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Cerebral White Matter Integrity and Cognitive Aging: Contributions from Diffusion Tensor Imaging

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Abstract

The integrity of cerebral white matter is critical for efficient cognitive functioning, but little is known regarding the role of white matter integrity in age-related differences in cognition. Diffusion tensor imaging (DTI) measures the directional displacement of molecular water and as a result can characterize the properties of white matter that combine to restrict diffusivity in a spatially coherent manner. This review considers DTI studies of aging and their implications for understanding adult age differences in cognitive performance. Decline in white matter integrity contributes to a disconnection among distributed neural systems, with a consistent effect on perceptual speed and executive functioning. The relation between white matter integrity and cognition varies across brain regions, with some evidence suggesting that age-related effects exhibit an anterior-posterior gradient. With continued improvements in spatial resolution and integration with functional brain imaging, DTI holds considerable promise, both for theories of cognitive aging and for translational application.

Keywords

Diffusion tensor imaging; White matter; Cognition; Aging; Information processing; Human development

Research in areas defined traditionally as clinical neuropsychology, cognitive neuroscience, and cognitive aging has coalesced recently into a new discipline, the cognitive neuroscience of aging (Cabeza et al., 2005; Grady, 2008). A major impetus in this research development has been the work conducted in structural and functional neuroimaging, especially positron emission tomography (PET), and magnetic resonance imaging (MRI). Imaging research has been extremely informative regarding the brain localization of cognitive function and age-related differences in brain structure and function. The majority of this work, however, has to date concentrated on cerebral gray matter. This is an understandable bias, given the importance of cortical activity for cognition. The remaining 40-50% of the brain volume, however, comprises white matter, regions where there is a preponderance of axons coated with myelin, which also contributes significantly to efficient cognitive functioning. Although some aspects of perceptual and cognitive performance are highly modular and localizable, others, such as attention and memory, depend on widely distributed neural systems. Thus, conditions leading

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to disconnection among these systems have significant consequences for behavior and cognitive functioning (Catani & ffytche, 2005; Filley, 2005; Geschwind, 1965a, 1965b; Mesulam, 1990).

Imaging studies of white matter volume have detected significant volumetric decline in healthy older adults, as compared to younger adults. Whereas the age-related decline in gray matter volume is relatively linear from younger adulthood, the corresponding decline in white matter tends to be nonlinear, with a plateau in middle-age and additional decline, beyond that of gray matter, in later adulthood (Guttmann et al., 1998; Jernigan et al., 2001; Raz, 2000; Raz et al., 2005; Salat et al., 1999).[1] Imaging studies of healthy adults also suggest an association between age-related decline in white matter volume and deficits in cognitive performance (Brickman et al., 2006), but the majority of previous research on the relation between white matter and cognition has been clinical studies of patient populations. In demyelinating diseases, such as multiple sclerosis (MS), many changes occur, from the level of visual psychophysical performance (Galvin et al., 1977; Regan et al., 1977), to information processing speed (Kail, 1998; Litvan et al., 1988) and memory (Thornton & Raz, 1997), although the effects of MS are not entirely uniform (Halligan et al., 1988; Jennekens-Schinkel et al., 1990; Rao, 1995).

During normal aging, ischemic lesions, expressed as white matter hyperintensities (WMH) on MRI, are common among older adults and are correlated with decreased performance on some measures of cognitive performance (DeCarli et al., 1995; Gunning-Dixon & Raz, 2000). These lesions occur in healthy adults, without significant impairment, although hypertension and cardiovascular disease appear to have some causal role (Raz et al., 2007). WMH tend to affect speed-dependent cognitive performance, and executive more than non-executive processing (Oosterman et al., 2004; Prins et al., 2005; D. M. van den Heuvel et al., 2006). There is some indication that WMH are more predictive of executive functioning decline when located in the frontal lobe (Gunning-Dixon & Raz, 2003). From a series of regression analyses conducted on a sample of 65 individuals 65-84 years of age, Rabbitt et al. (2007) proposed that WMH prevalence accounted for all of the age-related variance in psychometric tests of speed and executive functioning. However, performance on more general measures of fluid intelligence (verbal and nonverbal problem solving, mental arithmetic) exhibited decline as a function of increasing age but no relation to WMH prevalence.

Diffusion Tensor Imaging

Research on cerebral white matter volume and WMH demonstrates that age-related differences in white matter are relevant for understanding age-related effects in cognitive performance. A limitation of volumetric and lesion studies is that they provide little evidence regarding the microstructural properties of behaviorally relevant tissue. In addition, because cognition depends on the communication of widely distributed neural networks, information regarding the spatial organization and connectivity of white matter pathways would be valuable.

The development of diffusion tensor imaging (DTI) has provided a new avenue for understanding the relations among cerebral white matter integrity, cognitive functioning, and aging, and findings in this area have been accumulating rapidly (Johansen-Berg & Behrens, 2009). DTI is a form of MRI that uses a tensor model to measure both the rate and directionality of the displacement distribution of water molecules across tissue components. Excellent discussions of the technical foundations and physics of DTI are presented in several sources:

[1]Virtually all neuroimaging studies of aging, as well as behavioral studies, are cross-sectional investigations of different age groups, rather than longitudinal studies of the same individuals over time. In describing cross-sectional results as *age-related*, we recognize that the differences among age groups include influences other than age (e.g., cohort effects). Thus, differences among the age groups in the dependent variables, expressed as deficits or improvements in particular measures, do not necessarily represent age-related *change*, for which longitudinal data are required.

Basser and Jones (2002), Beaulieu (2002), Jones (2008), Le Bihan (2003), Mori and Zhang (2006), and Mori (2007). For each voxel, DTI estimates diffusion in terms of the axes (eigenvectors) of an ellipsoid, typically separated into one major axis of diffusion and two minor axes that are orthogonal to the primary eigenvector. In gray matter, the diffusion of molecular water is highly isotropic—the same in all directions. In white matter, however, diffusion is more anisotropic—restricted to a particular direction. There are several sources of this directionality, including the myelin sheaths of axons, axonal cell membranes, and neurofilaments (Beaulieu, 2002; Jones, 2008; Peled, 2007). Consequently, anisotropy is highest in white matter pathways with compact fiber bundles oriented in parallel, such as the corpus callosum and pyramidal tracts.

The most frequently used DTI summary measures are mean diffusivity and fractional anisotropy (FA). Mean diffusivity represents the average rate of diffusion, independent of the directionality, and is often expressed by the average of the apparent diffusion coefficients across the three orthogonal axes of the diffusion tensor. FA is a normalized (scalar) value that represents the fraction of the tensor that can be assigned to anisotropic diffusion. Because white matter with high structural integrity will typically place a greater degree of directional restriction on diffusion, increasing FA is frequently interpreted as reflecting a higher degree of white matter integrity. While this interpretation is a useful heuristic, it is important to recognize that the interpretation depends on the local architecture of white matter. When an imaging voxel contains crossing or kissing fibers, for example, then FA may be lowered even though axonal structural integrity is high (Pierpaoli & Basser, 1996; Virta et al., 1999).

Additional information regarding the neurobiological mechanisms of anisotropic diffusion can be derived from the rate of diffusion (eigenvalue) along the individual eigenvectors. Axial diffusivity refers to the eigenvalue ($\lambda 1$) of the primary axis, whereas radial diffusivity is defined by the average of the eigenvalues perpendicular to the primary axis ($\lambda 2$, $\lambda 3$). Results from animal models suggest that myelin-specific damage tends to lead to increased radial diffusivity without significant changes in axial diffusivity, whereas axonal damage leads to decreased axial diffusivity (Song et al., 2002; Sun et al., 2006; Sun et al., 2007). This pattern is a signature of secondary (Wallerian) white matter degeneration following a primary lesion. The interpretation of the neurobiological mechanism of altered diffusivity, however, is not straightforward and, as with the interpretation of FA, depends on the local fiber architecture. In areas comprising pathways of intersecting fibers, rather than fibers arranged uniformly in parallel, secondary degeneration may lead to small or inconsistent changes in diffusivity. If, for example, within a region of intersecting pathways, such as the rostral pons, secondary degeneration primarily affects fibers of one direction (e.g., descending motor pathways), then the remaining fibers (e.g., transverse pontine fibers) would determine the apparent orientation of the principal eigenvector, possibly leading to a paradoxical increase in FA (Pierpaoli et al., 2001).

Age-Related Differences in DTI Measures of White Matter Integrity

Several reviews of DTI methods are available that specifically address the application to aging (Malloy et al., 2007; Moseley, 2002; Sullivan & Pfefferbaum, 2006, 2007; Wozniak & Lim, 2006). We focus here on differences in the methods with which DTI data are extracted and analyzed, following image processing. These methods provide a context for the types of conclusions that are drawn, and each of the approaches has advantages and disadvantages for age-related comparisons.

Histogram analysis

Histogram analysis provides an assessment of the frequency distribution of selected DTI measures across a range of voxels. In theory, the frequency distribution can be derived from

any selected set of voxels (i.e., a region of interest, ROI), but histogram analysis has most often been applied to whole-brain data sets.Z. G. Chen et al. (2001) proposed that whole-brain histogram analysis is both more accurate and less biased than an ROI-based approach. A single, whole-brain value is consequently attractive as a summary measure for comparison between groups. Several studies have reported an increase in mean diffusivity as a function of increasing adult age, derived from whole-brain histograms, suggesting an age-related decline in white matter integrity (Z. G. Chen et al., 2001; Nusbaum et al., 2001; Rovaris et al., 2003). Z. G. Chen et al., however, found that the age-related increase was less pronounced for a tissue-specific estimate of mean diffusivity (1% per decade) than for a global estimate (3% per decade), implicating the potential contribution of cerebrospinal fluid (CSF) and large vessels to the global estimate. Whereas Z. G. Chen et al. considered anisotropy to be primarily a confounding influence in the measure of diffusivity, Rovaris et al. (2003) compared whole-brain FA and diffusivity histograms directly and found that although both types of histograms exhibited significant age-related effects, the age effect was strongest for FA, and the two histograms were not correlated. Rovaris et al. concluded that FA provides an independent index of white matter microstructure.

ROI analysis

Information regarding regional, rather than whole-brain, differences in white matter integrity is valuable, especially when the goal is to correlate white matter measures with cognitive measures. Defining white matter ROIs in a reliable and accurate manner, however, is challenging. Due to the higher level of distortion in tensor images (from B_0 field inhomogeneity and eddy currents) than in T_1-weighted anatomical imaging, ROIs drawn on T_1-weighted anatomical images cannot be applied to tensor images without significant post-processing techniques. It is possible to define ROIs within the tensor images, but as Pfefferbaum et al. (2000) pointed out, that approach entails the danger of using the dependent variable (FA) to define the independent variable (anatomical ROIs).

