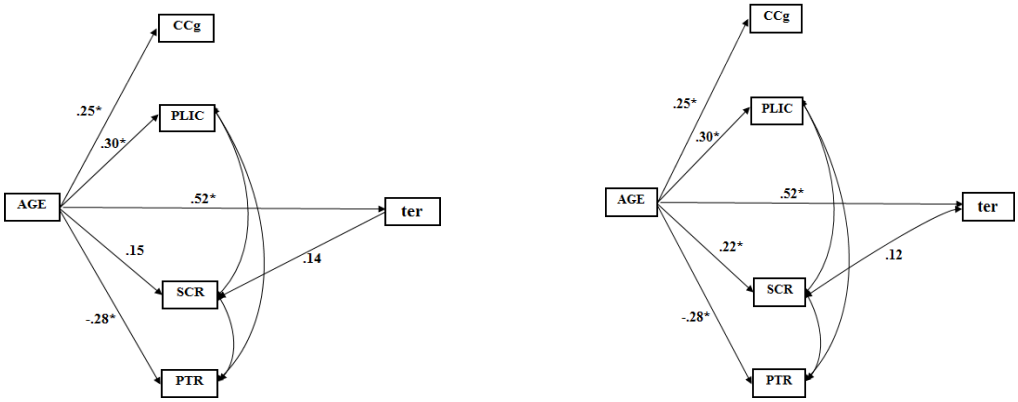
Model MMDter_1 Model MMDter_2

Note: CCg: genu of the corpus callosum; PLIC: posterior limb of the internal capsule; SCR: superior corona radiata; PCR: posterior corona radiata.

Path model of age, DA in normal-appearing white matter, and non-decision time



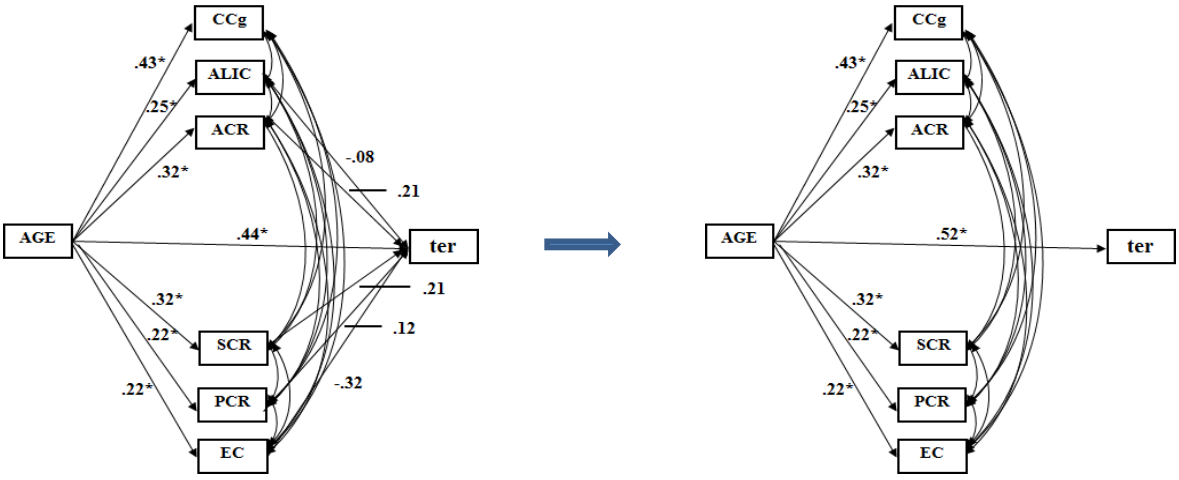
Model MDAter_1 Model MDAter_2



Model MDAter_3 Model MDAter_4

Note: CCg: genu of the corpus callosum; PLIC: posterior limb of the internal capsule; SCR: superior corona radiata; PTR: posterior thalamic radiation.

Path model of age, DR in normal-appearing white matter, and non-decision time



Model MDRter_1 Model MDRter_2

Note. CCg: genu of the corpus callosum; ALIC: anterior limb of the internal capsule; ACR: anterior corona radiata; SCR: superior corona radiata; PCR: posterior corona radiata; EC: external capsule.

In whole white matter

Similar processes were performed to investigate the mediation role of FA, MD, DA, and DR in whole white matter on age difference in RT components.

Drift rate. For FA in whole white matter, following white matter tracts were included based on their zero-order correlations with age: the genu of the corpus callosum, the anterior limb of the internal capsule, the superior longitudinal fasciculus, the anterior and superior corona radiata, the external capsule, the posterior thalamic radiation, and the retrolenticular part of the

internal capsule. The target model was constrained in the following way based on the previous hypothesis: paths between FA of the anterior limb of the internal capsule, the external capsule, the posterior thalamic radiation, and the retrolenticular part of the internal capsule and drift rate were set to zero (Figure 15: Model FAv_1). The fitness of the model is not very well: $\chi 2$ was not significant ($\chi 2$=7.33, df=4, p=.12); CFI=1.0; TLI=.94; RMSEA=.10. The reduced model through removal of the non-significant paths fitted the data reasonably well (Figure 15: Model FAv_2): ($\chi 2$=11.12, df=8, p=.19); CFI=1.0; TLI=.97; RMSEA=.07. As shown in these models, advanced age was associated with decreased FA in all white matter tracts examined. Older age was also associated with lower drift rate. However, there was no association between age difference in FA of any selected white matter tract and drift rate.

For MD, the following tracts were involved: the genu of the corpus callosum, the superior longitudinal fasciculus, the anterior, superior and posterior corona radiata, the external capsule, and the posterior thalamic radiation. The target model was constrained so that paths between MD of the posterior corona radiata, the external capsule, and the posterior thalamic radiation and drift rate were set to zero (Figure 15: Model MDv_1). The fitness of the model was not good: $\chi 2$ was significant ($\chi 2$=8.38, df=3, p=.04); CFI=.99; TLI=.92; RMSEA=.14. The reduced model by removing the non-significant paths fitted the data reasonably well (Figure 15: Model MDv_2): $\chi 2$ was not significant ($\chi 2$=8.74, df=6, p=.19); CFI=1.0; TLI=.98; RMSEA=.07. As revealed by these models, advanced age was associated with increased MD in all the examined white matter tracts. Older age was associated with lower drift rate and the latter was associated with increased MD in the genu of the corpus callosum ($p<.05$). Both the reversed model and correlational model

by reversing the direction between MD in the genu of the corpus callosum and drift rate or correlating these two variables did not fit the data well: $\chi 2$ was not significant ($\chi 2$=12.29, df=6, p=.06); CFI=.99; TLI=.95; RMSEA=.11. In addition, the directional path from drift rate to MD in the genu of the corpus callosum was not significant and there was no significant correlation between these two variables. The test of indirect effect between age and drift rate revealed there was marginally significant indirect effect between age and drift rate through MD of the genu of the corpus callosum (p=.07, 95% CI= -.006-.189). Therefore, MD in the genu of the corpus callosum might mediate the effect of age on drift rate.

