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Review

Diffusion tensor imaging and aging

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Abstract

Magnetic resonance diffusion tensor imaging (DTI) is a non-invasive in vivo method for characterizing the integrity of anatomical connections and white matter circuitry and provides a quantitative assessment of the brain's white matter microstructure. DTI studies reveal age-related declines in white matter fractional ansiotropy (FA) in normal healthy adults in whom volume declines are not necessarily detectable. The decline is equivalent in men and women, is linear from about age 20 years onwards, and has a frontal distribution. Studies combining regional DTI metrics and tests of specific cognitive and motor functions have shown that age-related declines in white matter integrity are associated with similar declines in interhemispheric transfer, especially dependent on frontal systems. Emerging from recent DTI findings and conceptualizations of neural causes of cognitive decline in aging, we propose three white matter-mediated neural system hypotheses of aging brain structure and function: (1) the anteroposterior gradient, (2) bilateral recruitment of brain systems via the corpus callosum for frontally based task execution, and (3) frontocerebellar synergism. These hypotheses are not mutually exclusive but establish a basis for posing testable questions about brain systems recruited when those used in youth are altered by aging.

Keywords: Aging; White matter; Microstructure; MRI; Age

Contents

1. Introduction

Over the past decade, approaches for identification of brain mechanisms underlying complex cognitive, motor, and other behavioral functioning have shifted from single structures or loci to systems and circuits. With this move from a one locus/one function position is the recognition of the relevance of brain circuitry and the possibility that disruption of the connections may be as effective as lesions in gray matter nodes in producing functional impairment. Magnetic resonance diffusion tensor imaging (DTI) is a

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non-invasive in vivo method for characterizing the integrity of these anatomical connections and provides a quantitative assessment of the brain's white matter microstructure (for reviews, Moseley, 2002; Kubicki et al., 2002; Lim and Helpern, 2002; Sullivan and Pfefferbaum, 2003; Pfefferbaum and Sullivan, 2005a; Adalsteinsson et al., 2002).

This review focuses on results from studies of normal aging using DTI to investigate degradation of white matter tissue integrity. To date, longitudinal studies have not been published; therefore, the findings described are based on cross-sectional work. Organizationally, this review begins with an overview of how decline in integrity of white matter systems may be key to identifying substrates of executive functional decline in normal aging. Next, we provide a brief but essential introduction to the rudimentary principles of DTI and a summary of postmortem characterization of age-related white matter tissue degradation, followed by summaries of DTI findings in normal adult aging and observed functional correlates of DTI metrics. Finally, we pose speculations and hypotheses about brain systems most vulnerable to normal aging and underlying functional declines characteristic of aging.

2. White matter systems and age-related decline in frontally based functions

The constellation of frontally based functions, including working memory, set shifting, problem solving, attention, and other executive functions (cf., Stuss and Alexander, 2000) is especially vulnerable to undesirable effects of advancing age. Although controversy exists regarding the primacy of the frontal lobe hypothesis to explain age-related functional declines (Greenwood, 2000), substantial evidence supports the position that aging disproportionately affects frontal lobe structure (e.g., DeCarli et al., 2005; Raz et al., 1997; Pfefferbaum et al., 1998; Raz, 1999; Hedden and Gabrieli, 2004; Buckner, 2004). Identification of brain mechanisms responsible for this time-linked functional demise currently focuses on the health of white matter systems necessary to form neural circuits of frontal processing sites (Filley, 2001; Tisserand and Jolles, 2003). Although performance of executive functions becomes inefficient with age, executive functioning is still possible and in fact may be enhanced when older individuals recruit wider-spread brain systems than those invoked by younger adults (Cabeza, 2002). For example, high-performing older adults show a bilateral pattern of brain systems recruitment not observed in younger adults or low-performing older adults (Cabeza et al., 2002; Rosen et al., 2002). Thus, we posit that adequate integrity of white matter systems connecting supplementary neural sites is a requirement for compensatory recruitment, a possibility testable with DTI.

A leading candidate for enabling age-related recruitment of bilateral brain systems for high performance is the corpus callosum, the target of many DTI studies. In addition to providing interhemispheric communication for sensory and motor integration (Gazzaniga, 1995), corpus callosum integrity may influence the allocation of resources when attentional or memory capacity is limited (Banich, 1998; Reuter-Lorenz and Stanczak, 2000; Zaidel and Iacoboni, 2003). Some have interpreted the bilateral pattern as evidence for decline in functional hemispheric laterality, arising from compromise of the callosum's capacity to inhibit participation of the hemisphere less suited to accomplish a task (Banich, 1998; Kinsbourne, 1974). The outcome can appear as "dedifferentiation" of hemispheric function (Dolcos et al., 2002). Given that age-related degradation of white matter is nonpathological, subtle compromise may actually enable bilateral engagement of the hemispheres by attenuating cross-hemisphere inhibition (Buckner, 2004), but more demonstrative compromise may attenuate efficient interhemispheric information transfer. Thus, compensatory mechanisms must be in place to meet the challenge of difficult tasks (Buckner, 2004)—those requiring greater resources, especially from frontal sites (Anderson and Grady, 2001).

3. Diffusion tensor imaging (DTI)

DTI is sensitive to the detection of white matter's linear structure, composed principally of axons (Waxman et al., 1995). Physical characteristics of axons vary widely in length, diameter, and myelination and by region. Axons coursing through the genu of the corpus callosum are typically a fraction of the diameter of those in the splenium and are also less heavily myelinated (Aboitiz et al., 1996; Bartzokis, 2004; LaMantia and Rakic, 1990). With aging, disease, or physical trauma, the axon's cytoskeleton, including the linear orientation of neurofilaments, can be perturbed (Arfanakis et al., 2002).