Sullivan, Pfefferbaum, and colleagues developed a method of ROI analysis as a basis for their seminal series of DTI studies, which were the first to document programmatically the variation in white matter integrity associated with aging (Pfefferbaum & Sullivan, 2003; Pfefferbaum et al., 2000; Sullivan et al., 2001). These authors used a tissue segmentation procedure to distinguish white matter, gray matter, and CSF in the tensor images, and then applied ROIs derived from anatomical imaging to the segmented DTI data. Pfefferbaum et al. (2000) assessed FA (among other measures) for five ROIs in a sample of 31 healthy men between 23 and 76 years of age. The correlation between FA and age was negative for all of the ROIs, except the splenium. Sullivan et al. (2001) compared these 31 men to 18 women between 23 and 79 years of age and found a similar pattern of age-related effects for men and women. Pfefferbaum and Sullivan (2003) applied systematic morphological expansion and restriction of selected brain regions and found that partial volumning effects had significant influences on DTI measures, but that the age-related differences (decline in FA, increase in diffusivity) could not be attributed entirely to partial volumning (see also [Bhagat & Beaulieu, 2004]). Pfefferbaum et al. (2000) concluded that the age-related decline in FA represented a decline in white matter integrity, possibly involving mild demyelination and loss of myelinated axons. These authors also suggested that the differential age-related effects in anterior regions were due to the later myelination of these regions.

Other methods of ROI analysis have yielded age-related differences consistent with those of Sullivan, Pfefferbaum, and colleagues (Abe et al., 2002; Nusbaum et al., 2001; O'Sullivan et al., 2001; Yoon et al., 2008). In several studies, Madden and colleagues have defined ROIs within the tensor images, in native space (Bucur et al., 2008; Madden et al., 2007; Madden et al., 2004). These authors reduced the potentially confounding effect of FA by lowering the

maximal FA value in the image during ROI definition, so that relevant white matter structures were delineated as pure white. Data analyses are then performed with the FA limit removed. Gold et al. (2008) have also used this method. Figure 1 provides an example of ROIs defined in native space within the tensor images. The studies using this method generally confirm the previous findings, in that age-related decline in FA was typically greater in magnitude for anterior regions (e.g., genu, pericallosal frontal), although age-related decline was evident in posterior ROIs also.

Voxelwise analysis

Defining ROIs anatomically has the advantage of using a common anatomical boundary for each participant, but the boundary definition depends on the judgment of individual operators. In addition, significant differences in the measures of interest may occur outside the selected ROIs. Alternatively, integration of DTI data with high-resolution anatomical images (or with the *b*0 image from the DTI series) is possible, using normalization and smoothing methods similar to those used in functional imaging (Friston et al., 1995; Smith et al., 2004). Although the transformation will entail the loss of some information, the DTI data for each participant are referenced to a standardized stereotaxic space. As a result, analyses can also be conducted on a voxelwise basis throughout the brain rather than limited to selected ROIs. Head et al. (2004), Salat et al. (2005), and Ardekani et al. (2007) conducted both voxelwise analyses and ROI analyses on spatially normalized DTI data. The results support the anterior-posterior gradient of age-related decline in white matter integrity (FA). Salat et al. also noted, however, that FA exhibited significant age-related decline in the posterior periventricular region. This latter region is a common location of WMHs in older adults (Holland et al., 2008; Vernooij et al., 2008).

A variant of the voxelwise approach, tract-based spatial statistics (TBSS) (Smith et al., 2006; Smith et al., 2007), provides more specific information about individual white matter tracts, without spatial smoothing. With the TBSS analysis, individual diffusion images are first aligned to a standard template. These images are then averaged across all participants to form a mean diffusion image that is used to generate a white matter "skeleton," representing the center of white matter tracts that are shared by all participants (Figure 2). The FA values within the skeleton can then be obtained for each participant. Several studies, using TBSS, have confirmed the anterior-posterior gradient of decline in FA that was observed with ROI and voxelwise methods, for healthy younger and older adults (Bennett et al., 2009; Burzynska et al., 2009; Damoiseaux et al., 2009).

DTI tractography

Recently, considerable interest has been generated by DTI tractography (Catani, 2006; Ciccarelli et al., 2008; Mori & van Zijl, 2002; Nucifora et al., 2007; Wakana et al., 2004). Like voxelwise methods, a goal in tractography is to minimize the reliance on operator-defined parameters. But tractography places a higher premium on identifying the relevant white matter pathways within each participant, rather than on the degree to which the individual pathway is shared with the group average. Typically, tractography is an automated algorithm, conducted in native space, which estimates the most likely structure of an individual white matter pathway, either propagating from a specified source region or connecting source and target regions. Because tractography is conducted in native space, the spatial structure of the tracts will vary across participants.

Tractography algorithms can be broadly categorized as being either deterministic or probabilistic (Jones, 2008; Nucifora et al., 2007). Deterministic algorithms reconstruct tracts by estimating a trajectory from each seed point along a streamline that is estimated from the primary diffusion directions of adjacent voxels (Basser et al., 2000; Conturo et al., 1999; Mori

et al., 1999). In quantitative tractography (Corouge et al., 2006; Sullivan et al., 2006; Sullivan et al., 2008), FA and diffusivity values are obtained continuously (e.g., at millimeter intervals) along the length of the tract. With probabilistic algorithms, in contrast, trajectories follow a probabilistic distribution of potential primary diffusion directions that are estimated for each voxel (Behrens et al., 2003; Parker et al., 2003). Probabilistic tractography is valuable for tracking into regions with low anisotropy, such as cortical and subcortical gray matter and areas with crossed or kissing fibers (Jones, 2008; Nucifora et al., 2007).

Overall, DTI tractography has been successful in isolating white matter pathways with a remarkably high degree of correspondence to classical, post-mortem dissection and histology (Catani et al., 2002; Conturo et al., 1999; Dauguet et al., 2007; Lawes et al., 2008). To date, investigations of adult age differences using tractography have relied primarily on deterministic methods. Sullivan et al. (2006) reported the first application of fiber tracking to aging. These authors focused on the corpus callosum, using the high-resolution T_1-weighted images to create an averaged image space for 10 younger and 10 older adults combined. Thus, target and source regions could be defined within a common anatomical space and transformed back into native space for quantitative fiber tracking. Fibers were estimated across six sections spanning the anterior-posterior length of the corpus callosum, yielding within-section estimates of number of fibers, fiber length, FA and mean diffusivity. The two most anterior sections of the callosum exhibited significant age-related decline in FA and increase in diffusivity, whereas age differences were more variable for the measures of fiber number and length.

Subsequent applications of quantitative fiber tracking to other white matter pathways have generally confirmed the age-related pattern reported by Sullivan et al. (2006) for callosal fibers (Davis et al., 2009; Madden et al., 2009; Sullivan et al., 2008; Zahr et al., 2009). Figure 3 presents an example of deterministic tractography, from Madden et al. (2009). The FA data averaged across 20 younger and 20 older adults are presented along the length of four separate tracts in Figure 4. These data, with healthy, community-dwelling individuals, reveal that age-related decline in FA is most apparent in frontal pericallosal regions, consistent with the anterior-posterior gradient of previous studies. Sullivan et al. (2008), however, completed tractography on 11 bilateral pathways, in addition to the callosum, and proposed that a superior-inferior gradient is also evident. Greater age-related decline occurred in the microstructure of frontal, limbic, striatal, and superior pathways of the supratentorium, as compared to infratentorial (pontine and cerebellar) systems. Zahr et al. (2009), in a fiber tracking study of eight pathways, have also confirmed that both anterior-posterior and superior-inferior gradients were present.

Axial and radial diffusivity

As noted previously, the commonly used DTI summary metrics FA and mean diffusivity are calculated from the individual eigenvalues of the tensor matrix, λ1, λ2, λ3, which in turn comprise axial diffusivity (λ1) and radial diffusivity (mean of λ2 and λ3). Examining the individual eigenvalues can provide information regarding the neurobiological mechanisms of age-related effects in the summary metrics. There is some evidence, for example, that the age-related differences in FA and mean diffusivity are driven primarily by an increase in radial diffusivity (Bhagat & Beaulieu, 2004; Madden et al., 2009; Zhang et al., 2008). Given the association of radial diffusivity with myelin-related effects (Song et al., 2002; Sun et al., 2006; Sun et al., 2007), an age-related increase in radial diffusivity suggests a differential contribution of demyelination (i.e., a thinning or deterioration of the axonal myelin sheath) to age-related decline in FA. Analyses focusing on the regional changes in axial and radial diffusivity suggest that the differential age-related increase in radial diffusivity is more pronounced in the prefrontal regions. That is, the anterior-posterior gradient of FA may reflect

a comparable gradient of declining myelin integrity (Davis et al., 2009; Sullivan et al., 2006; Zahr et al., 2009).

Other patterns of age-related differences in axial and radial diffusivity, however, have been observed. Sullivan et al. (2008), Vernooij et al. (2008), and Zahr et al. (2009) reported significant age-related increases in both the axial and radial components of diffusivity, across a wide selection of white matter pathways. Using TBSS, Bennett et al. (2009) and Burzynska et al. (2009) categorized various white matter regions according to the relative change in the axial and radial components of diffusivity. In both of these latter studies, radial diffusivity increased with age across the majority of tracts, but the occurrence of a concomitant increase in axial diffusivity was more variable. The genu of the corpus callosum consistently exhibited age-related increases in both axial and radial diffusivity, whereas increased diffusivity was more likely to be limited to the radial component in association tracts connecting anterior and posterior regions (e.g., superior longitudinal fasciculus). Further, both Bennett et al. and Burzynska et al. found that, in some white matter tracts, aging was associated with decreased axial diffusivity.