IQ from CFIT was introduced to investigate whether the association between MD of the genu of the corpus callosum and drift rate was due to the influence of this third variable. The model fitted the data reasonably well: $\chi 2$ was not significant ($\chi 2$=20.79, df=14, p=.11); CFI=.99; TLI=.97; RMSEA=.07. The results showed that advanced age was associated with lower IQ (p<.001), but there was no association between IQ with either MD of the genu of the corpus callosum or drift rate.

For DA, the involved tracts included the genu of the corpus callosum, the posterior limb of the internal capsule, the anterior and posterior corona radiata, and the posterior thalamic radiation. The target model was constrained so that paths between DA of the posterior limb of the internal capsule, the posterior corona radiata, and the posterior thalamic radiation and drift rate were set to zero (Figure 15: Model DAv_1). The model fitted the data less well as suggested by RMSEA: $\chi 2$ was not significant ($\chi 2$=5.01, df=3, p=.17); CFI=1.0; TLI=.95; RMSEA=.09. The reduced model by removing the non-significant paths fitted the data well (Figure 15: Model

DAv_2): $\chi 2$ was not significant ($\chi 2$=5.19, df=4, p=.27); CFI=1.0; TLI=.98; RMSEA=.06. As shown in these models, advanced age was associated with increased DA in the genu of the corpus callosum, the anterior and the posterior corona radiata, and the posterior thalamic radiation; but decreased DA in the posterior limb of the internal capsule. Older age was associated with lower drift rate and higher DA in the anterior corona radiata was associated with greater drift rate ($p<.05$). Both the reversed model and correlational model fitted the data reasonably well (equally): $\chi 2$ was not significant ($\chi 2$=6.06, df=4, p=.19); CFI=1.0; TLI=.96; RMSEA=.08. The directional path from drift rate to DA in the anterior corona radiata was significant and there was significant correlation between these two variables (Figure 15: DAv_3 and DAv_4). Therefore, there was no preferred direction between these two variables and age-related increase in DA in the anterior corona radiata was associated with higher drift rate.

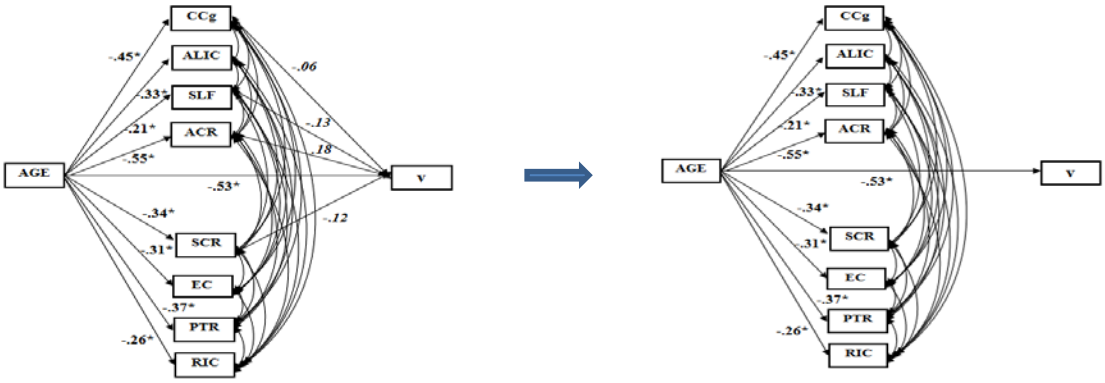
Additional model was constructed to test the potential influence of IQ on the association between DA in the anterior corona radiata and drift rate. The final model fitted the data well: $\chi 2$ was not significant ($\chi 2$=13.15, df=10, p=.22); CFI=.99; TLI=.97; RMSEA=.06. The results showed that advanced age was associated with lower IQ ($p<.001$), but there was no association between IQ with either DA of the anterior corona radiata or drift rate.

The following tracts were involved for DR: the genu of the corpus callosum; the anterior limb of the internal capsule; the superior longitudinal fasciculus, the anterior and superior corona radiata; the external capsule, the posterior thalamic radiation, and the retrolenticular part of the internal capsule. The initial model included the following paths: age to all other variables, DR of these selected white matter tracts to drift rate. Based on the previous hypothesis, the model was

constrained so that paths between DR of the anterior limb of the internal capsule, the external capsule, the posterior thalamic radiation, and the retrolenticular part of the internal capsule and drift rate were set to zero (Figure 15: Model DRv_1). The model fitted the data reasonably well: $\chi 2$ was not significant ($\chi 2$=7.86, df=4, p=.10); CFI=1.0; TLI=.95; RMSEA=.10. The reduced model by dropping the non-significant paths fitted the data well (Figure 15: Model DRv_2): $\chi 2$ was not significant ($\chi 2$=8.50, df=7, p=.29); CFI=1.0; TLI=.99; RMSEA=.05. As demonstrated in these models, advanced age was associated with higher DR in all the examined tracts. Older age was associated with lower drift rate and DR in the genu of the corpus callosum was positively associated with drift rate (p<.05). Both the reversed model and correlational model fitted the data reasonably well: $\chi 2$ was not significant ($\chi 2$=10.98, df=7, p=.14); CFI=1.0; TLI=.97; RMSEA=.08. However, neither the directional path nor correlation between drift rate and DR in the genu of the corpus callosum was significant. The test of indirect effect between age and drift rate revealed that DR of the genu of the corpus callosum might mediate the effect of age on drift rate (p=.052, 95% CI= -.001 - .20). Thus, part of age-related decrease in drift rate might be attenuated by age-related increase in DR in the genu of the corpus callosum. The model testing a potential influence of IQ on the association between DR of the genu of the corpus callosum and drift rate fitted the data well: $\chi 2$ was not significant ($\chi 2$=22.18, df=17, p=.18); CFI=.99; TLI=.98; RMSEA=.06. The results did not show any association between IQ with either DR of the genu of the corpus callosum or drift rate.

Figure 15. Structural models for the relationships between DTI indices of white matter tracts in whole white matter and drift rate (v)

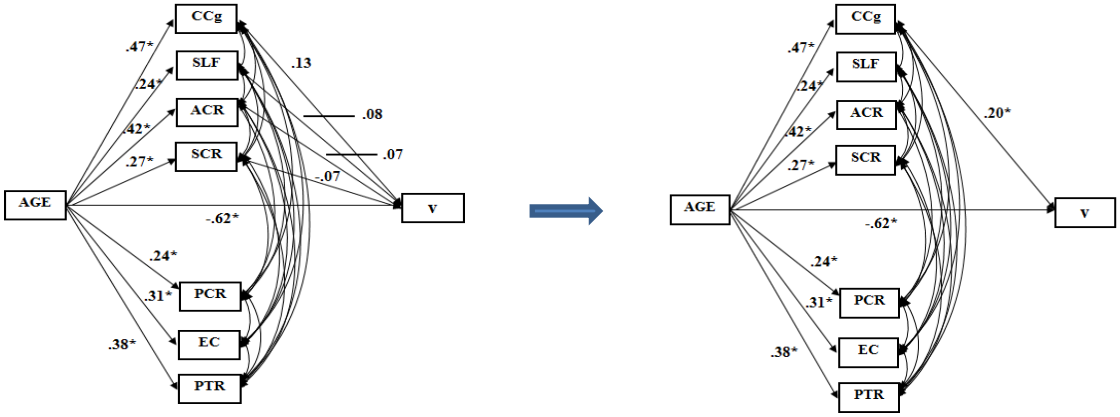
Path model of age, FA in whole white matter, and drift rate



Model FAv_1 Model FAv_2

Note: CCg: genu of the corpus callosum; ALIC: anterior limb of the internal capsule; SLF: superior longitudinal fasciculus; ACR: anterior corona radiata; SCR: superior corona radiata; EC: external capsule; PTR: posterior thalamic radiation; RIC: retrolenticular part of the internal capsule.