Molecular movement, or diffusion, of water molecules in white matter is present in two principal compartments, extracellular and intracellular space. Extracellular, or interstitial, fluid in spaces between fibers provides an avenue for water diffusion. Diffusion experiments based on lower organisms provide support for extracellular space as the main avenue of the diffusion detected with DTI and thus may be especially sensitive to the integrity of the myelin sheath. Intracellular space, while crowded with cytoskeletal constituents, has cytoplasm as another medium for water diffusion. DTI can detect the amount and linearity of water movement in these two compartments, deviations from which can indicate abnormality or degradation (Song et al., 2002; Basser, 1995; Moseley et al., 1990). Disruption of white matter microstructure detectable with DTI can reflect breakdown of myelin, certain constituents of cytoskeleton, and axon density (Basser, 1995; Basser and Pierpaoli, 1996; Spielman et al., 1996; Sehy et al., 2002; Beaulieu and Allen, 1994; Fenrich et al., 2001; Silva et al., 2002), which, along with decline in the number and length of myelinated fibers (Marner et al., 2003), can occur in normal aging (Aboitiz et al., 1996; Meier-Ruge et al., 1992; Kemper, 1994). A predilection of

loss occurs for thin, unmyelinated fibers, which are in greatest abundance in the frontal lobes and callosal genu (Aboitiz et al., 1996; Bartzokis, 2004).

Water diffusion in white matter is anisotropic (i.e., has a preferential orientation) because its motion is restricted by fiber constituents. This restriction is typically expressed as fractional anisotropy (FA) (Pierpaoli and Basser, 1996), which as a measure of orientational coherence, varies in magnitude in different brain structures and tissue types. FA is near 0 in ventricular CSF but can approach 1.0 in callosal regions where fibers are arranged in parallel. FA, however, is sensitive to tissue inhomogeneity from crossing fibers within a voxel (Virta et al., 1999; Pierpaoli et al., 2001) and partial voluming (Pfefferbaum and Sullivan, 2003; Bhagat and Beaulieu, 2004), factors that can reduce FA. Diffusivity, expressed as apparent diffusion coefficient (ADC), bulk mean diffusivity ($\langle D \rangle$ or MD), or trace of the tensor matrix, is a quantitative metric of water motility (independent of orientation) in a voxel and is commonly but not necessarily negatively correlated with FA in white matter (Pfefferbaum and Sullivan, 2003, 2005b).

The diffusion tensor contains information about spatial orientation of fiber tracts (eigenvectors) which can be used for "fiber tracking," and many approaches for analysis of white matter connectivity have been proposed (Pierpaoli and Basser, 1996; Tang et al., 1997; Basser, 1998; Mori et al., 2002; Masutani et al., 2003; Conturo et al., 1999; Pajevic et al., 2002; Jones et al., 1999; Pfefferbaum et al., 2000a; Lazar and Alexander, 2005). Although the connectivity and coherence between different brain regions are readily apparent on visual fiber tracking displays (Xu et al., 2002; Lehericy et al., 2004; Stieltjes et al., 2001), these displays are difficult to quantify and only recently have been applied to study normal aging (Sullivan et al., 2006).

4. Brain white matter in normal adult aging

Cross-sectional and longitudinal, structural MRI studies consistently show age-related volume increases in CSF-filled spaces that occur primarily at the expense of cortical gray matter and with most showing little volume change in white matter (Raz et al., 1997, 2005, 2004; Blatter et al., 1995; Jernigan et al., 1990; Pfefferbaum et al., 1994; Sullivan et al., 2001a, 2004) (Fig. 1). A few studies, however, report the opposite pattern, with greater volume decline in white matter than gray matter (Guttmann et al., 1998; Jernigan et al., 2001), but such loss is typically small, ~2% per decade in a neuropathology study (Miller et al., 1980) and <1% per year in the corpus callosum examined longitudinally (Sullivan et al., 2002). Such volume shrinkage may accelerate in very old age (Raz et al., 2005; Salat et al., 1999).

DTI studies reveal age-related declines in white matter FA in normal healthy adults (Pfefferbaum and Sullivan, 2003; Pfefferbaum et al., 2000a; O'Sullivan et al., 2001; Chun et al., 2000; Nusbaum et al., 2001; Stebbins et al., 2001; Madden et al., 2004; Salat et al., 2004; Head et al., 2004, but see Chepuri et al., 2002) in whom volume declines were not necessarily detectable. The decline is equivalent in men and women (Sullivan et al., 2001b) and appears to be linear from about age 20 years onwards (Pfefferbaum and Sullivan, 2003; Ota et al., 2006) (Fig. 2).

White matter tissue integrity, as measured by FA and diffusivity, varies considerably across brain regions not only because of age-related effects but also because of type of fibers present in a region (Barkovich, 2000; Peters and Sethares, 2003), homogeneity of fiber orientations within each voxel, and spatial distortion from echo-planar B_0 field inhomogeneity and eddy currents inherent in the most common, i.e., echo-planar, DTI image acquisition approach (Virta et al., 1999; Jones et al., 2002; Bammer et al., 2003; Le Bihan, 2003). Further, inadvertent inclusion of non-target tissue (i.e., non-white