These results suggest that an age-related decrease in myelin integrity alone cannot account for the pattern of age-related differences in axial and radial diffusivity. The relevant neurobiological mechanisms are not currently known. Prefrontal regions are among the last to myelinate during development, and thus a "last-in-first-out" principle may contribute to the observed anterior-posterior gradient (Bartzokis et al., 2004; Davis et al., 2009; Pfefferbaum et al., 2000; Raz, 2000). Myelin is only one of the variables, however, leading to restricted diffusion (Beaulieu, 2002; Jones, 2008). Decreased density of axonal packing within a voxel, due to decreased axonal diameter, fewer axons, or both, would also lead to increased diffusivity in all directions (Sullivan et al., 2008; Zahr et al., 2009). Decreased axial diffusivity may represent an initial response to lost axons (i.e., increased extracellular matrix and glia), which is followed by increased axial diffusivity as cellular debris is cleared by microglia (Burzynska et al., 2009). Decreased axial diffusivity may also reflect macrostructural effects, such as a decreased coherence in the orientation of axons, within voxels, for older adults relative to younger adults (Bennett et al., 2009). That is, for two axonal bundles of comparable structural integrity, the bundle in which the axons are less consistently aligned will have lower axial diffusivity.

A related issue, emphasized by Wheeler-Kingshott and Cercignani (2009), is that an individual eigenvalue does not necessarily reflect the same biophysical substrate across data sets, if the data sets differ in the orientation of the principal eigenvector. Whether changes in the individual eigenvalues, which are properties of the tensor, reflect true changes in the tissue microstructure, depends on the mathematical and geometrical properties of the data, especially the orientation of the principal eigenvector. Thus, axial and radial diffusivity are important as additional sources of information regarding differences across DTI data sets, but interpreting the neurobiological substrate of these variables is limited, without determining the orientation of the principal eigenvector.

Cognitive Correlates of White Matter Integrity in Aging

Identifying the cognitive correlates of age-related differences in white matter integrity has been a central concern of DTI research (Gunning-Dixon et al., 2009; Moseley, 2002; Sullivan & Pfefferbaum, 2006, 2007). This goal, however, depends on the available data regarding the relation between white matter integrity and cognition in healthy adults, independently of age effects. The relation between white matter and cognition has not yet been established clearly, and though consistent trends are evident, no single classification scheme adequately characterizes the extant findings.

Speed of processing and executive functioning

As discussed previously, some indication of a relation between white matter integrity and cognition derives from research on ischemic lesions of white matter, which have demonstrated that increasing WMH volume is associated with decreasing performance on tests of elementary perceptual speed (Rabbitt et al., 2007; Raz et al., 2007; D. M. van den Heuvel et al., 2006). One general principle that emerges from DTI studies is that, independently of age effects, decreasing integrity of normal appearing white matter is associated with worse performance on tests that rely on processing speed and executive functioning. This relation has been confirmed with both voxelwise (Turken et al., 2008), and tractography-based (Correia et al., 2008) DTI techniques. The relation between white matter integrity and speed also extends to tasks such as lexical decision (word/nonword discrimination), which rely on the retrieval of semantic memory information (Gold et al., 2007).

Although most measures of processing speed are defined on the basis of manual reaction times and thus have a significant motor component, the white matter-speed relation appears to hold for information processing stages that precede the motor response. Gold et al. (2007) found that, in younger adults, decreased white matter integrity (FA) in language regions of the left hemisphere (inferior frontal and inferior parietal) was correlated with slower lexical decisions, but that a corresponding effect was not evident in regions mediating visual/motor processing (optic radiation and posterior limb of the internal capsule, bilaterally). Similarly, data from combined imaging modalities of DTI and magnetoencephalography (MEG) suggest that the correlation between white matter integrity and the latency of peak visual responses during an eye movement task, in younger adults, holds at an early stage of information processing, within the first 120 ms of saccade initiation (Stufflebeam et al., 2008).

Vernooij et al. (2009) provided a particularly strong source of support for the relation between white matter integrity and processing speed in a population-based sample of 860 older adults 61-92 years (Rotterdam Study). These authors conducted regression analyses of whole-brain DTI variables and cognitive performance that statistically controlled the relative volume of both normal appearing white matter (i.e., atrophy effects) and white matter lesions. A variety of cognitive measures yielded composite measures of information processing speed, motor speed, memory, and executive functioning (e.g., response fluency and inhibition). Declining FA of normal appearing white matter was related significantly to declines in both motor speed and processing speed, but only the latter relation held for mean FA when lesion volume was controlled. In addition, both axial and radial diffusivity exhibited more widespread relation, than mean FA, to the cognitive measures. Both diffusivity measures were correlated significantly with information processing speed and executive functioning, with lesion volume controlled (i.e., higher diffusivity associated with worse performance). None of the DTI variables was related to memory performance. Vernooij et al. also used age as a covariate in their analyses, however, and thus the observed correlations between white matter integrity and processing speed were independent of age-related variability in processing speed.

Aging, white matter integrity, and cognition: Interpretive issues

The DTI studies reviewed to this point lead to two conclusions. First, age-related differences occur both in the overall measures of white matter integrity (e.g., FA) and in component measures (e.g., axial and radial diffusivity), especially in prefrontal regions. Second, independently of age, variation in white matter integrity is correlated with cognitive performance, particularly in tests relying on speed of information processing and executive functioning. An independent question is whether there are interactive effects in the aging-white matter and cognition-white matter trends. Although individual research studies bearing on this question have been accumulating rapidly, several issues should be considered in interpreting the results.

The most fundamental question to be addressed is the causal role of white matter integrity in age-related differences in cognitive performance. Specifically, to what extent is age-related variability in cognitive performance shared with age-related differences in white matter integrity? To date, however, few studies have conceptually framed the research in this manner. Individual studies have addressed a variety of different, though related, issues that do not always map directly onto this fundamental question. For example, the demonstration of a correlation between white matter integrity and some cognitive measure, for older adults, does not necessarily imply that white matter integrity is associated with the *age-related* variance in the cognitive measure. Similarly, if age groups are analyzed separately, and a correlation between white matter integrity and cognition is statistically significant for older adults but not for younger adults, this pattern, by itself, does not necessarily imply that the correlation differs significantly between the age groups. The correlation may be slightly above threshold for older adults, but slightly below threshold for younger adults. A direct comparison of the age groups, or some test of the age-related difference in the relation between the DTI and cognitive measures, is necessary.

In addition, although both the cognitive and DTI measures may vary with age, this pattern is not sufficient to infer that white matter integrity has a direct influence on age-related effects in cognitive performance. To infer a mediating or causal role, the DTI measures should have a significant relation to the measures of cognition that is independent of age, and the age-related variance in the cognitive measure should be attenuated by including the DTI measures in the regression model predicting cognition from age (Baron & Kenny, 1986; Lindenberger & Pötter, 1998; Salthouse, 1992).

Related to these methodological concerns is the issue of identifying specific cognitive effects in aging. Although the general trend of DTI studies suggests that the pronounced influence of white matter integrity is related to processing speed and executive functioning (Correia et al., 2008; Stufflebeam et al., 2008; Turken et al., 2008; Vernooij et al., 2009), it is not clear whether age-related differences in these aspects of cognitive functioning are entirely separable at the behavioral level. Some behavioral studies suggest that age-related differences in executive functioning are empirically separable from speed-dependent differences (Keys & White, 2000; Rodriguez-Aranda & Sundet, 2006), and the anterior-posterior gradient that has been noted in DTI studies of aging and white matter integrity (Davis et al., 2009; Madden et al., 2009; Sullivan & Pfefferbaum, 2006, 2007) is consistent with the assumption of an identifiable role of executive functioning. Elementary measures of information processing speed, however, share age-related variance with a wide variety of cognitive tasks (Madden, 2001; Salthouse, 1996; Salthouse & Madden, 2007), including executive functioning (Salthouse et al., 2003), and neuropsychological tests that are assumed to measure frontal lobe functioning correlate highly with non-frontal tests (Salthouse et al., 1996). Thus, interpreting age-related variation in white matter integrity in terms of the anterior-posterior gradient and executive functioning may be a useful starting point for DTI research but ultimately is not likely to account for all of the findings (Bennett et al., in 2009; Greenwood, 2000; Kennedy & Raz, 2009; Madden et al., 2009).

Finally, the potential role of health-related variables, in the interaction of age-related change in the brain and cognition, is not well understood. As noted previously, the relation of DTI measures to cognitive performance is influenced by the presence of WMH (Vernooij et al., 2009), and WMH tend to increase as a function of both age and cardiovascular risk (e.g., hypertension). Thus, variation in DTI measures of white matter integrity, across age groups, is likely influenced by WMH and cardiovascular health.

Nitkunan et al. (2008), for example, examined the relation between white matter integrity measures from DTI and brain biochemistry from magnetic resonance spectroscopy (MRS),

within a single ROI (white matter of the centrum semiovale). These authors examined cerebrovascular status by comparing three groups of older adults: individuals with cerebral small vessel disease (SVD), hypertensive individuals without a history of stroke, and normotensive controls. Within each group, the DTI measures correlated significantly with MRS measures indicating axonal loss/dysfunction, and the magnitude of the correlations was generally graded with the severity of cerebrovascular disease, with the hypertensive group intermediate between the normotensive and SVD groups. The Nitkunan et al. analyses, however, did not focus specifically on the age-related variation in white matter integrity; age-related effects were covaried. Vernooij et al. (2008), examined the age-related effects and found that, in their Rotterdam Study participants, few age-related differences in FA remained significant once white matter atrophy and WMH lesion load were controlled statistically. Vernooij et al. concluded that age-related differences in white matter integrity reflect a pathophysiologic process rather than aging per se.

Alternatively, cardiovascular status and WMH volume may alter the normal relation between adult age and white matter integrity rather than entirely subsuming the relation between age and white matter integrity. Correia et al. (2008) derived several quantitative metrics of white matter integrity, based on deterministic tractography, and compared individuals with known vascular white matter injury (40-79 years) to a control group of demographically similar, healthy individuals (44-84 years). Metrics calculated from whole-brain data indicated significantly lower white matter integrity for the vascular group than for the controls. In addition, the metrics exhibited significant age-related decline for the healthy group but not for the vascular group, suggesting that subcortical vascular disease disrupted the normal variation in white matter integrity with age.

Aging, white matter integrity, and cognition: Empirical findings

The results of DTI studies, regarding cognitive correlates of age-related differences in white matter integrity, have yielded a complex pattern. But the data generally incorporate the trends that we have noted for 1) the relation between aging and white matter (anterior-posterior gradient); and 2) the relation between cognition and white matter (correlation with speed and executive functioning).