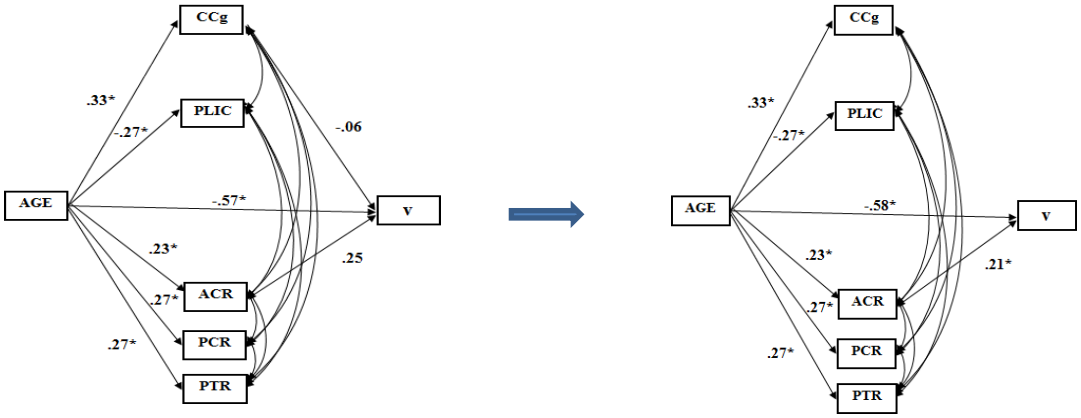
Path model of age, MD in whole white matter, and drift rate



Model MDv_1 Model MDv_2

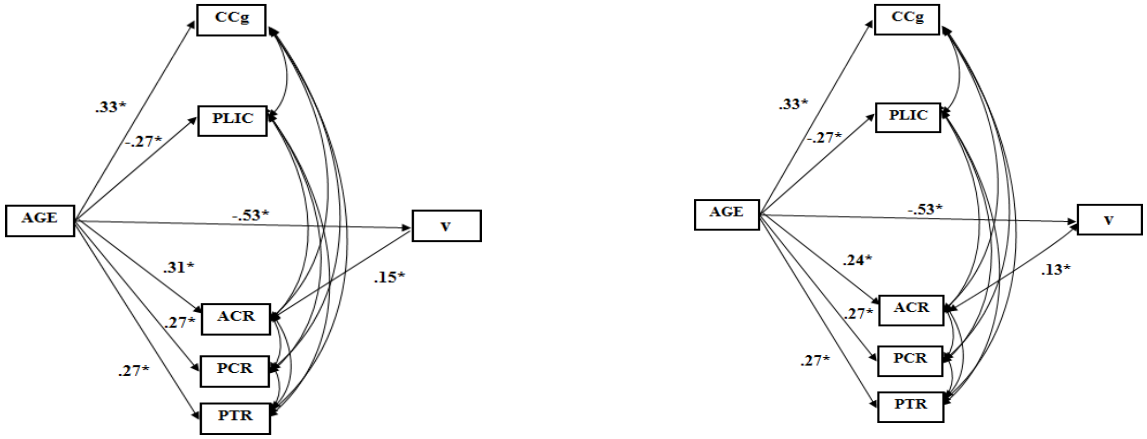
Note: CCg: genu of the corpus callosum; SLF: superior longitudinal fasciculus; ACR: anterior corona radiata; SCR: superior corona radiata; PCR: posterior corona radiata; EC: external capsule; PTR: posterior thalamic radiation.

Path model of age, DA in whole white matter, and drift rate



Model DAv_1

Model DAv_2

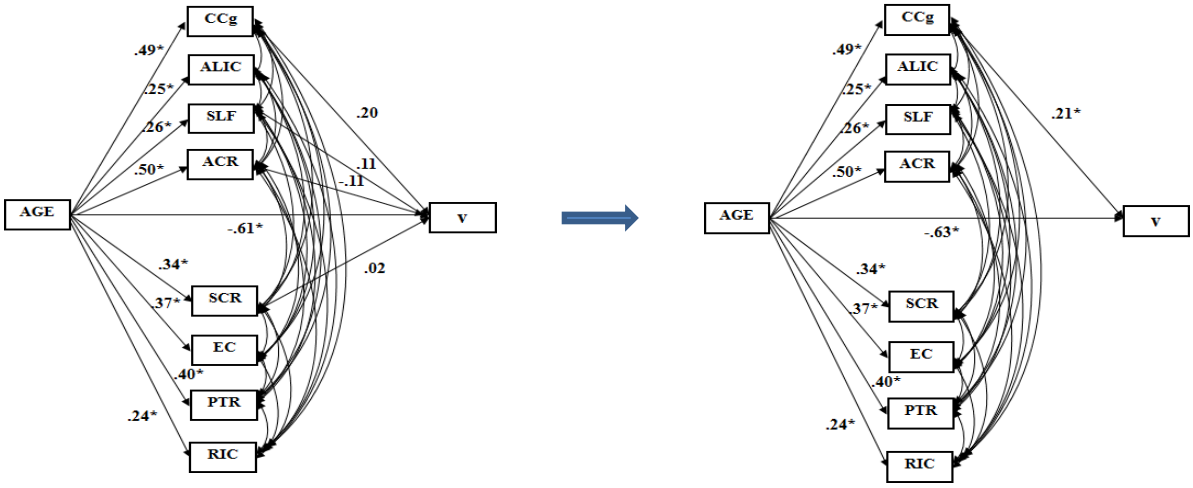


Model DAv_3

Model DAv_4

Note: CCg: genu of the corpus callosum; PLIC: posterior limb of the internal capsule; ACR: anterior corona radiata; PCR: posterior corona radiata; PTR: posterior thalamic radiation.

Path model of age, DR in whole white matter, and drift rate



Model DRv_1 Model DRv_2

Note. CCg: genu of the corpus callosum; ALIC: anterior limb of the internal capsule; SLF: superior longitudinal fasciculus; ACR: anterior corona radiata; SCR: superior corona radiata; EC: external capsule; PTR: posterior thalamic radiation; RIC: retrolenticular part of the internal capsule.