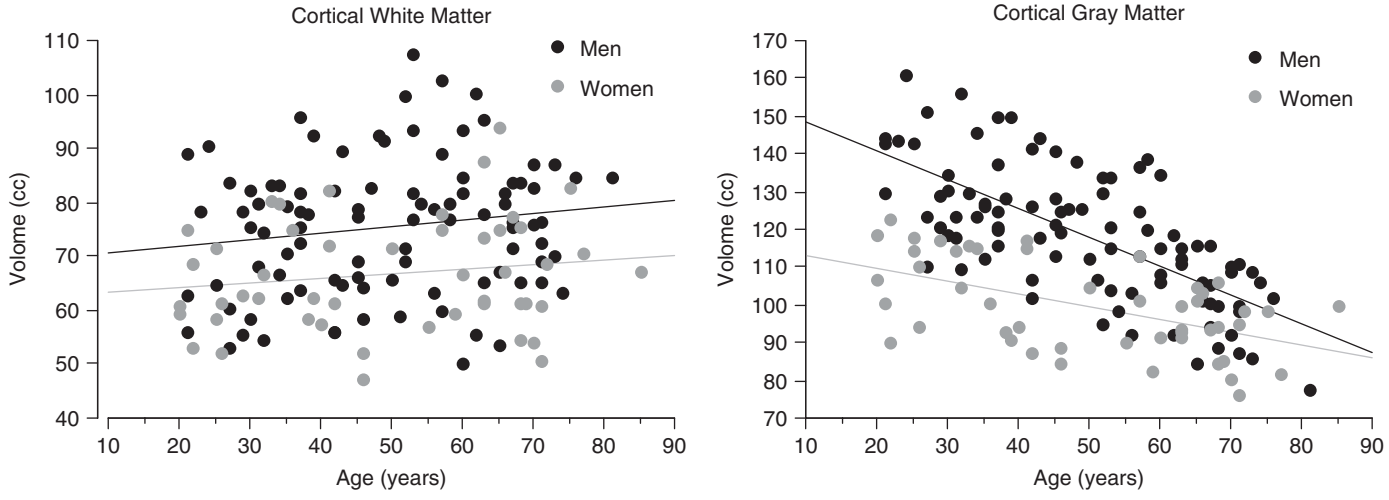

Fig. 1. A cross-sectional study revealed age-related decline in cortical gray but not white matter volumes in healthy adults (95 men and 48 women). Reprinted from Sullivan et al. (2004).

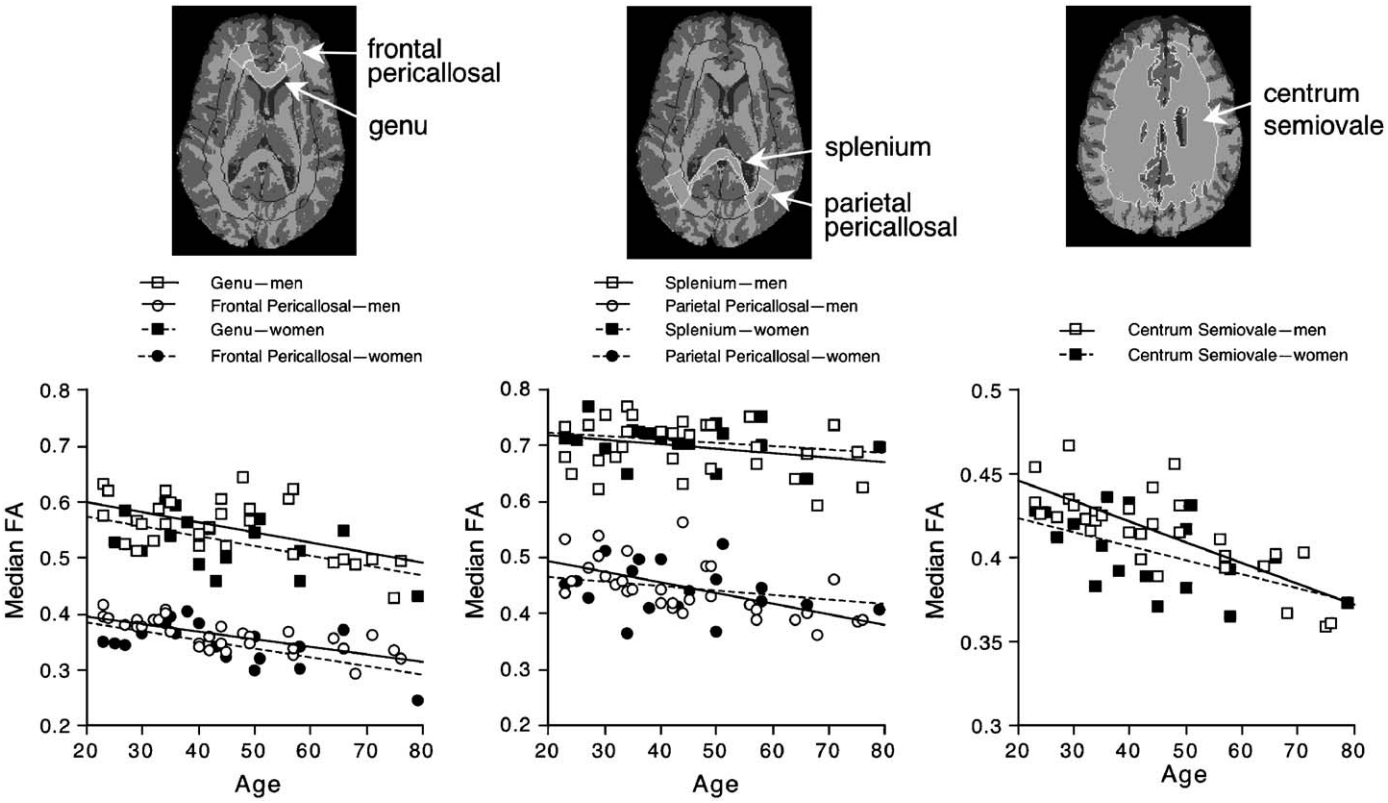

Fig. 2. Healthy men and women showed equivalent and significant decreases in FA with advancing age, which was greater in the genu than the splenium and greatest in the centrum semiovale. Modified from (Sullivan et al., 2001b).

matter) will depress FA; regions with low SNR can have inflated FA; and occult pathology can also influence FA. We observed substantial regional variability in white matter, ~43% for FA and ~16% for diffusivity, as well as aging effects in adults 23–85-year old (Pfefferbaum and Sullivan, 2003). A sampling of other published studies indicated a wide range of FA—22–88%—for young adults, age 20 to about 40 years (Pfefferbaum and Sullivan, 2003; Bhagat and Beaulieu, 2004; Pfefferbaum et al., 2000a; O'Sullivan et al., 2001; Nusbaum et al., 2001; Madden et al., 2004; Salat et al., 2004; Head et al., 2004; Foong et al., 2000).