O'Sullivan et al. (2001) reported one of the initial correlations between DTI and cognitive data for older adults. These authors used relatively broad ROIs (whole-brain white matter divided into anterior, middle, and posterior regions) and correlated mean diffusivity and FA with several psychometric tests of cognitive function. Correlations performed within the older adult group indicated that mean diffusivity in the anterior ROI was correlated with a neuropsychological measure of executive functioning (Trail Making), whereas FA in the middle region was correlated with verbal fluency. These analyses, however, were conducted only within the older group, and the effect of age was covaried. O'Sullivan et al. suggested that the age-related decline in white matter integrity would lead to a disconnection of neural networks necessary for efficient cognitive performance. This concept of disconnection has been discussed widely as an explanatory construct for age-related cognitive decline, although whether the relevant neurobiological mechanism is demyelination, axonal loss, macrostructural organization, or a combination of these, is being investigated currently (Andrews-Hanna et al., 2007; Bartzokis, 2004; Bartzokis et al., 2004; Charlton et al., 2006; Charlton et al., 2008; Damoiseaux, et al., 2009).

Contemporaneously with the O'Sullivan et al. (2001) report, Sullivan et al. (2001) confirmed that white matter integrity was correlated with a behavioral measure, for 51 participants across a wide range of 23-79 years. A sensory/motor task requiring interhemispheric transfer (alternating finger tapping) correlated positively with mean FA, whereas a baseline version of the task (unimanual finger tapping) did not. Two aspects of the Sullivan et al. findings are

particularly relevant: First, the positive correlation between FA and alternating finger tapping held within posterior ROIs (splenium and parietal pericallosal), whereas the age-related decline in mean FA was greater for more anterior regions. Second, in a regression model containing both age and FA, from the posterior ROIs, predicting finger tapping output, FA remained a significant predictor whereas age did not. This finding suggests that white matter integrity may have a more direct influence than age on this form of sensory/motor performance.

Madden et al. (2004) reported a similar pattern in an ROI analysis of 16 younger and 16 older adults. Mean reaction time in a choice response task (visual oddball) correlated with splenium FA for younger adults, but with FA within the anterior limb of the internal capsule for older adults. Rather than comparing the effectiveness of age and FA as predictors, Madden et al. took the approach of testing the age group difference in the correlation between mean reaction time and FA. This comparison, illustrated in Figure 5, was significant, which provided the first direct test of an age-related difference in the correlation between white matter integrity and a behavioral measure of cognitive performance. In addition, as in the Sullivan et al. (2001) study, those regions exhibiting significant correlations with behavioral measures were not those exhibiting the most pronounced age-related decline in mean FA.

Several subsequent studies have also focused specifically on age-related differences in the relation between white matter integrity and cognition. In their tractography study of younger and older adults, Davis et al. (2009) used a regression model that included the interaction between age group and FA as a predictor of each of several neuropsychological tests. These authors found that several tracts exhibited a stronger correlation between FA and cognitive performance for older adults than for younger adults. Specifically, older adults' increasing FA within frontal regions (genu, uncinate fasciculus) was correlated with better performance on several tests of executive functioning (e.g., spatial working memory, set shifting), whereas the corresponding effect within older adults' more posterior brain regions (e.g., splenium, inferior longitudinal fasciculus) reflected increasing FA and better performance on visual memory tests. Further, when the components of FA were distinguished, the correlations were nearly entirely due to radial diffusivity rather than axial diffusivity.

Similarly, Kennedy and Raz (2009), in their ROI analysis, also used regression models that tested for age-related differences in the relation between FA and several composite measures of cognitive performance. The regional variation in the correlations, however, was somewhat different than that reported by Davis et al. (2009). In the Kennedy and Raz data, age-related decline in white matter integrity within more anterior brain regions was associated with decreased processing speed and working memory, whereas decline within more posterior brain regions was associated with reduced inhibition and task switching. Kennedy et al. emphasized that the targeted cognitive domains, though differentiated into speed, executive functioning, and several forms of memory, still relied on widely distributed white matter pathways, in which disruption can have wide-reaching effects.

In recent studies, researchers have taken the further step of identifying the age-related variance in cognition and estimating the degree to which age-related variance in DTI is shared with age-related variance in cognition. Madden et al. (2009) and Gold et al. (2008) were both concerned with specific components of information processing. Madden et al. used a model of reaction time distributions to distinguish the efficiency of retrieval of semantic information (drift rate), in a word categorization task, from the more peripheral processes of display encoding and response time. In a series of regression analyses, age-related variance in the drift rate measure was attenuated substantially by individual differences in FA within regions of frontoparietal white matter pathways (central genu and splenium-parietal). Using a similar application of regression models, Gold et al. focused on the time required to switch between different tasks (letter or number decisions), rather than on the efficiency of individual decisions. Gold et al.

found that FA within a frontoparietal pathway, the superior longitudinal fasciculus of the left hemisphere, was a significant mediator of age-related variance in task switching.

Zahr et al. (2009) examined domains of cognition: working memory, motor performance, and problem solving, rather than specific information processing components. As in the Madden et al. (2009) and Gold et al. (2008) studies, Zahr et al. found that the DTI measures led to significant attenuation of age-related variance in the cognitive measures. The genu and fornix were mediators of all three cognitive domains, whereas age-related differences in motor performance were influenced by a wider range of pathways, including the splenium and uncinate fasciculus in addition to the genu and fornix.

Charlton et al. (2008) used structural equation modeling to determine whether mean diffusivity within a relatively large ROI (primarily centrum semiovale) was a mediator of the relation between age and several measures of cognitive performance: speed, cognitive flexibility, working memory, and fluid intelligence, for 118 adults 50-90 years of age. Surprisingly, although speed mediated the age-related effects in all of the other cognitive measures, diffusivity was a significant mediator only of the age-related variance in working memory. The authors obtained an identical model using mean FA rather than diffusivity as the DTI mediator.

As a preliminary, semi-quantitative roadmap through the diverse findings of DTI studies on aging and cognition, we have listed in Table 1 the results of 18 published reports of a statistical relation between one or more DTI variables and a behavioral measure of cognition, with a sample of older adults. We selected these studies from PubMed searches using the terms “white matter integrity AND aging” and “diffusion tensor imaging AND aging AND cognitive.” The selected articles used DTI to assess white matter integrity, examined white matter-cognition effects in healthy older adults, were not review papers, and used regional rather than whole-brain DTI measures. The table values are the mean effect sizes (Rosenthal & DiMatteo, 2001) for the white matter-cognition relation within a brain region. We have used bold font for effect sizes that are moderate or larger (> .30). Note, however, that these effect sizes refer to the overall effect of the white matter-cognition relation, in studies of older adults, not to the age-related variation in this effect. In addition, the values are likely underestimates of true effects, because nonsignificant findings were assigned an effect size of zero.

From this table, some support is present for the general trends of the anterior-posterior gradient and prominence of speed and executive functioning that we have discussed previously. These trends do not combine in a regionally definitive manner, however, and considerable variability is evident. The largest mean effect size, for example, is in the cell representing the correlation between composite measures of executive functioning and the genu of the corpus callosum. But several cells of the table representing the posterior regions also contain moderate effects for executive functioning and processing speed. The frontal table-cells include notable effects for other cognitive processes, including recognition memory, word reading, and postural stability.

While recognizing this variability, we would also emphasize two points: First, the vast majority of the table values are positive, reflecting a consistent relation between increasing white matter integrity and better cognitive and sensory/motor performance. Second, the selected studies were uniformly empirical in nature, but still adopted varying approaches to define the cognitive outcome measure. Whereas some studies focused on specific components of information processing (Gold et al., 2008; Madden et al., 2009), others used a broad range of tasks to construct composite measures of cognitive domains (Kennedy & Raz, 2009; Zahr et al., 2009). As research in this area continues beyond these early stages, a more comprehensive account of the relation between age-related differences in white matter integrity and cognition will emerge. Using composite cognitive measures will be most valuable in investigations based

on large sample sizes to establish the reliability and validity of effects, whereas using specific information processing components will be valuable in theory-driven studies that focus on the characteristics of individual neural systems (Paus et al., 2001).

Future Directions of DTI and Cognitive Aging

In this rapidly developing area of neuroimaging, progress in several directions will be valuable to the cognitive neuroscience of aging.

Clinical application

DTI is already widely used in diagnosis and prognosis of neurological disease, especially MS (Filippi et al., 2001; Ge, Law, & Grossman, 2005; Goldberg-Zimring et al., 2005; Kealey et al., 2005), and stroke (Mukherjee, 2005; Yu et al., 2009). Several studies demonstrate that DTI can provide insight into the neurobiological mechanisms of Alzheimer's disease and related dementias disease (Bozzali et al., 2001; Song et al.,2004). Empirical results from this type of application can contribute to theoretical issues in cognitive aging. For example, is there a qualitative difference between normal brain aging and dementia? Investigations that have included patients with Alzheimer's disease, as well as healthy younger and older adults, suggest that the regional changes in white matter integrity associated with dementia are not simply an exaggeration of normal aging (Damoiseaux et al., 2009; Head et al., 2004). Similarly, given the relation among cardiovascular risk factors, WMH, and cognitive decline (Rabbitt et al., 2007; D. M. van den Heuvel et al., 2006), DTI can potentially help differentiate age-related effects from health-related effects (Raz et al., 2005; Raz et al., 2003; Raz et al., 2007).

The documentation of recovery and rehabilitation following brain injury is also an expanding area of DTI application (Johansen-Berg & Behrens, 2006). Bendlin et al. (2008) tested 46 traumatic brain injury patients at two time points, approximately two months following their injury and one year later. These authors found that DTI defined areas of decreased FA and increased MD at the one-year point, relative to controls, that were not indicated by high resolution T_1-weighted images. In response to normal adult developmental changes in gray matter and white matter, the plasticity of the central nervous system may lead to changes in cognitive strategy, which are expressed behaviorally as the age differences measured in tests of cognitive performance (Greenwood, 2007). Thus, the clinical studies of brain injury may be an informative model for applying DTI to investigate the role of functional plasticity in cognitive aging.

An emerging area in neuroimaging studies of aging and functional plasticity is the effect of aerobic exercise and cardiovascular fitness. Both cross-sectional and longitudinal studies suggest that a higher level of cardiovascular fitness can help slow the trajectory of age-related decline in cortical and white matter volume (Colcombe et al., 2003; Kramer et al., 1999; Kramer & Hillman, 2006). To date, studies have relied primarily on estimates of gray and white matter density, from voxel-based morphometry. Although preliminary evidence from DTI indicates that aerobic fitness is associated with increased FA, independently of age (Marks et al., 2007), additional research with DTI on this topic is necessary.