Response conservativeness. For FA, the target model was constrained in a way that paths between FA of the genu of the corpus callosum, the external capsule, the posterior thalamic radiation, and the retrolenticular part of the internal capsule and response conservativeness were set to zero (Figure 16: Model FAa_1). This model fitted the data well: $\chi 2$ was not significant ($\chi 2$=2.64, df=4, p=.62); CFI=1.0, TLI=1.03, RMSEA=.00, and removal of the non-significant paths did not worsen the fit of the reduced model (Figure 16: Model FAa_2): $\Delta\chi 2$ (4) =4.35, p>.05. As shown in these models, advanced age was associated with decreased FA in all examined white matter tracts. Older age was also associated with higher response

conservativeness. However, there was no association between age difference in FA of any tract and response conservativeness.

For MD, the target model was constrained so that paths between MD of the genu of the corpus callosum, the posterior corona radiata, the external capsule, and the posterior thalamic radiation and response conservativeness were set to zero. This model showed a good fit with the data: $\chi 2$ was not significant ($\chi 2$=3.65, df=4, p=.46); CFI=1.00; TLI=1.00; RMSEA=.00. The reduced model by removing the non-significant paths did not fit the data worse (Figure 16: Model MDa_2): $\Delta\chi 2$ (3) =1.17, p>.05. As revealed by these models, advanced age was associated with increased MD in all the examined white matter tracts. However, there was no association between age difference in MD of selected white matter tracts and age-related increase in response conservativeness.

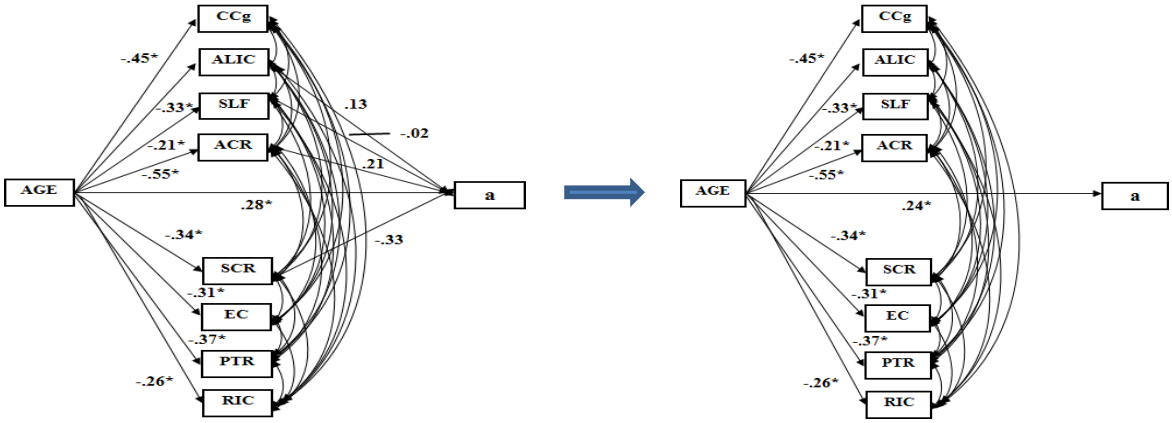
The target model was constrained For DA in a way that paths between DA of the genu of the corpus callosum, the posterior limb of the internal capsule, the posterior corona radiata, and the posterior thalamic radiation and response conservativeness were set to zero (Figure 16: Model DAa_1). The fit of the model to the data was reasonably well*:* $\chi 2$ was not significant ($\chi 2$=6.22, df=4, p=.18); CFI=.99; TLI=.95; RMSEA=.08. The reduced model by removing the non-significant paths fitted the data well (Figure 16: Model DAa_2): $\chi 2$ was not significant ($\chi 2$=6.8, df=5, p=.24); CFI=.99; TLI=.97; RMSEA=.06. As shown in these models, advanced age was associated with increased DA in the genu of the corpus callosum, the anterior and posterior corona radiata, and the posterior thalamic radiation; but decreased DA in the posterior

limb of the internal capsule. However, age difference in DA of selected white matter tracts was not associated with age-related increase in response conservativeness.

For DR, the target model was constrained so that paths between DR of the genu of the corpus callosum, the external capsule, the posterior thalamic radiation, and the retrolenticular part of the internal capsule and response conservativeness were set to zero (Figure 16: Model DRa_1). The model fitted the data well: $\chi 2$ was not significant ($\chi 2=5.37$, df=4, p=.25); CFI=1.0; TLI=.98; RMSEA=.06. The reduced model by deleting the non-significant paths did not show worse fit (Figure 16: Model DRa_2): $\Delta\chi 2$ (4) =2.11, p>.05. As shown in these models, advanced age was associated with higher DR in all the examined white matter tracts. However, there was no correlation between age difference in DR of any selected white matter tracts and age-related increase in response conservativeness.

Figure 16. Structural models for the relationships between DTI indices of white matter tracts in whole white matter and response conservativeness (a)

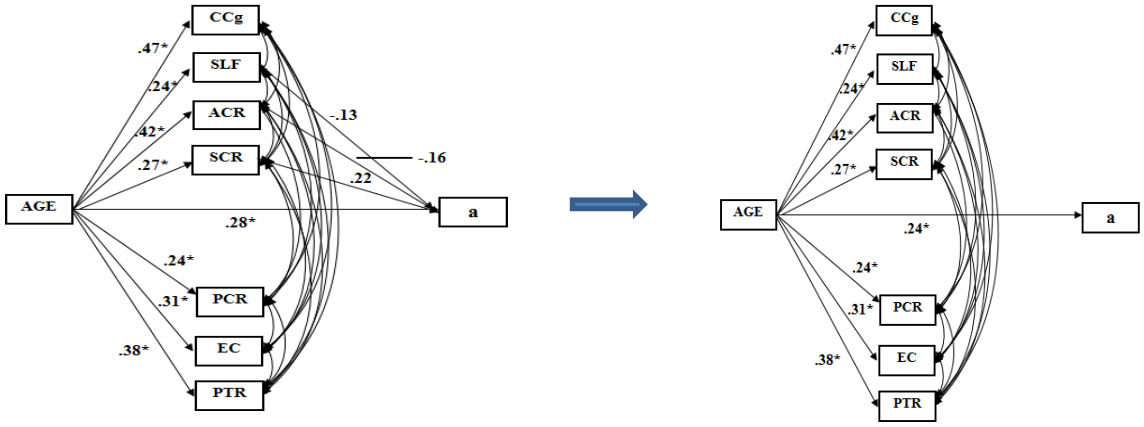
Path model of age, FA in whole white matter, and response conservativeness



Model FAa_1 Model FAa_2

Note: CCg: genu of the corpus callosum; ALIC: anterior limb of the internal capsule; SLF: superior longitudinal fasciculus; ACR: anterior corona radiata; SCR: superior corona radiata; EC: external capsule; PTR: posterior thalamic radiation; RIC: retrolenticular part of the internal capsule.