Severe age-related declines in white matter anisotropy have been detected in the anterior cingulum and middle frontal gyrus (Pfefferbaum et al., 2005), sites identified in functional imaging studies as comprising the specific frontal network "consistently recruited for solution of diverse cognitive problems," including response selection, executive control, working memory, episodic memory, problem solving, and aspects of perception that require conflict resolution (Duncan and Owen, 2000). Further, frontal sites develop relatively late (Sowell et al., 1999) and are under proportionately greater environmental than genetic control than are posterior regions, as evidenced in our study of twins revealing that the proportion of genetic to environmental contributions to FA was 3:1 for the splenium but only 1:1 for the genu (Pfefferbaum et al., 2001).

Regardless of method used, one of the most robust findings describing age-related differences in regional FA has been a frontal distribution of low FA selective to frontal white matter. Following our initial report (Sullivan et al., 2001b), other studies presented converging evidence supporting an anterior-posterior gradient of FA decline and diffusivity increase with age (Salat et al., 2004; Head et al., 2004; but see Madden et al., 2004). We confirmed this frontally based pattern in a profile analysis of white matter FA subtending the full rostral to caudal extent of the supratentorium in a group of young healthy subjects, mean age 29 years, and older healthy, high-functioning subjects, mean age 72 years (Pfefferbaum et al., 2005). DTI data were collected at 3T with isotropic voxels, permitting images to be reformatted and resliced in any plane, minimizing partial voluming error or bias that might occur if the through-plane dimension were much smaller than in-plane voxel size (cf., Jones et al., 2002). Field map and high-resolution MRI data were concurrently collected to allow accurate quantification of artifact-prone, anterior and inferior brain regions and determination of the white matter skeleton from the structural images for determination of DTI locations for FA maps. As a further precaution against partial voluming from non-white matter tissue, the structural MRI-determined white matter skeleton was eroded (Pfefferbaum and Sullivan, 2003, 2002). Three sagittal profiles were constructed on a 1 mm thick coronal slice-by-slice basis: midline 10 mm profile, which included

the corpus callosum, and left and right hemispheric profiles (Fig. 3). Whether midline or lateral, the prominent difference was significantly lower FA in frontal white matter in the older relative to the younger group, with relative sparing of posterior white matter systems. This anteroposterior aging pattern was also evident in a quantitative fiber tracking analysis of these data (Sullivan et al., 2006). Selective disruption of frontally based fibers are likely structural substrates of age-related declines in cognitive processes dependent on functioning of the prefrontal circuitry (Raz et al., 1998; Gunning-Dixon and Raz, 2003).

In complement to white matter FA decline in aging, diffusivity increases (Pfefferbaum and Sullivan, 2003; Head et al., 2004; Pfefferbaum et al., 2005; Chen et al., 2001; Naganawa et al., 2003; Engelter et al., 2000; Helenius et al., 2002; Ota et al., 2006). Along with negative correlations between advancing age and FA in the genu and splenium (Pfefferbaum and Sullivan, 2003) and bilateral frontal and parietal pericallosal white matter (Pfefferbaum et al., 2000b) are positive correlations between older age and diffusivity in the genu, splenium, and centrum semiovale (Pfefferbaum and Sullivan, 2003). In our profile analysis (Pfefferbaum et al., 2005), we found that the primary locus of the age effect was in anterior white matter (Figs. 3 and 4).

A technical caveat is the fact that diffusivity can be inflated by partial voluming (Bhagat and Beaulieu, 2004). We have demonstrated, however, that the age-related increase in diffusivity remains even after rarifying the region by eroding its peripheral voxels, that is, by removing rows of voxels in the periphery of white matter regions of interest, which are most likely to contain signal from non-white matter tissue (Pfefferbaum and Sullivan, 2003, 2002). The magnitude of the FA-diffusivity relationship varies across brain regions, being greater in the centrum semiovale than corpus callosum, and with age, being greater in older than younger healthy individuals (Pfefferbaum and Sullivan, 2003), and may reflect age-related loosening of myelin, dense cytoplasm, and formation of fluid-filled balloons observed in area 46 white matter in nonhuman primate models of normal aging (Peters and Sethares, 2003). Relevant to identification of the locus of age's effect on anisotropy, we found through multiple regression analysis that age made a unique contribution to low FA that was selective to anterior white matter regions. The FA-diffusivity inverse relationship suggests that decreased brain white matter intravoxel coherence is attributable, at least in part, to the accumulation of interstitial or intracellular fluid, or both fluid compartments (e.g., Sehy et al., 2002; Silva et al., 2002; Pfefferbaum and Sullivan, 2005b; Rumpel et al., 1998; Norris et al., 1994).

5. Functional correlates of white matter microstructural degradation

Brain structure–function relationships in normal individuals have been difficult to establish with volume measures of white matter, but have been regularly observed with DTI measures of white matter's microstructure. A number of studies have examined the corpus callosum and its