Improvements in DTI methodology

The current implementation of DTI often suffers from fluid and flow contaminations from CSF and vasculature due to partial volumning. This is particularly true in the ventral brain regions, within the periventricular space or close to the cortical surface, as a result of the hyper-intensity of fluid in the T_2 weighted baseline image (Bhagat & Beaulieu, 2004). In addition, because there are many variables contributing to anisotropy within a large imaging voxel, acquisition techniques that can distinguish the various sources will be critical to understanding the

mechanisms of age-related differences in diffusivity. New methodologies provide the ability to identify some of the relevant microstructural variables, such as the axon density and axon diameter distribution within a voxel (Alexander, 2008; Assaf et al., 2008).

DTI involves the acquisition of diffusion-weighted images sensitized in various gradient directions. While the inhomogeneous field is the primary reason for the base image distortion, the distortion of the diffusion weighted images results from the combination of the inhomogeneous field (which is the same for the base image) and eddy currents from strong diffusion gradients. A direct method to correct for distortion is to acquire magnetic field maps that correspond to the various diffusion weighting directions. The individual field maps can then be used to correct both the static and dynamic distortions (B. Chen et al., 2006). Truong et al., (2008) have recently applied this technique, combined with sensitivity encoding (SENSE) DTI acquisition, with a high-order polynomial correction to remove both distortions. Shown in Figure 6 are colored FA maps and the original T_2* maps. The uncorrected FA map is presented in Panel A. FA maps are presented with ΔB_0 correction (Panel B) and ΔB_0 plus eddy current correction (Panel C). Compared with the current best practice method (Panel D), a double-refocused spin-echo DTI acquisition (Reese et al., 2003), the Truong et al. method achieves further improved spatial accuracy within the frontal lobe, gray/white matter boundaries, and along the edge, as well as 19.8% higher signal-to-noise ratio.

Researchers are also actively seeking to improve the angular resolution of tensor images. Accurate reconstruction of neural connectivity patterns from DTI has been hindered by the relatively low in-plane resolution of DTI (typically 1-2.5 mm^2), which limits the discrimination of crossing fibers. Techniques such as q-ball imaging (Tuch et al., 2003) and diffusion spectrum imaging (Schmahmann et al., 2007) provide estimates of multiple fiber orientations, although validation with anatomical techniques (e.g., autoradiography) has not yet been achieved (Catani, 2007).

Liu and colleagues (Liu et al., 2004; Liu et al., 2009) have developed the self-navigated interleaved spiral (SNAILS) sequence for DTI, which can provide higher resolution than the sequences typically used in investigations of aging and cognition. SNAILS is a multi-shot, fat-saturated diffusion-weighted spin echo sequence. The technique oversamples the center of k-space, which provides an inherent motion compensation capability. Figure 7 is an example of DTI imaging acquired with SNAILS, which yielded an in-plane resolution of 390 μm^2. This represents one of the highest spatial resolutions that has been achieved *in vivo* on a human brain. Evident in the figure is the discrimination of multiple fiber orientations, which match the tissue morphology in corresponding myelin-stained sections.

The SNAILS and related methodologies will be particularly valuable in application to aging, because for any white matter pathway, FA is influenced by the anatomical architecture of the pathway. For example, Tuch et al. (2005), in a study of younger adults, found that increasing FA in the optic visual pathway of the right hemisphere regions was correlated with *slower* performance in a choice reaction time task, in contrast to the trends illustrated in Table 1. Tuch et al. suggest that in this case, lower FA may reflect increased crossing of fibers within the visual pathways, rather than decreased myelin integrity.

Integration with fMRI: Task-related activation

A central theme of DTI research has been the characterization of the effects of decline in white matter integrity as disconnection within the neural systems mediating cognitive functioning (Andrews-Hanna et al., 2007; Bartzokis et al., 2004; Charlton et al., 2006; Sullivan & Pfefferbaum, 2006). This theoretical perspective, in turn, builds on the view that cognition is a product of distributed and interrelated neural systems (LaBerge, 2000; Mesulam, 1990). To develop this characterization further, in the context of aging, it will be necessary to integrate

findings from DTI, behavioral measures of cognition, and functional MRI ([fMRI]; Ramnani et al., 2004; Sullivan & Pfefferbaum, 2006).

An ubiquitous finding in fMRI research on cognitive aging is the increased activation for older adults, compared to younger adults, during some cognitive tasks (Dennis & Cabeza, 2008; Madden et al., 2005). This age-related increased activation often occurs in frontal and parietal regions and may represent a compensatory shift to more elaborative (top-down) processing in response to age-related decline in more peripheral (bottom-up) encoding and response processing (Davis et al., 2008; Madden, 2007). A related theory is that the plasticity of the aging central nervous system drives the development of behavioral strategies, with the goal of adapting to the effects of volumetric decline and related structural changes (Greenwood, 2007).

An open and important question is whether age-related differences in white matter integrity have a mediating role in the age-related differences in cortical activation. Nordahl et al. (2006) found that increasing volume of prefrontal WMH, defined from structural imaging, was associated with lower levels of task-dependent fMRI activation, suggesting an interruption of the task-relevant neural systems (see also Colcombe, Kramer, Erickson, and Scalf [2005]). From a compensation theory view, however, *increased* functional activation would be expected, if decreasing white matter integrity were driving cortical recruitment. One DTI study did find that older adults with lower FA in the frontoparietal network exhibited higher fMRI activation in the superior parietal lobule, but this effect did not have a reliable role in task performance (Madden et al., 2007). An intriguing finding that is consistent with the compensation theory occurred in a study of MS patients (Rocca et al., 2007). Relative to controls, the MS patient group exhibited increased task-related fMRI activation of motor regions and increased functional connectivity between the motor regions and cerebellum. The patients' DTI data indicated that declining white matter integrity, in pathways between the motor regions and cerebellum, was associated with increased fMRI functional connectivity. Whether this type of pattern will occur in age-related comparisons of healthy individuals has yet to be determined. The Rocca et al. data are also consistent with the superior-inferior gradient proposed by Sullivan and colleagues (Sullivan & Pfefferbaum, 2006; Sullivan et al., 2008; Zahr et al., 2009).

Integration with fMRI: Intrinsic functional connectivity

Although research interest in fMRI has concentrated on the variations in task-related activation, it is worth noting that task-related activity is only approximately 5% of the fMRI signal. The remaining 95% is spontaneous, low-frequency (< 0.1 Hz) fluctuations that reflect the intrinsic activity of the brain, which is often referred to as the default mode (Fox et al., 2005; Raichle et al., 2001). This intrinsic or default brain activity, which occurs in the absence of a specific task, also exhibits reliable patterns of regional correlation. These patterns, in turn, appear to represent the neural systems activated during cognitive tasks, such as the dorsal and ventral frontoparietal networks of attention (Fox et al., 2006). Recent DTI studies suggest that intrinsic functional connectivity depends on the structural integrity of associated white matter (Greicius, Supekar, Menon, & Dougherty, 2009; M. van den Heuvel et al., 2008).

How this intrinsic functional connectivity changes with age, and the role of white matter integrity, are largely unexplored. It is known that intrinsic functional connectivity varies with adult age. Across several investigations, intrinsic functional connectivity has been found to be lower for healthy older adults than for younger adults (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Sambataro et al., 2008; Wu et al., 2007), with further decline evident in early-stage Alzheimer's disease (Greicius et al., 2004). Andrews-Hanna et al., conducting correlations within an older adult group, found that increasing FA, from a relatively large ROI, was associated with an increasing level of intrinsic functional connectivity.

N.-k. Chen et al. (2009) developed a new method of identifying behaviorally relevant networks of intrinsic functional connectivity. These authors demonstrated that intrinsic connectivity within a prefrontal network (centered around the inferior prefrontal gyrus) was a significant mediator of the age-related variability in older adults' choice reaction time. Further, for older adults, increasing FA within the genu of the corpus callosum was correlated with increasing functional connectivity (Figure 8). Thus, the structural and functional integrity of this prefrontal network may be a mechanism of age-related slowing of perceptual-motor speed, which in turn contributes to age-related differences in attention, memory, and other cognitive abilities (Madden, 2001; Salthouse, 1996; Salthouse & Madden, 2007). Given that the majority of the variability in the fMRI signal reflects these spontaneous, low-frequency fluctuations, age-related differences in white matter integrity may have a more direct influence on intrinsic functional connectivity than on the task-related component of the fMRI signal.

Conclusion

The wide array of DTI research investigations has contributed significantly to the cognitive neuroscience of aging. The results confirm the role of disconnection among distributed neural systems as a fundamental mechanism of age-related variability in cognitive performance. Several trends occur across studies, notably the anterior-posterior gradient of the decline in white matter integrity with increasing age, the influence of white matter integrity on information processing speed and executive functioning, and the dependence of DTI measures on local tissue architecture. Age-related differences in white matter integrity occur throughout the brain, however, and the influence of white matter integrity has been evident in composite measures of broad functional domains, as well as in specific forms of information processing speed. To date, investigations have typically considered the relation between aging and white matter integrity, and between cognition and white matter, as separate issues. Further progress will be achieved as researchers focus on white matter integrity as a mediator of the age-related variance in cognitive performance. New information regarding the patterns of age-related differences in axial and radial diffusivity will help identify the relevant neurobiological mechanisms. These new directions in DTI research will not only help shape theories of cognitive aging but also guide translational applications to diagnosis and rehabilitation.

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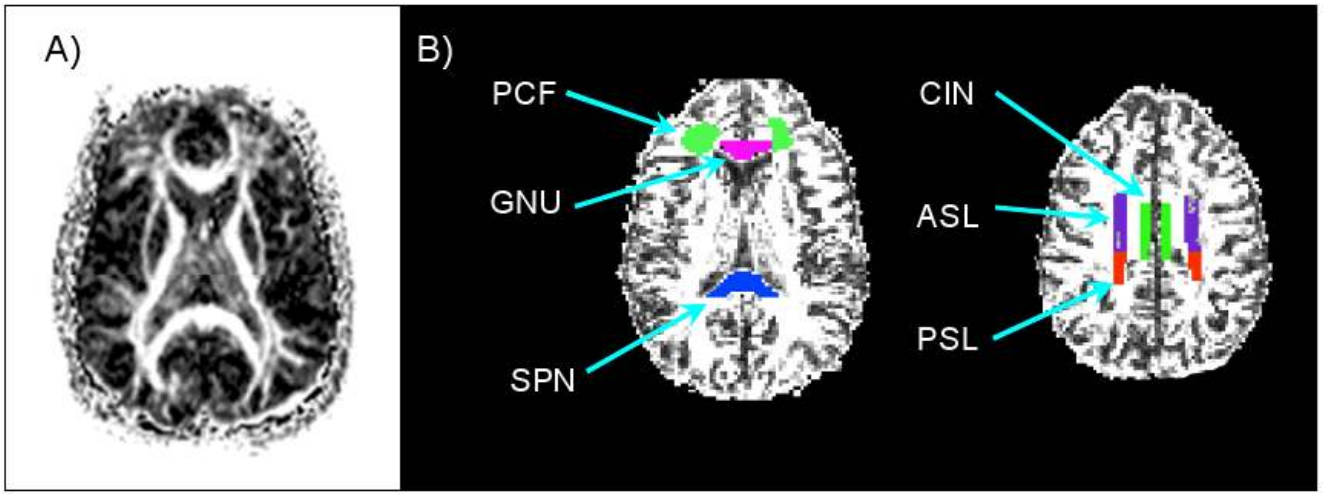

Figure 1.
Examples of regions of interest (ROIs) used in the analysis of the diffusion tensor imaging (DTI) data. Panel A = raw tensor image, with increasing fractional anisotropy (FA) represented as increasing brightness; Panel B = tensor images with maximum value for fractional anisotropy set to a lower threshold. Lowering the maximal FA threshold decreases the potential contribution of variation in FA to the ROI definition. PCF = pericallosal frontal; GNU = genu of corpus callosum; SPN = splenium of corpus callosum; CIN = cingulum bundle; ASL = anterior portion of the superior longitudinal fasciculus; PSL = posterior portion of the superior longitudinal fasciculus. Figure modified from N.-k. Chen et al. (2009).