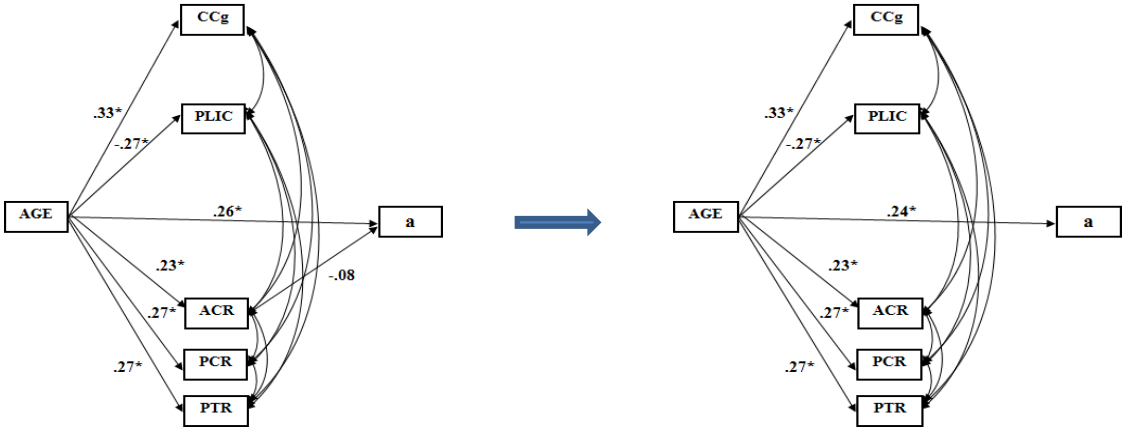
Path model of age, MD in whole white matter, and response conservativeness



Model MDa_1 Model MDa_2

Note: CCg: genu of the corpus callosum; SLF: superior longitudinal fasciculus; ACR: anterior corona radiata; SCR: superior corona radiata; PCR: posterior corona radiata; EC: external capsule; PTR: posterior thalamic radiation.

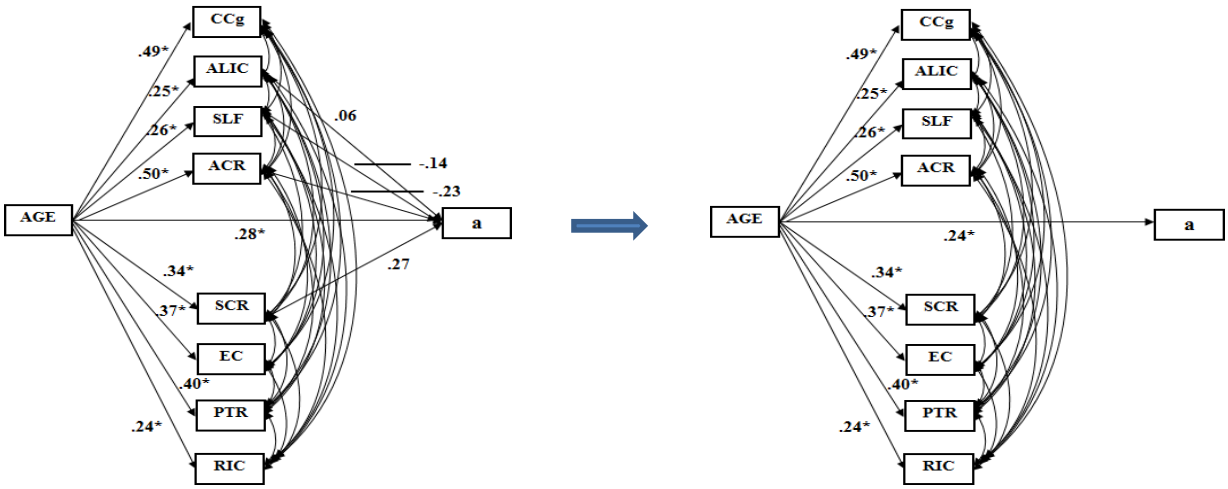
Path model of age, DA in whole white matter, and response conservativeness



Model DAa_1 Model DAa_2

Note: CCg: genu of the corpus callosum; PLIC: posterior limb of the internal capsule; ACR: anterior corona radiata; PCR: posterior corona radiata; PTR: posterior thalamic radiation.

Path model of age, DR in whole white matter, and response conservativeness



Model DRa_1 Model DRa_2

Note: CCg: genu of the corpus callosum; ALIC: anterior limb of the internal capsule; SLF: superior longitudinal fasciculus; ACR: anterior corona radiata; SCR: superior corona radiata; EC: external capsule; PTR: posterior thalamic radiation; RIC: retrolenticular part of the internal capsule.

Non-decision time. For FA, the target model was constrained in the following way: paths between FA of the genu of the corpus callosum and superior longitudinal fasciculus with non-decision time were set to zero (Figure 17: Model FAter_1). This model fitted the data very well: $\chi 2$ was not significant ($\chi 2$=.05, df=2, p=.97); CFI=1.0; TLI=1.07; RMSEA=.00, and removal of the non-significant paths did not worsen the fit of the reduced model (Figure 17: Model FAter_2): $\Delta\chi 2$ (5) =2.76, p>.05. As shown in these models, advanced age was associated with decreased FA in all the examined tracts. Age-related increase in non-decision time tended to be related to age-related decrease in FA in the external capsule (p=.07).

For MD, the target model was constrained so that paths between MD of the genu of the corpus callosum and superior longitudinal fasciculus with non-decision time were set to zero (Figure 17: Model MDter_1). This model showed good fit with the data: $\chi 2$ was not significant ($\chi 2$=2.21, df=2, p=.33); CFI=1.0; TLI=1.0; RMSEA=.03. The reduced model with dropping the non-significant paths did not fit the data worse (Figure 17: Model MDter_2): $\Delta\chi 2$ (5) =2.14, p>.05. The results suggested that advanced age was associated with increased MD in all the examined white matter tracts. However, there was no correlation between age difference in MD of any selected white matter tracts and age-relate increase in non-decision time.

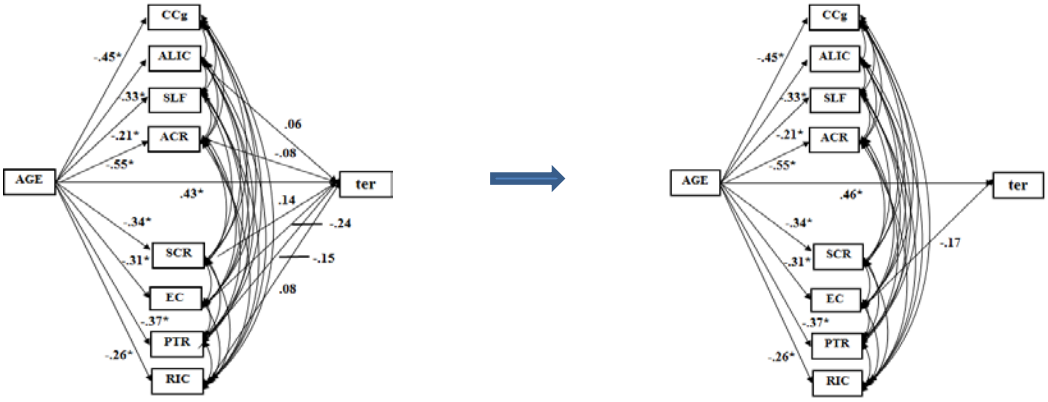
For DA, the target model was constrained so that paths between DA of the genu of the corpus callosum with non-decision time were set to zero (Figure 17: Model DAter_1). This model fitted the data well: $\chi 2$ was not significant ($\chi 2$=1.11, df=1, p=.29); CFI=1.0; TLI=.99; RMSEA=.03. The reduced model by removing the non-significant paths did not show worse fit (Figure 17: Model DAter_2): $\Delta\chi 2$ (4) =4.32, p>.05. As revealed by these models, advanced age