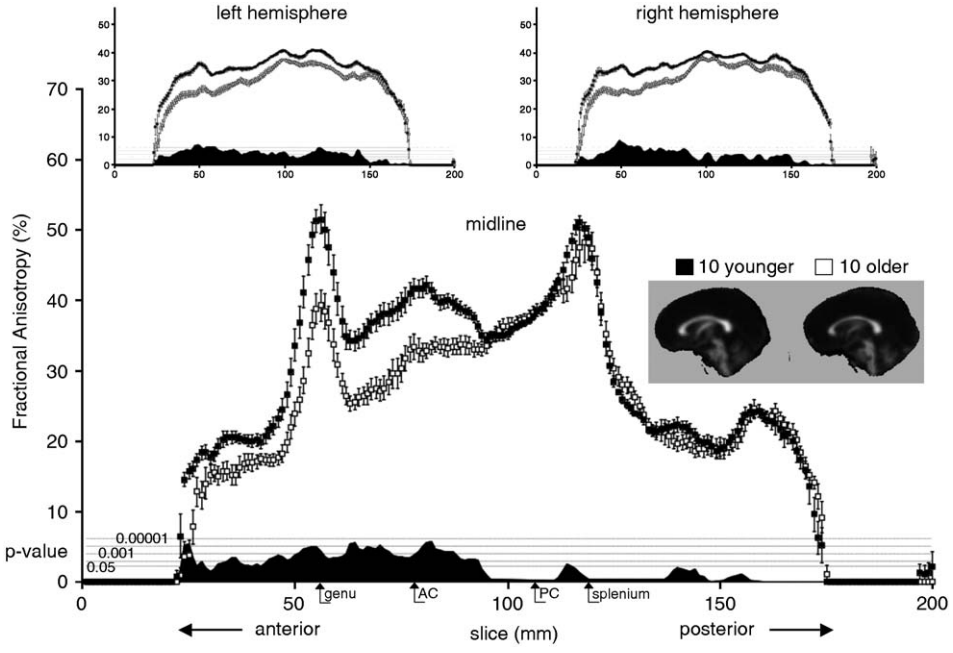

Fig. 3. Profile of mean ± SEM FA in segmentation-defined supratentorial white matter presented slice-by-slice from frontal to occipital brain regions in 10 younger and 10 older healthy subjects. The sagittal brain images are grand averages of FA of the 10 younger and 10 older adults; the corpus callosum is prominent in cross-section. The large profile is taken from the medial 10 mm of the brain; the small profiles are taken from the remaining white matter lateral to the midline sample. Note the systematic FA difference in the anterior regions with higher FA in the younger compared with older subjects. The black mounds on the *x*-axis indicate the *p*-value for group differences for each slice. The gray horizontal lines over the mounds designate *p*-values, with the bottom line being $p = .05$ and the top line $p = .00001$. Reprinted from (Pfefferbaum et al., 2005).

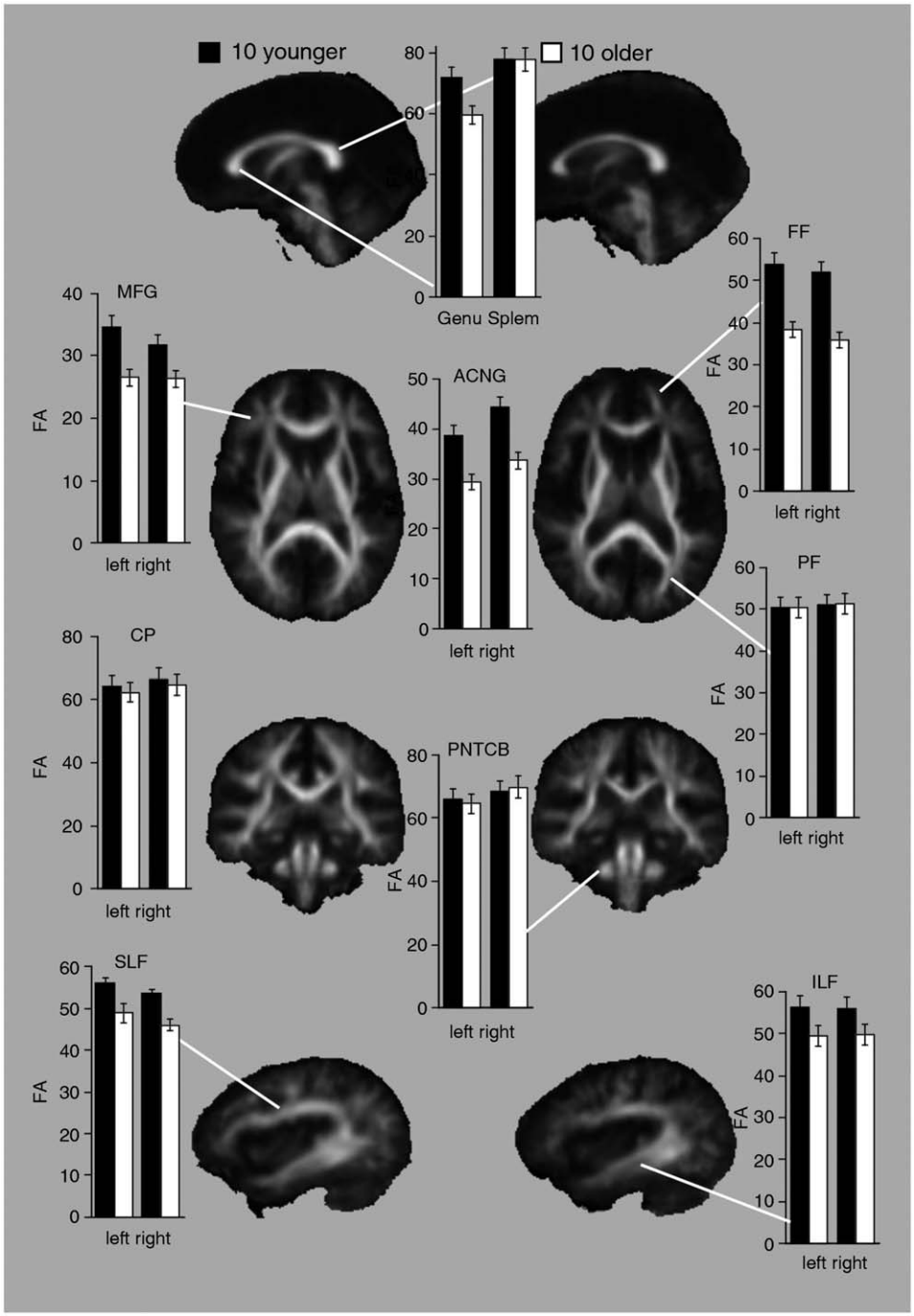

Fig. 4. Mean ± SEM for focal regional FA for the younger and older groups. The FA images are grand averages of the 10 younger and 10 older healthy subjects warped to a common template. SLF superior longitudinal fasciculus; ILF inferior longitudinal fasciculus; FF frontal forceps; PF posterior forceps; MFG middle frontal gyrus; ACNG anterior cingulate bundle; CP cerebral peduncle; PNTCB pontocerebellar tract; Genu; and Splen = splenium. Reprinted from Pfefferbaum et al. (2005).