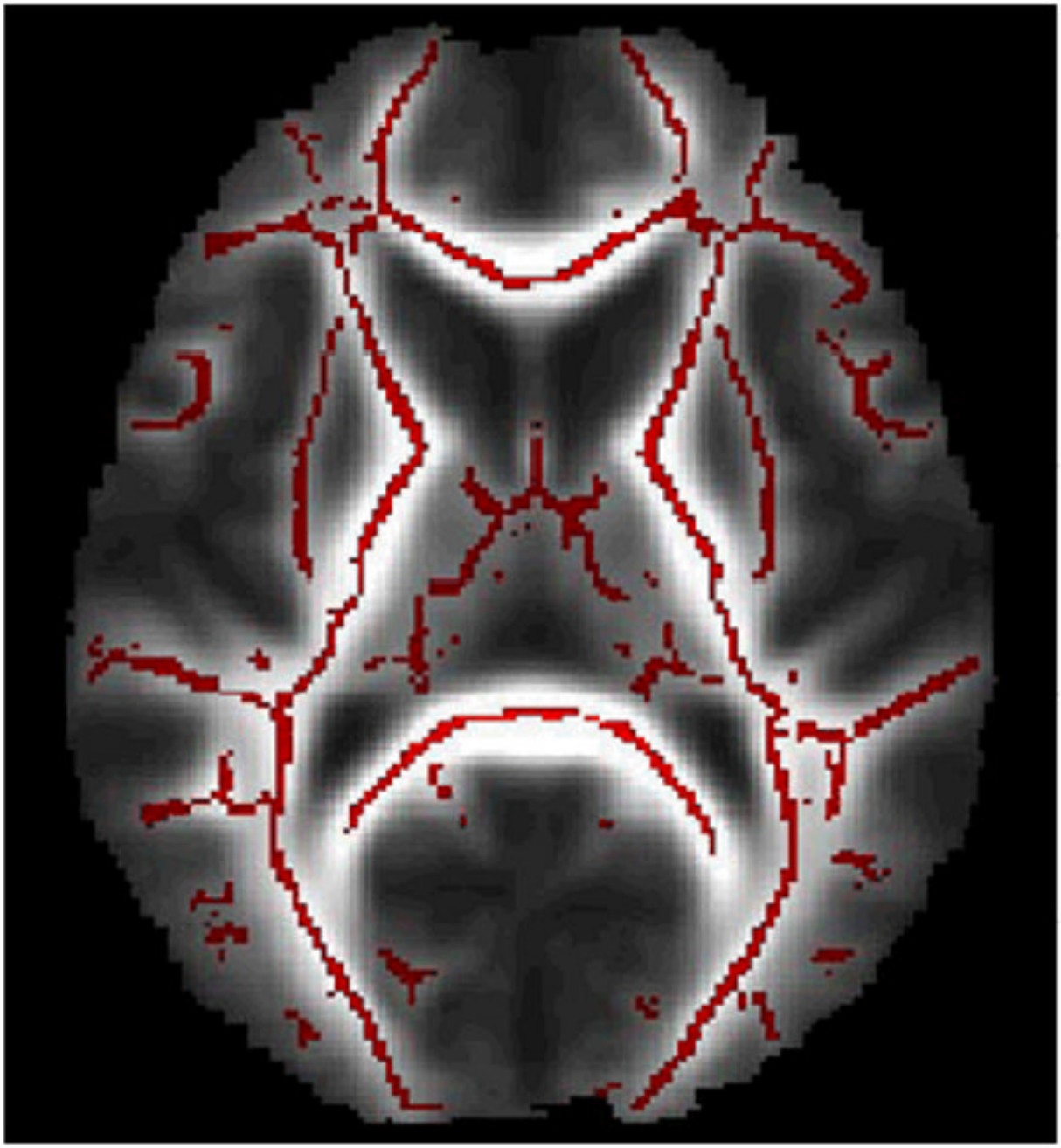

Figure 2.
Example of a white matter skeleton used in tract-based spatial statistic (TBSS) analyses. The white matter skeleton (red) represents the center of tracts common to all participants. It is superimposed on the mean diffusion image, which was created by averaging aligned FA diffusion images from each individual in the group. Figure modified from Bennett et al. (2009). © *Human Brain Mapping* and Wiley-Liss, Inc., 2009.

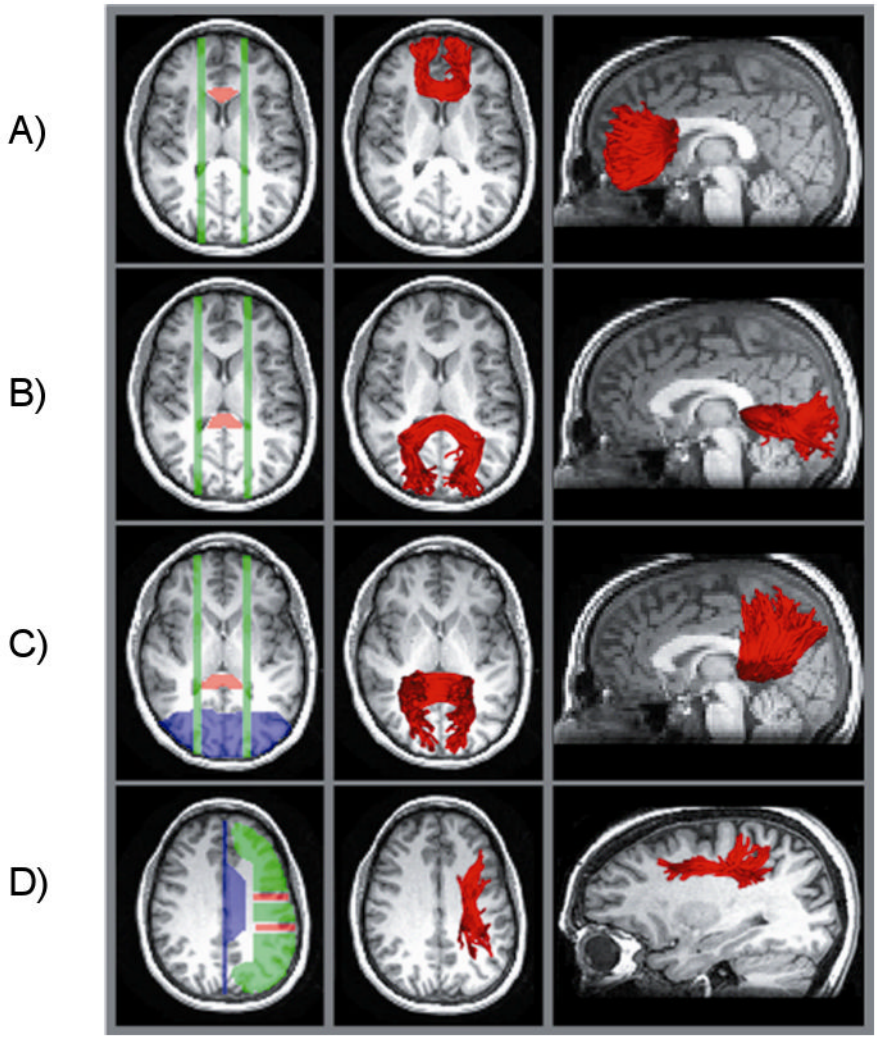

Figure 3.
Examples of deterministic tractography. Fiber tracts (in red) generated by target and source region placement, for a single participant. The orange areas are target regions, the green areas are source regions, and the blue areas are exclusion regions. All of these regions are operator defined, for each participant, using anatomical boundaries. The fiber tracking algorithm estimates tracts that pass through the target regions from the source regions, eliminating any fibers terminating in the exclusion regions. The approximate locations of output fiber tracts are illustrated by overlaying on a single-slice T_1-weighted image. Panel A = genu; Panel B = splenium-occipital; Panel C = splenium-parietal; Panel D = superior longitudinal fasciculus. Figure modified from Madden et al. (2009). © *Journal of Cognitive Neuroscience* and MIT Press, 2009.