was associated with increased DA in the genu of the corpus callosum, the anterior and posterior corona radiata, and the posterior thalamic radiation; but decreased DA in the posterior limb of the internal capsule. However, there was no association between age difference in DA of any selected white matter tracts and age-related increase in non-decision time.

For DR, the model was constrained so that paths between DR of the genu of the corpus callosum and the superior longitudinal fasciculus with non-decision time were set to zero (Figure 17: Model DRter_1). The model fitted the data well: $\chi 2$ was not significant ($\chi 2$=.26, df=2, p=.88); CFI=1.0; TLI=1.05; RMSEA=.00. The reduced model by removing the non-significant paths did not show worse fit (Figure 17: Model DRter_2): $\Delta\chi 2$ (6) =3.75, p>.05. As demonstrated in these models, advanced age was associated with higher DR in all examined white matter tracts. However, age difference in DR of selected white matter tracts was not associated with age-related increase in non-decision time.

Figure 17. Structural models for the relationships between DTI indices of white matter tracts in whole white matter and non-decision time (ter)

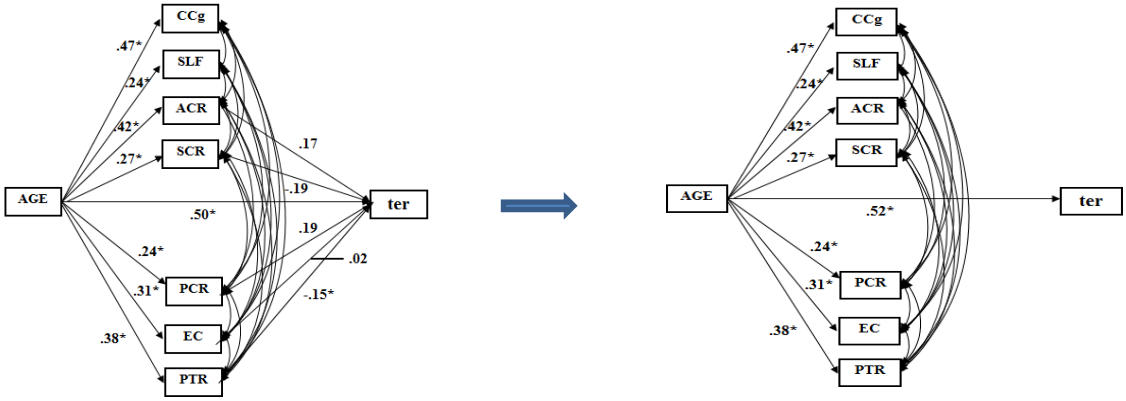
Path model of age, FA in whole white matter, and non-decision time



Model FAter_1 Model FAter_2

Note: CCg: genu of the corpus callosum; ALIC: anterior limb of the internal capsule; SLF: superior longitudinal fasciculus; ACR: anterior corona radiata; SCR: superior corona radiata; EC: external capsule; PTR: posterior thalamic radiation; RIC: retrolenticular part of the internal capsule.

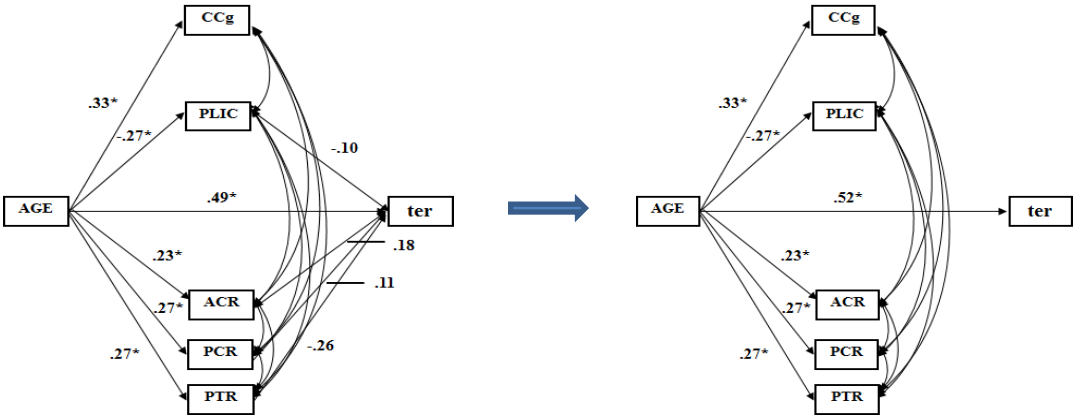
Path model of age, MD in whole white matter, and non-decision



Model MDter_1 Model MDter_2

Note: CCg: genu of the corpus callosum; SLF: superior longitudinal fasciculus; ACR: anterior corona radiata; SCR: superior corona radiata; PCR: posterior corona radiata; EC: external capsule; PTR: posterior thalamic radiation.

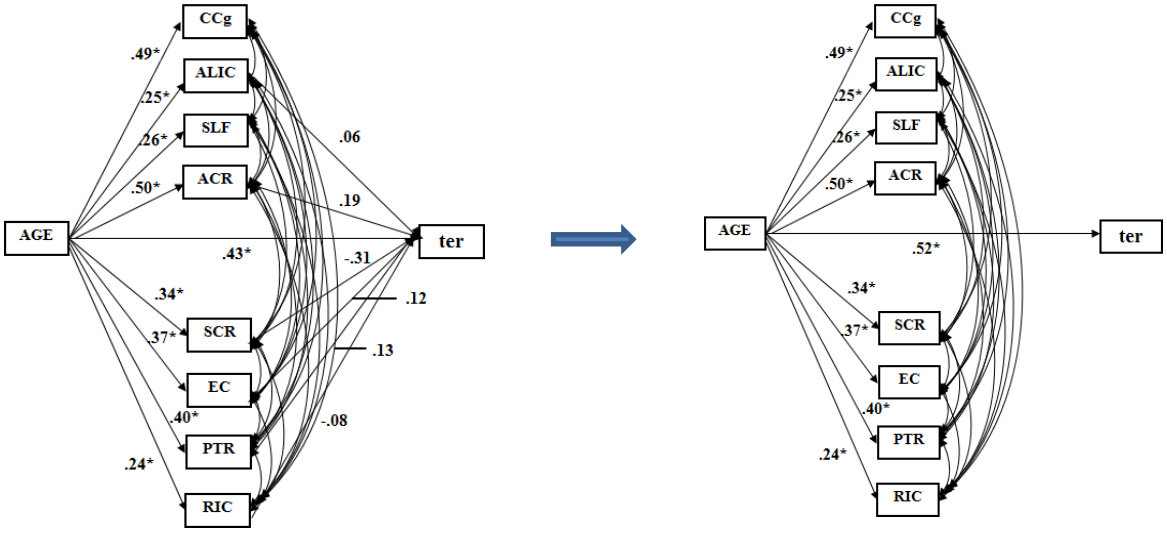
Path model of age, DA in whole white matter, and non-decision time



Model DAter_1 Model DAter_2

Note: CCg: genu of the corpus callosum; PLIC: posterior limb of the internal capsule; ACR: anterior corona radiata; PCR: posterior corona radiata; PTR: posterior thalamic radiation.