relationship with tests of cognitive and motor functions. The full anterior to posterior extent of the corpus callosum is readily visible and regionally diversified in the bilaterally-distributed cortical regions it connects and consequent functions it subservs. For example, fibers coursing through the genu connect left and right hemisphere sites in dorsolateral prefrontal cortex, whereas the dorsal and rostral regions of splenium connect bilateral areas 18 and 19 in occipital cortices (Pandya and Seltzer, 1986). Thus, it may be assumed that functions and processes requiring information exchange between the hemispheres can be disrupted by degraded integrity of selective callosal regions. Disturbance of such interhemispheric functions, as they relate to the DTI-determined condition of local white

matter, has been considered manifestations of a disconnection syndrome (O'Sullivan et al., 2001), albeit subtle to mild in severity and clinically silent.

Quantitative DTI and functional analysis can detect even subtle relationships and may be central to identifying the neural mechanisms that underlie the common age-related shift from unilateral processing marking youthful performance to bilateral processing marking elderly performance (Cabeza, 2002; Cabeza et al., 2004). In addition to slowed processing of interhemispheric transfer, age-based callosal degradation can result in a reduction in either hemisphere's ability to inhibit the other in ensuring that task processing demands are confined to the hemisphere more suited to process the task. So, elderly performers who score equivalently on certain tests of working memory may invoke bilateral brain regions to accomplish the task, patterns observed in functional MRI experiments. By contrast, elderly poor performers tend to follow the youthful pattern of unilateral activation (Cabeza et al., 2002). The lack of compensation evidenced in the elderly poor performance group may be attributable to more advanced disruption of callosal fibers than in the high performance elderly group. It must be remembered, however, that in no case of *normal* aging are there instances of complete severing of brain fiber tracts. Rather, the age-related degradation is small and the lesion incomplete but measurable and graded, thereby amenable to regression analysis. The DTI-function relationships reviewed here were based on normal healthy subjects but were not necessarily focused on age-related differences. In some instances, these may be inferred because both the DTI and the functional measures were significantly related to age. In other studies, age was used as an explicit predictor of the DTI-functional relationship.

As a measure of interhemispheric transfer and processing speed, we used alternated finger tapping task (Pelletier et al., 1993). The procedure employed two conditions, each done three times. Subjects tapped a key with their left and right forefingers separately (control conditions) and then in alternation (callosal transfer test) for 15 s trials. Scores on the alternating condition, but not the unimanual conditions, correlated selectively with FA in the splenium ($r = .56$, $p < .02$) and parietal pericallosal region ($r = .61$, $p < .008$) (Fig. 5). When both age and FA were used as predictors of alternated finger tapping in multiple regression analysis, only FA endured as a significant, unique predictor of performance over and above the contribution from age (Sullivan et al., 2001b).

In contrast to these selective relationships, these subjects also showed non-specific relationships between a measure of postural stability and DTI coherence metrics. To assess gait and balance, subjects were administered the Walk-a-Line Ataxia Battery (Fregly et al., 1972), which consists of three parts, each performed with eyes open and then eyes closed. Correlational results indicated that lower intravoxel (FA) and intervoxel (C) coherence correlated with shorter time an individual balanced on one leg with eyes closed. These significant correlations ranged from −.44 to −.77 and were not specific to any supratentorial region examined: genu, splenium, pericallosal white matter, and centrum semiovale. Thus, the DTI measures combined with a quantitative balance test were adequately sensitive to reveal a relationship previously detected only in abnormal tissue and those with quantitatively determined postural instability (Sullivan et al., 2001b).

Another study of normal aging observed lower anterior than posterior FA in older than younger subjects and an apparent DTI-function dissociation. In particular, lower attentional set shifting scores, measured as the difference in performance between Trails B and Trails A, correlated with greater diffusivity in an anterior brain region, whereas lower verbal fluency scores correlated with lower FA in central sample of white matter taken in their older group of 17 healthy subjects. These correlations, however, were independent of age (O'Sullivan et al., 2001). The authors

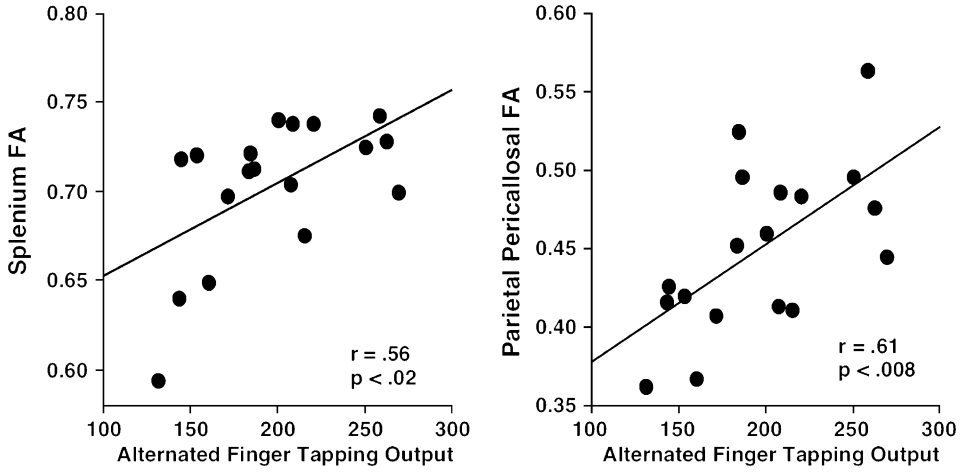

Fig. 5. The alternating condition correlated with FA in the splenium and parietal pericallosal region, whereas the control conditions involving unimanual tapping did not correlate with any measure of FA. Reprinted from Sullivan and Pfefferbaum (2003).

interpreted these DTI-functional relationships as evidence for cortical "disconnection" as contributing to age-related cognitive declines.