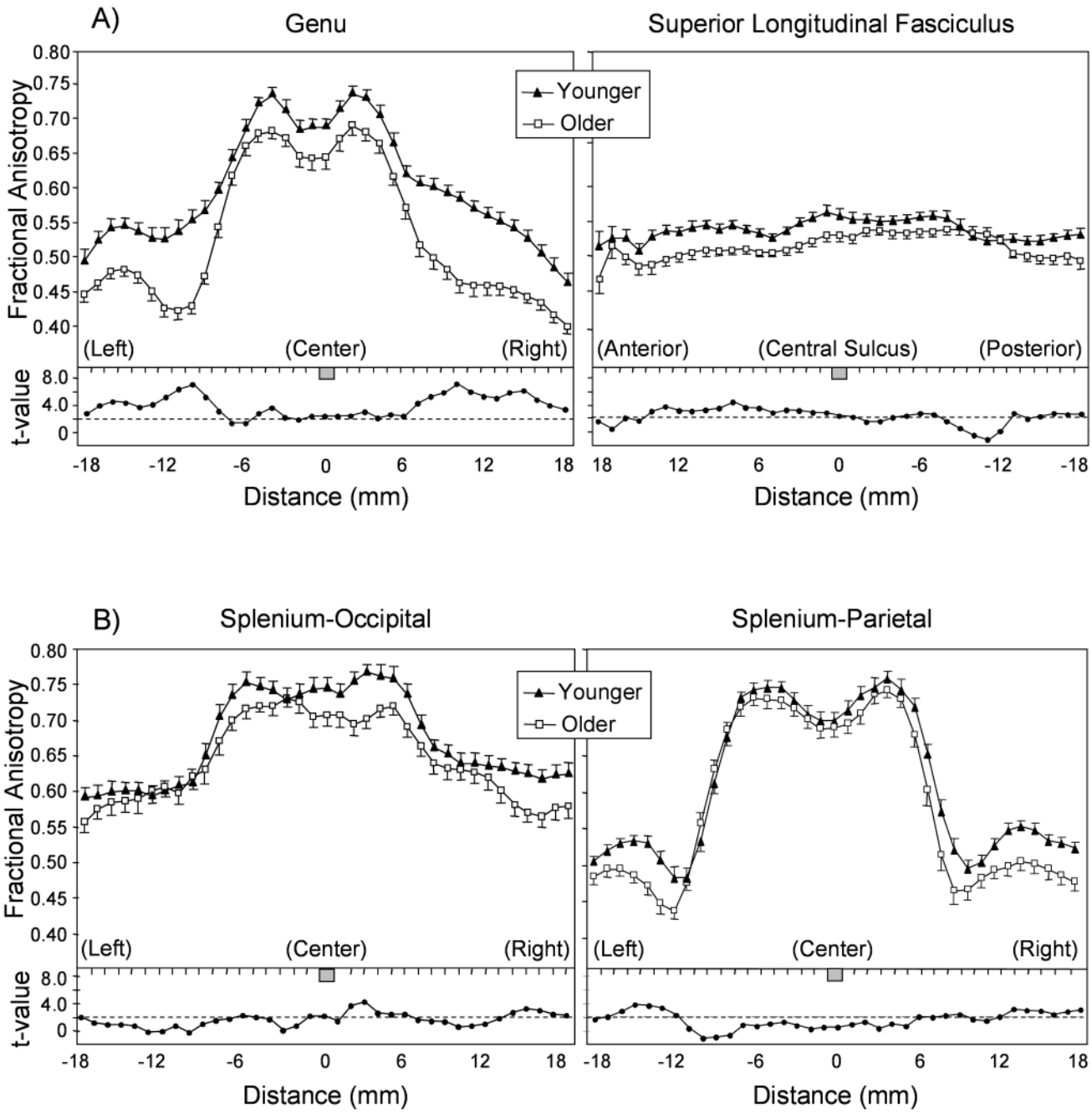

Figure 4.

Mean FA as a function of age group and interval along the tract. Error bars represent 1 *SE*. Panel A = genu and superior longitudinal fasciculus; Panel B = splenium-occipital and splenium-parietal. For genu and splenium, the tracts are oriented left-right, with 0 = axial midline. For the superior longitudinal fasciculus, the tracts are oriented anterior-posterior and 0 = central sulcus. Below the mean FA data, *t*-values are plotted for the age group comparison at each point along the tract. The dotted line represents the significant *t* value for $p < .05$, two-tailed. Figure modified from Madden et al. (2009). © *Journal of Cognitive Neuroscience* and MIT Press, 2009.

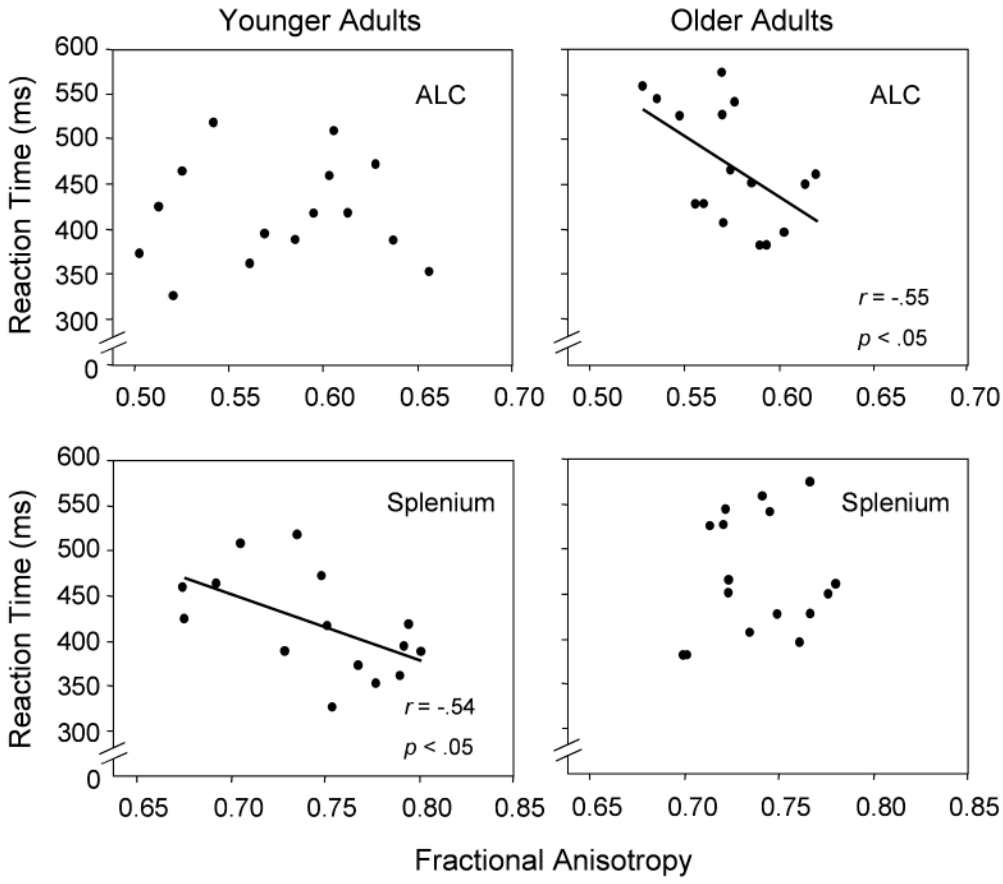

Figure 5.
Relation between choice reaction time and FA, for younger and older adults. ALC = anterior limb of internal capsule. Figure modified from Madden et al. (2004). © *Neuroimage* and Elsevier, 2004.

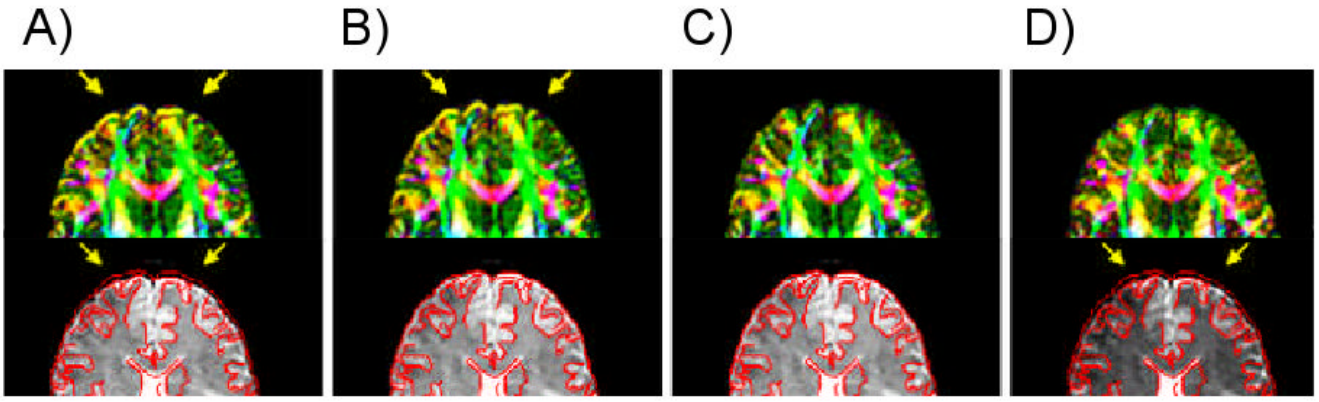

Figure 6.
FA maps (top) acquired with sensitivity encoding (SENSE) DTI and base image (bottom, with anatomical reference shown in red). Panel A = without correction; Panel B = with ΔB_0 correction; Panel C = with ΔB_0 and eddy current correction. The artificially high FA values at the edge, frontal lobe, and gray/white matter boundary are completely removed with correction in Panel C. The technique also showed improved distortion correction and higher signal-to-noise ratio (by 19.8%), compared to the DTI acquisition using a double-refocused spin-echo sequence (Panel D). Figure modified from Truong et al. (2008). © *Neuroimage* and Elsevier, 2008.