Path model of age, DR in whole white matter, and non-decision time



Model DRter_1 Model DRter_2

Note: CCg: genu of the corpus callosum; ALIC: anterior limb of the internal capsule; SLF: superior longitudinal fasciculus; ACR: anterior corona radiata; SCR: superior corona radiata; EC: external capsule; PTR: posterior thalamic radiation; RIC: retrolenticular part of the internal capsule.

Summary of the results

The results of this study revealed that

1) Advanced age was associated with lower drift rate, greater response conservativeness and longer non-decision time.

2) There were age-related decrease in FA, and increase in MD, DA, and DR in most of the examined white matter tracts in both normal-appearing and whole white matter.

3) There were anterior-posterior gradient in age-related decrease of FA and increase of MD, DA, and DR in the corpus callosum, internal capsule, and corona radiata in normal-appearing and whole white matter.

4) Age-related differences in DTI indices were greater in whole than in normal-appearing white matter.

5) Age-related differences in white matter integrity were greater in normotensive men than in normotensive women.

6) DA of the superior corona radiata in normal-appearing white matter was positively associated with non-decision time.

7) No associations were observed between age-related differences in DTI indices of examined white matter tracts and drift rate and response conservativeness in healthy normotensive participants.

CHAPTER 4

DISCUSSION

Age-relate Differences in Drift Rate, Response Conservativeness, and Non-Decision Time

The results revealed that advanced age was associated with lower drift rate, longer non-decision time and greater response conservativeness. These findings extend the observations reported by Ratcliff and colleagues in extreme age groups to an adult life-span sample. Studies fitting diffusion model to RT data suggested that old adults were more conservative and had longer non-decision time in comparison to younger adults (Ratcliff, 2008b; Ratcliff, Thapar, & McKoon, 2001). Older adults had lower drift rate than college students had in letter discrimination task (Ratcliff, Thapar, & McKoon, 2006, 2007; Thapar, Ratcliff, & McKoon, 2003).

Our data also showed that drift rate had stronger association with accuracy than RT, whereas both response conservativeness and non-decision time were mainly associated with RT. This was in accordance with the extant literature. The correlations between accuracy with drift rate and RT with response conservativeness and non-decision time have been established by studies across various RT tasks (Ratcliff et al., 2006).

However, we did not replicate Ratcliff's finding of association between IQ and drift rate (Ratcliff, Thapar, & McKoon, 2010). This could have been because the task we used involved less central cognitive process than the tasks they used.

Age-related Differences in DTI Indices (FA, MD, AD, and RD)

In accord with a common finding in the literature (Sullivan, Rohlfing, & Pfefferbaum, 2010a), we observed lower FA and greater MD, DA and DR with advanced age in several examined white matter tracts in both normal-appearing and whole white matter. The observed anterior-posterior gradient decrease in FA and increase in diffusivity measures of several white matter structures were also consistent with previous findings (Head et al., 2004; Sullivan & Pfefferbaum, 2006; Sullivan et al., 2010a). The analyses of axial and radial diffusivity suggested that age-relate difference in FA and MD was mainly, but not entirely attributed to increased DR. These results confirmed earlier findings (Bhagat & Beaulieu, 2004). Although it is appearing to attribute age-related reduction in white matter integrity to myelin degeneration based on observed age-related difference in DR, current evidence indicates that it is inappropriate to link radial diffusivity to demyelination unless the direction of the principle eigenvector is aligned with the corresponding tissue architecture. However, this is not the case in areas with crossing fibers or in voxels with partial volume (Wheeler-Kingshott & Cercignani, 2009).

Overall, more white matter tracts showed age differences in DTI indices when white matter hyperintensities volume was not taken into account. The comparison in strengths of age-DTI indices associations in normal-appearing and whole white matter with Steiger's Z also revealed that only the posterior limb of the internal capsule showed stronger age association for FA after controlling for WMH burden, whereas stronger age associations were observed in FA, MD, and DR of several other white matter tracts when white matter hyperintensity was not controlled (see table 14). The observed increase in age-related differences in whole rather than in

normal-appearing white matter suggests that failure to exclude WMH could have accounted to some degree for the associations of DTI indices and age reported in the literature. These results also provided the support for the need to separate WMH from whole white matter in studies of brain aging.

The difference between normal-appearing and whole white matter results was especially striking in the posterior limb of the internal capsule, where all DTI indices (except DR) were positively associated with age after correction for WMH, but not in whole white matter. It is hard to interpret this result because aging is commonly associated with decrease FA and increased MD, DA, and DR in white matter. This could not be explained by the presence of WMH because all the diffusivity measure of this tract showed negative or no association with age in whole white matter. One possibility might be related to iron deposition in this area because iron deposits could lead to increase anisotropy by introducing local field gradients (Pal, 2011). Iron deposits have been found in both normal-appearing white matter and the edges of WMH (Bagnato et al., 2011; Paling et al., 2012).

We observed stronger age DTI indices association in men than in women in several white matter tracts. This finding is in contradiction to an earlier report suggesting no sex difference in age DTI indices association (Inano, Takao, Hayashi, Abe, & Ohtomo, 2011). The reason for the discrepancy is unclear. An important factor should be noted is that the participants in that study were not screened for vascular diseases, whereas the participants in our study were exclusively normotensives. One possibility is that vascular risk factor and sex play roles in modify the association between age and DTI indices simultaneously. Therefore, the effect of sex might be

masked across people with different vascular risk factors. Indeed, Kennedy and Raz (Kennedy & Raz, 2009) found significant age × sex × hypertension interaction. In men, the age MD association was not significant for hypertensives, but highly significant ($r=.77$, $p<.001$) for normotensives. Whereas the correlations between age and MD might be higher in hypertensive women ($r=0.60$, $p=0.015$) than in normotensive women ($r=.53$, $p=.014$). This finding underscores the importance to take into consideration of vascular risk factor in modifying brain aging.