In another study, we examined interhemispheric transfer speed of visuomotor information. Here, we calculated the difference in response speed between the hand with direct connections to the hemisphere preferred for stimulus processing and the hand with an indirection connection, that is, requiring interhemispheric transfer of information. Specifically, subjects were required to respond quickly and accurately to spots of light flashed either in the visual hemifield and processing hemisphere of the motor response hand (uncrossed) or in opposing visual processing and motor response hemispheres (crossed) (after Poffenberger, 1912). The crossed-uncrossed difference (CUD) reflects interhemispheric transfer time, because the uncrossed response can be processed within the same hemisphere, whereas crossed responses require transfer of visuomotor information between hemispheres via the corpus callosum. It was assumed that greater CUDs reflect longer interhemispheric transfer time. In healthy adults spanning a 40-year age range, a greater CUD was indeed related to low FA and high diffusivity in the genu (Fig. 6) and splenium irrespective of age. Multiple regression analysis showed that diffusivity of the combined genu, body, and splenium entered as predictors of CUD accounted for 50% of the variance and stepwise analysis identified the genu as a significant unique predictor of CUD, thereby indicating that the relationship between CUD and genu diffusivity was selective. The results were interpreted as evidence that decline in corpus callosum microstructural integrity influences efficiency in interhemispheric processing (Schulte et al., 2005).

A DTI-behavioral study provided support for age-related differences in frontal vs. posterior brain regions invoked for processing demanding tasks. This study used an odd-ball visual target detection paradigm requiring speed and accuracy in reaction time (RT) to rare targets performed by healthy men and women in two age groups: a younger group, age 19–25 years, and an older group, age 60–70 years. Slow RT was best predicted by FA in the anterior limb of the internal capsule of older adults but from the splenium in younger ones. The authors interpreted this pattern of differences as evidence for "an age-related increase in the attentional control of responses mediated by corticostriatal or corticothalamic circuits" (p. 1174) rather than visual parietal attentional systems, possibly invoked by younger subjects (Madden et al., 2004).

6. Age-related degradation of frontocerebellar circuitry: another potential source of decline in executive and attentional functions

Aging has subtle but significant untoward effects on the cerebellum. Because of their far-reaching circuitry, disruption of selective cerebellar loci can have significant effects on remote brain regions, including the prefrontal cortex (Schmahmann, 1996, 1997; Middleton and Strick, 1998, 2001). Thus, we propose that disruption of cerebellar circuitry substantially contributes to aging's salient effect on executive functions, including verbal working memory and attentional processing, in parallel to its effect on well-established cerebellar functions, such as postural stability. Although yet to be explored systematically with DTI, we further speculate that compromised white matter involving frontocerebellar and parietocerebellar circuitry can impair synergism between these brain sites, and propose using DTI to test these hypotheses.

Lesions of the cerebellum can disrupt functions classically associated with the frontal lobes, including verbal associate learning, word production, problem solving, cognitive planning, attentional set shifting, and working memory (e.g., Courchesne et al., 1994; Schmahmann, 2000; Ivry and Keele, 1989; Fiez, 1996; Dreher and Grafman, 2002), although controversy persists regarding the cerebellum's influence on cognitive processes (Fiez, 1996). Decline in cerebellar integrity may in turn exacerbate the age-

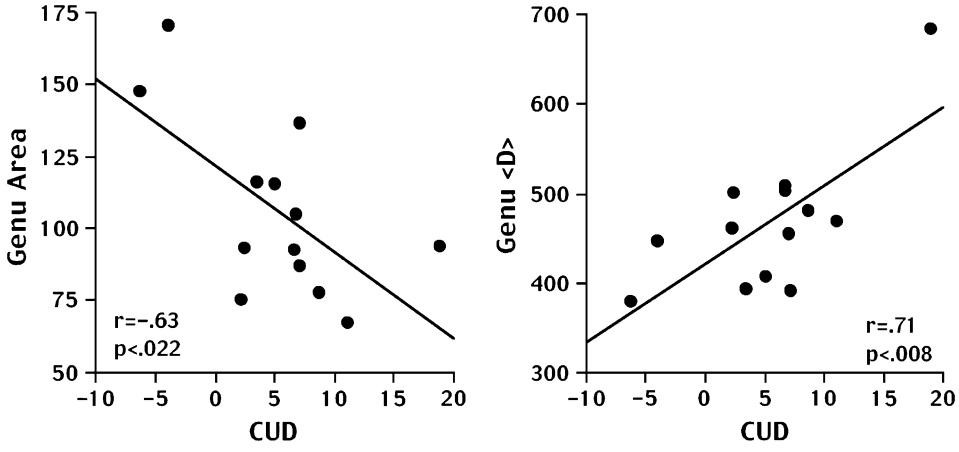

Fig. 6. A greater crossed-uncrossed difference (CUD), an index of interhemispheric transfer time, correlated with smaller area and higher diffusivity in the genu. Modified from Schulte et al. (2005).

related decline in these functions associated with prefrontal integrity; neuroimaging studies have demonstrated significant volume declines of the cerebellum that are profound in the anterior superior vermis (Luft et al., 1999; Sullivan et al., 2000; Raz et al., 2003; Woodruff-Pak et al., 2001). With advancing age, cerebellar hemispheres also decline in volume (Luft et al., 1999; Sullivan et al., 2000; Raz et al., 2003), which is selective to gray matter (Sullivan et al., 2000); however, central white matter, which encompasses the dentate nucleus, shows an age-related decrease in signal intensity, possibly reflecting iron deposition (Maschke et al., 2004).