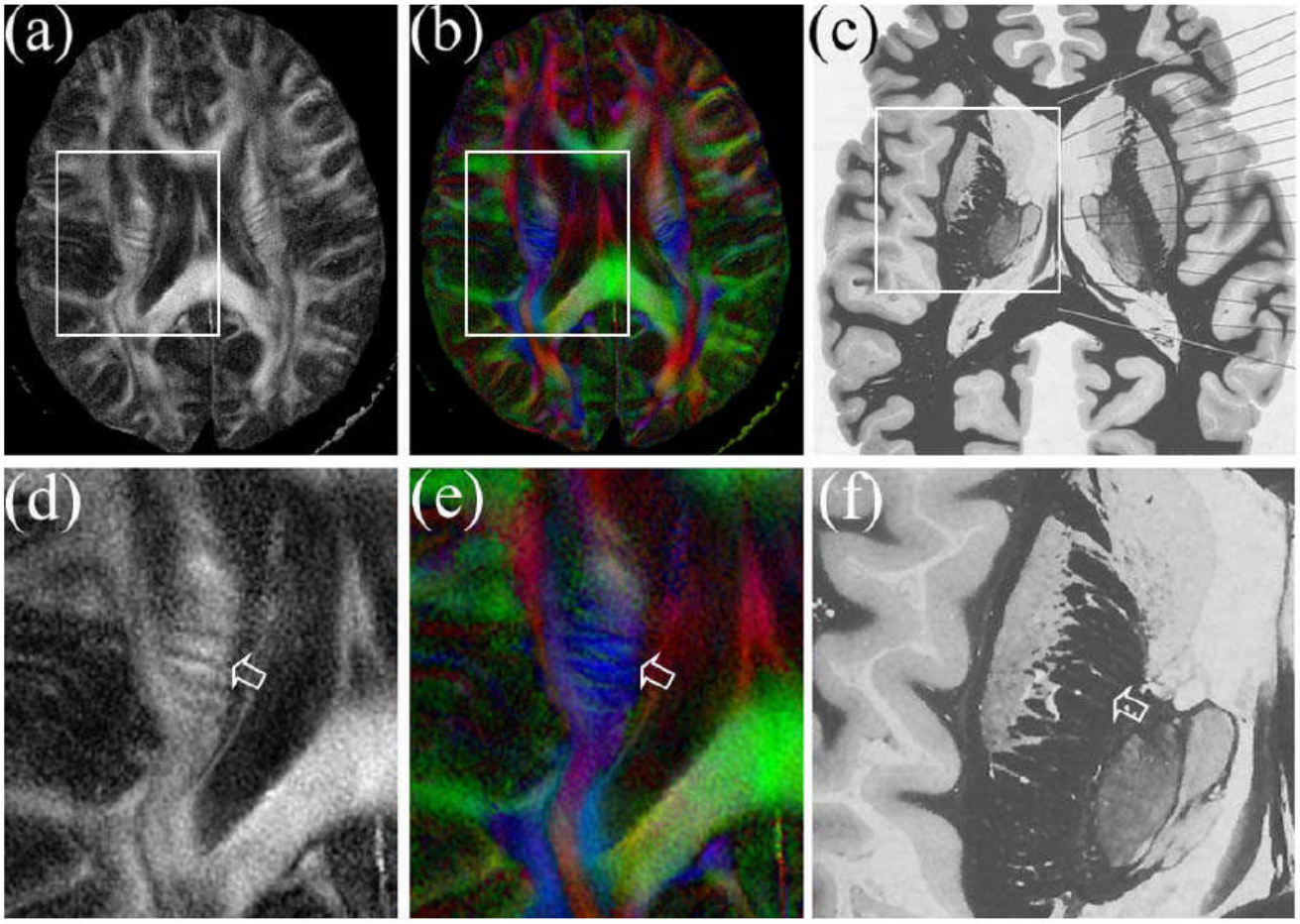

Figure 7.

High resolution self-navigated interleaved spiral (SNAILS) DTI with an in-plane resolution of $390 \times 390\ \mu m^2$. Panel A = FA map; Panel B = color-coded FA map with red representing the direction of anterior-posterior, green representing the direction of left-right and blue representing the direction of superior-inferior; Panel C = myelin stained brain section in a similar location obtained from the Yakovlev collection (National Museum of Health and Medicine, Washington, DC); Panels D, E, and F = an enlarged ROI indicated by the rectangular boxes in A, B and C showing the FA map, the color-coded FA map and the brain section respectively. Substructures of the internal capsule are shown clearly in the FA maps that match the tissue morphology (arrow). Figure modified from Liu et al. (2009). © *Magnetic Resonance in Medicine* and Wiley-Liss, Inc., 2009.

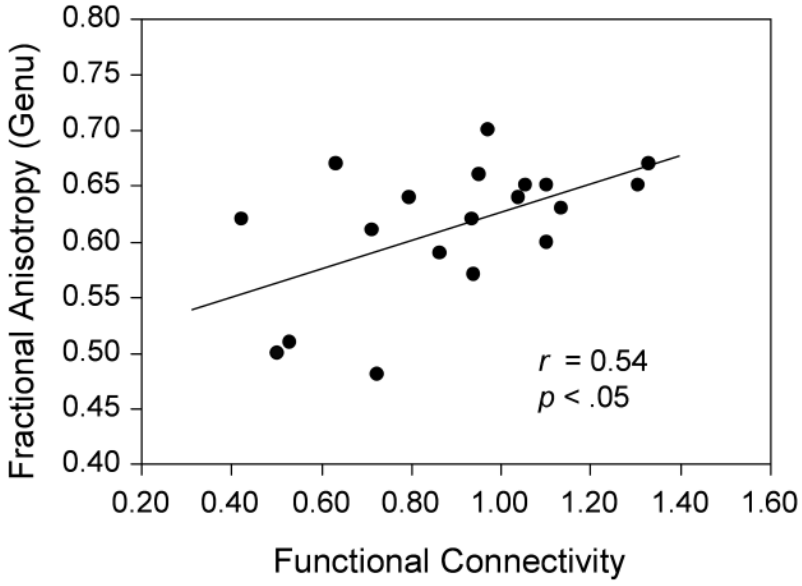

Figure 8.
Relation between white matter integrity (fractional anisotropy) in the genu of the corpus callosum and intrinsic functional connectivity (in networks connected with inferior frontal gyri), for older adults. Figure modified from N.-k. Chen et al. (2009).

Table 1

Summary of Aging Studies Examining Relationships between Fractional Anisotropy (FA) and Cognitive Functioning

	Frontal			Middle					Superior			Posterior		
	Front	**aPERI**	**CCg**	**Mid**	**ALIC**	**PLIC**	**UNC**	**Temp**	**CING**	**CS**	**Par**	**CCs**	**pPERI**	**Occ**
Executive Functioning														
Composite measures [7, 14, 18]	0.19	—	**0.80**	0.05	—	—	**0.35**	**0.34**	0.29	—	-0.26	0.16	—	—
Working memory [8, 10, 15, 16]	0.01	0.09	0.11	—	0.15	0.0	**0.57**	0.11	0.0	**0.41**	-0.08	0.0	0.28	-0.01
Set shift/task switch [1, 10, 12, 15-16]	0.01	0.16	0.0	0.09	0.0	0.0	0.24	-0.12	0.0	—	0.05	0.0	—	-0.03
Memory span [10, 15, 16]	0.17	—	0.20	—	0.0	0.0	0.0	0.0	0.0	—	0.01	0.0	—	0.02
Fluency [1, 3, 6, 8]	-0.05	0.17	—	**0.69**	—	—	—	—	—	0.20	**0.37**	—	0.16	0.22
Inhibition [16]	0.0	—	0.0	—	0.0	0.0	—	0.0	—	—	0.21	0.0	—	0.0
Processing Speed														
Composite measures [7, 16, 18]	0.18	—	0.13	0.09	0.0	0.0	**0.65**	**0.55**	**0.43**	—	-0.06	0.06	—	0.0
Digit symbol [8, 13]	**0.30**	0.14	0.14	0.10	0.14	—	—	-0.01	0.14	**0.36**	0.23	0.26	0.10	0.25
Simple/choice RT [4, 8, 10]	-0.13	0.15	0.0	—	**0.31**	—	—	-0.05	—	**0.43**	-0.19	0.0	0.01	-0.04
Finger tapping [2, 10]	0.18	0.0	0.0	—	—	—	—	0.28	—	0.0	0.17	**0.56**	**0.61**	0.18
Interhemispheric processing [5]	—	—	**0.48**	—	—	—	—	—	—	—	—	**0.51**	—	—
Finger movements [13]	0.19	—	0.05	0.18	**0.35**	—	—	0.03	0.06	—	0.24	0.05	—	0.21
Memory														
Recognition [11, 15]	—	**0.49**	0.16	—	—	—	0.08	0.0	0.22	—	-0.03	**0.35**	—	—
Free recall [6, 14, 16]	0.00	—	0.0	—	0.23	0.10	—	**0.41**	—	0.12	0.0	0.0	—	0.0
Paired-associate learning [15, 16]	0.0	—	0.0	—	0.0	0.27	0.0	0.20	**0.47**	—	0.0	0.0	—	0.0
Mental Ability														
Reasoning [3, 6, 8]	0.10	0.28	—	—	—	—	—	—	—	0.16	—	—	0.23	0.10
Irregular word reading ability [3, 6, 8]	0.04	0.08	—	—	—	—	—	—	—	0.23	—	—	0.03	0.07
Global cognitive functioning [3, 6, 8]	0.03	0.25	—	—	—	—	—	—	—	0.30	—	—	0.22	0.06
Word reading [9, 17]	—	—	**0.55**	—	—	—	—	—	—	—	0.0	**0.38**	—	—
Postural Stability														
Balance [2, 13]	**0.32**	0.0	0.18	0.03	0.15	—	—	-0.03	-0.06	**0.63**	0.13	0.23	**0.77**	0.04

Note. Values are mean effect sizes (Pearson *r*) for effects reported in the following studies:

[1] O'Sullivan et al. (2001),

[2] Sullivan et al. (2001),

[3] Shenkin et al. (2003),

[4] Madden et al. (2004),

[5] Schulte et al. (2005),

[6] Shenkin et al. (2005),

[7] Charlton et al. (2006),

[8] Deary et al. (2006),

[9] Sullivan et al. (2006),

[10] Grieve et al. (2007),

[11] Bucur et al. (2008),

[12] Gold et al. (2008),

[13] Sullivan et al. (Sullivan, Rohlfing, & Pfefferbaum, 2008),

[14] Ziegler et al. (2008),

[15] Davis et al. (2009),

[16] Kennedy and Raz (2009)

[17] Madden et al. (2009), and

[18] Zahr et al. (2009). Moderate effect sizes and larger (> 0.30) are listed in bold font.

Mean effect sizes were computed following the method of (Rosenthal & DiMatteo, 2001). Pearson *r* values were obtained from *F* and Spearman *p* statistics (in the latter case via conversion to standard normal deviate *Z*), averaging *r* values after transforming them to weighted Fisher z scores, and giving an r value of zero to effects described as not statistically significant. In some cases, *r* values were adjusted such that positive relationships indicate where better performance is associated with higher FA, and age-controlled r values were used when available. Data from Charlton et al. (2008), Thomas et al. (2008), and part of Sullivan et al. (2001) were not included because there was not enough information to obtain Pearson *r* values. RT = reaction time.

White matter tracts and regions were grouped into four broadly defined areas (Frontal, Middle, Superior, Posterior). Front = frontal white matter (including forceps minor); aPERI = anterior pericallosal white matter; CCg = genu of the corpus callosum (including prefrontal, premotor/precentral, and postcentral subregions of the corpus callosum); Mid = middle white matter (including fornix and external capsule); ALIC = anterior limb of the internal capsule; PLIC = posterior limb of the internal capsule; UNC = uncinate fasciculus; Temp = temporal white matter (including inferior longitudinal fasciculus); CING = cingulum bundle; CS = centrum semiovale (including large regions of interest from slices of superior white matter); Par = parietal white matter (including superior longitudinal fasciculus); CCs = splenium of the corpus callosum (including posterior parietal, superior temporal, and inferior temporal/occipital subregions of the corpus callosum); pPERI = posterior pericallosal white matter; and Occ = occipital white matter (including forceps major).