Association between age-related DTI Indices and RT Components

Drift rate. We did not observe the hypothesized associations between age-related differences in DTI indices of examined white matter tract in both normal-appearing and whole white matter and drift rate. To date, only one study examined the association between white matter integrity and RT components and found that higher FA in the central portion of the genu and splenium-parietal fiber was associated with larger drift rate (Madden et al., 2009). However, this study differs from present study in RT task employed. Task switching which involves greater attentional demand was used in that study whereas relatively simple letter discrimination task was used in the current study. Therefore, it may be the case that performance on more complex task on which older adults exhibit more deficits is more likely associated with degraded white matter integrity. It is also possible that the lack of association was due to the absence of vascular risk in our sample because WMH load could have been too small to have an influential effect. In addition, information accumulation has been found to depend on other brain areas such as the dorsal lateral prefrontal cortex and lateral intraparietal region (Bogacz, Wagenmakers,

Forstmann, & Nieuwenhuis, 2010), so it is likely that age-related reduction in drift rate is related to synergic role played by both age-related deterioration in those brain structures and relevant white matter tracts.

The results also revealed that MD in the genu of the corpus callosum in both normal-appearing and whole white matter was positively associated with drift rate. The relationships with drift rate hold for both axial and radial diffusivity measure in normal-appearing white matter, and for DR only in the whole white matter. In addition, there was a positive association between DA of the anterior corona radiata in whole white matter and draft rate. The reason underlying this observation is unclear. One possibility pertains to a third variable mediating the relationship between DTI indices and drift rate. However, the potential mediating role of IQ had been tested, and was not confirmed by the data. Thus, the exact variable mediating the claimed association is still a question to be answered by further studies.

Response conservativeness. In contrast to the initial prediction, we did not find any association between DTI indices of any examined white matter tracts and response conservativeness. Although FA in the anterior limb of the internal capsule has been found to predict RT in older adults (Madden et al., 2004), it should be noted that the evidence supporting hypothesized involvement of the frontal-striatal network in controlling decision boundary came from fMRI studies (Bogacz et al., 2010). Those fMRI studies found that speed emphasis increased activity in pre-supplementary motor area and the stratum (Forstmann et al., 2008), and that larger boundary separation was related to higher striatal activity (Kühn et al., 2011). Therefore, it is possible that the integrity of those structures themselves play a more important

role in adjusting response threshold. A second possibility pertains to the lack of vascular risk factor in our sample because it is hard for small white matter degradation to exert any significant effect on cognition. Another possibility is the contribution of the subthalamic nucleus (SN) in setting response threshold (Mansfield, Karayanidis, Jamadar, Heathcote, & Forstmann, 2011), and the integrity of SN was not assessed in our study.

Non-decision time. We found that DA of the superior corona radiata in normal appearing white matter was positively associated with non-decision time. This finding may reflect the fact that superior corona radiata contains motor pathway, and reduction in DA diffusivity would reflect damage to the motor fibers that are necessary for speedy RT. In addition, there was a trend for an association between age-related decrease in FA in the external capsule in whole white matter and increased non-decision time. This is in line with the extant finding that the integrity of the external capsule was related to motor performance (Sullivan, Rohlfing, & Pfefferbaum, 2010b). Although it is unclear why distinct connections occurred in particular white matter tracts in the normal-appearing and whole white matter, this finding suggested that white matter hyperintensity contributed to the differential associations.

Limitations and Conclusions

This study has several limitations. First, this study relies on cross-sectional data, which can be contaminated by cohort effect and uncontrolled individual differences, and thus precludes gauging true change with age. Indeed, magnitude of the age-related decline in RT had been shown to be underestimated by cross-sectional designs (Schaie, 1989). In addition, cross-sectional designs may lack sensitivity to brain-cognition associations revealed by longitudinal

studies (e.g., Raz, Rodrigue, Kennedy, & Acker, 2007). Second, all participants in this study were normotensive healthy adults. Although this sample selection is for the purpose of reducing some confounding factors associated with hypertension and antihypertensive medication, it may conceal the brain-cognition association modified by vascular risk factors. Vascular risk factors may matter more than age for WMH progression and cortical shrinkage in posterior brain regions and accelerated declines in cognitive performance, especially in the domain of executive functions, are associated with elevated vascular risk (Raz, Rodrigue, & Acker, 2003; Raz, Rodrigue, Kennedy, & Acker, 2007). Third, some important pathways such as the uncinate fasciculus were not included in the analysis. Thus, the role played by the integrity of this white matter tract in RT parameters remains to be explored. Finally, diffusion tensor model, as implemented in this study and in almost all previous studies, is inadequate to characterize white matter voxels containing crossing fibers (Jones, Knösche, & Turner, 2013).

In summary, this study investigated the associations between age-related difference in three RT components derived from the full diffusion model and white matter integrity of selected white matter tracts with and without controlling for WMH in normotensive healthy adults. We replicated all the major findings in the extant literature: advanced age was associated with lower drift rate, greater response conservativeness and longer non-decision time. Age-related reduction in FA and increase in MD was observed in most examined white matter tracts in both normal-appearing and whole white matter. There were anterior-posterior gradient decrease in FA and increase in MD, DA, and DR in several white matter structures: the corpus callosum, internal capsule, and the corona radiata in normal-appearing and whole white matter. In addition, the

results revealed that even in healthy normotensive adults, WMH burden could account for some DTI indices and age associations. Age-related difference in white matter integrity was greater in normotensive men than in normotensive women. Age-related increase in DA of the superior corona radiata in normal appearing white matter was associated with longer non-decision time. However, we did not find any of the hypothesized associations between age-related differences in DTI indices of examined white matter tracts with both drift rate and response conservativeness. Future longitudinal study including hypertensive participants and employing more advanced HARDI (High-angular-resolution diffusion imaging) and Q-ball vector analysis will provide a clearer picture of the relationship between age-related change in white matter integrity and RT components.

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ABSTRACT

WHITE MATTER INTEGRITY AND AGE RELATED DIFFERENCES IN REACTION TIME COMPONENTS

by

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Reduced speed in information processing is a well-documented phenomenon associated with advanced aging. Age-related deterioration in white matter integrity might play a role in age-related increase in reaction time (RT). However, the association between microstructural differences in particular white matter regions or tracts with RT is unclear. Decomposing RT into parts might be a better way to understand the relationship due to multiple processes involved in RT. In a lifespan sample of 90 healthy normotensive participants, this study examined the association between RT components derived from the Ratcliff diffusion model with age related difference in DTI indices of a wide variety of white matter tracts in both normal-appearing and whole white matter. The results revealed that advanced age was associated with lower drift rate, greater response conservativeness and longer non-decision time. Age-related reduction in FA and increase in MD was observed in most examined white matter tracts in both normal-appearing and whole white matter. Even in healthy normotensive adults, WMH burden could account for part of variance between age and DTI indices. Greater age-related difference in white matter integrity

was observed in normotensive men than in normotensive women. Increased axial diffusivity of the superior corona radiata in normal appearing white matter was associated with longer non-decision time. However, there was no association between age-related differences in DTI indices of examined white matter tracts and both drift rate and response conservativeness in healthy normotensive participants.

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