These in vivo studies are consistent with postmortem reports of age-related volume decline and Purkinje cell loss, predominantly in anterior cerebellum (Andersen et al., 2003; Ellis, 1920; Torvik et al., 1986). Taken together with shrinkage of the prefrontal cortex, these observations point to the possibility of frontocerebellar circuitry disruption as a source of at least certain components of executive function declines characteristic of aging (Schmahmann, 1997). Relevant to this speculation, we found that focal regions of cerebellar volume shrinkage were selective and better predictors of executive and balance impairment in patients with alcoholism than were frontal lobe volumes (Sullivan, 2003). Others report that age can reduce cerebellar involvement in accomplishing diverse tasks, from odor detection (Ferdon and Murphy, 2003) to eye blink conditioning (Schreurs et al., 2001). Conversely, these associations implicate a role for the cerebellum when frontal and parietal systems are compromised by disease or age (Filley, 2001; Sullivan, 2000), and suggest reduced compensation opportunities if the cerebellum or its connections are also damaged.

Evidence for cerebellar recruitment derives from a Sternberg verbal working memory paradigm (Desmond et al., 1997), which increases demands on processing capacity by increasing the number of items to keep in mind over a retention interval. A series of functional imaging experiments provided evidence for selective recruitment of left prefrontal and right superior cerebellar regions during articulation and of left inferior parietal and right inferior cerebellar regions during phonological memory tasks (Desmond et al., 1997, 2003; Chen and Desmond, 2005; Kirschen et al., 2005). Further support for cerebellar involvement in frontally based functions derives from an MRI-neuropsychological study of healthy volunteers, age 22–88 years (Raz et al., 2000). Although subjects of all ages showed improved performance with repeated practice on a pursuit rotor task, indicative of procedural learning, older subjects showed declines in procedural learning that were related to volumes of the cerebellar hemispheres and lower nonverbal working memory scores. We posit that compromise of either the cortical or the cerebellar system, indexed by MRI volume and DTI metrics, can dampen performance. This possibility has not been considered in the context of aging.

7. Neural system compensation

At first reading one might find apparent contradictions in our hypotheses regarding age-related neural system compensation that we further elaborate here. Specifically, we propose that when confronted with a challenging task, neural systems invoked to manage the task include those primarily suited to perform it. If those systems are mildly compromised by age, then those plus additional systems will be recruited to complete the task, and the selection of compensatory systems will determine performance outcome. If, however, either the compensatory systems chosen included inappropriate ones or are themselves compromised (as may well happen in conditions such as Alzheimer's disease (e.g., Backman et al., 1999)), then the performance outcome will still be impaired. In the longitudinal analysis of the Bookheimer et al. (2000) fMRI memory study, the extent of compensation (measured as average increase in signal intensity in the memory vs. control conditions) detected at initial testing correlated with increase in dementia severity and decline in performance in non-demented carriers of the APOe4 allele compared with carriers of the APOe3 allele. One interpretation of this type of correlation is that recruitment of secondary neural systems to compensate for impaired primary ones may boost performance early in a progressive condition or disease (albeit, these subjects were not demented but did exhibit function decline over 2 years) but will be insufficient to overcome the impairment with the further demise of the neural systems supportive of a task. This interpretation is also consistent with the Backman et al. (1999) study, showing that simple over-recruitment of neural systems is not necessarily an effective compensatory strategy for boosting performance in retrieval of episodic memory in Alzheimer's disease patients. The fMRI component of the Egan et al. (2001) study, which showed that a higher COMT Met allele load predicted more efficient physiological response in prefrontal cortical activation, also supports the position that integrity of a neural system is a prerequisite for efficient performance. With neural functional degradation by aging or disease, compensatory recruitment may enhance otherwise impaired performance, if appropriate systems are recruited and if those systems themselves are not so severely compromised as to be functionally ineffective or even interfering. But, with progressive deterioration, even the compensatory systems may become too degraded to be supportive.

8. Conclusion

With advancing age, waning brain integrity is especially notable in prefrontal regions. To maintain youthful performance levels, older individuals may recruit brain regions, often bilaterally distributed (Cabeza et al., 2002), not invoked by the young. Given the far-reaching circuitry of frontal systems, we also speculate that the cerebellum

may be an additional source of compensation for age-compromised executive or attentional functions. Thus, white matter systems that express age-related degradation may serve as potential mechanisms of correlated age-related functional decline. Emerging from recent DTI findings and conceptualizations of neural causes of cognitive decline in aging, we propose three white matter-mediated neural system hypotheses of aging brain structure and function: (1) the anteroposterior gradient of aging, (2) bilateral recruitment of brain systems via the corpus callosum for frontally based task execution, and (3) frontocerebellar synergism. These hypotheses are not mutually exclusive but establish a basis for posing testable questions about brain systems recruited when those used in youth are altered by aging.

Unlike neurodegenerative diseases and neurological events, the effects of normal adult aging are subtle, accrue insidiously, and can be elusive to detection with conventional structural neuroimaging techniques. Observation of expected associations and establishment of double dissociations using regression analysis provide support for FA and diffusivity as functionally relevant metrics that are continuous and demonstrable within the range of normal age-related brain deterioration (Bates et al., 2003; Jernigan et al., 2003). The growing body of DTI research substantiates its utility for in vivo detection of patterns of sparing and compromise of white matter integrity in normal aging, subtle on the macrostructural level but more reliably detectable on the microstructural level. As an index of brain tissue quality, DTI permits examination of regional patterns of neural circuitry degeneration associated with aging not possible with other imaging modalities. Quantitative tractography may be particularly useful for delineation and assessment of neural circuitry integrity and functional correlates (c.f., Sullivan et al., 2006). Future work combining DTI tractography and functional imaging should guide in dissociating brain areas activated during task performance forming the adequate circuit for performance from those activated in compensation for age-related decline (cf., Molko et al., 2002; Ramnani et al., 2004).

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