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Quantitative fiber tracking of lateral and interhemispheric white matter systems in normal aging: Relations to timed performance

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Abstract

The integrity of white matter, as measured in vivo with diffusion tensor imaging (DTI), is disrupted in normal aging. A current consensus is that in adults advancing age affects anterior brain regions disproportionately more than posterior regions; however, the mainstay of studies supporting this anterior–posterior gradient is based primarily on measures of the corpus callosum. Using our quantitative fiber tracking approach, we assessed fiber tract integrity of samples of major white matter cortical, subcortical, interhemispheric, and cerebellar systems (11 bilateral and 2 callosal) on DTI data collected at 1.5 T magnet strength. Participants were 55 men (age 20–78 years) and 65 women (age 28–81 years), deemed healthy and cognitively intact following interview and behavioral testing. Fiber integrity was measured as orientational diffusion coherence (fractional anisotropy, FA) and magnitude of diffusion, which was quantified separately for longitudinal diffusivity (λL), an index of axonal length or number, and transverse diffusivity (λT), an index of myelin integrity. Aging effects were more evident in diffusivity than FA measures. Men and women, examined separately, showed similar age-related increases in longitudinal and transverse diffusivity in fibers of the internal and external capsules bilaterally and the fornix. FA was lower and diffusivity higher in anterior than posterior fibers of regional paired comparisons (genu versus splenium and frontal versus occipital forceps). Diffusivity with older age was generally greater or FA lower in the superior than inferior fiber systems (longitudinal fasciculi, cingulate bundles), with little to no evidence for age-related degradation in pontine or cerebellar systems. The most striking sex difference emerged for the corpus callosum, for which men showed significant decline in FA and increase in longitudinal and transverse diffusivity in the genu but not splenium. By contrast, in women the age effect was present in both callosal regions, albeit modestly more so in the genu than splenium. Functional meaningfulness of these age-related differences was supported by significant correlations between DTI signs of white matter degradation and poorer performance on cognitive or motor tests. This survey of multiple fiber systems throughout the brain revealed a differential pattern of age's effect on regional FA and diffusivity and suggests mechanisms of functional degradation, attributed at least in part to compromised fiber microstructure affecting myelin and axonal morphology.

Keywords: Brain; Aging; DTI; White matter; Fiber tracking; Diffusion

1. Introduction

With the advent of diffusion tensor imaging (DTI) in human applications, novel opportunities have emerged for in vivo characterization of qualitative features of the brain's white matter microstructure, such as fiber organization and myelin development. DTI studies have focused on examination of white matter because of the modality's sensitivity to the detection of tightly packed fibers in locally parallel orientation (Basser, 1995; Moseley et al., 1990), typifying white matter commissures, bundles, and fasciculi of the brain. DTI has revealed evidence of microstructural disruption of brain white matter in healthy adults as they age, even in regions appearing normal on conventional volume imaging (for reviews, Minati et al., 2007; Moseley, 2003; Pfefferbaum and Sullivan, 2005a; Sullivan and Pfefferbaum, 2003, 2007; Wozniak and Lim, 2006).

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As stochastic descriptions of the movement of water molecules entrapped in fibers, DTI's metrics provide a quantitative method for characterizing the integrity of different features of white matter. The two principal DTI metrics are fractional anisotropy (FA), which is a measure of degree to which water diffusion has a common orientation, and diffusivity, which is a measure of the magnitude of water diffusion (Pierpaoli and Basser, 1996). Highly myelinated fiber bundles with a common orientation will have high anisotropy (usually measured as fractional anisotropy, FA). Breakdown of the myelin sheath, for example, with aging or disease can result in increases in extracellular fluid and transverse diffusivity (Song et al., 2002, 2005). Axonal damage has been associated with decreased FA and a disproportionate increase in longitudinal relative to transverse diffusivity (Song et al., 2003).

In general, studies on differences across the adult age range have quantified white matter integrity in focal brain regions and report average DTI metrics within those regions. Another analysis approach involves voxel-based morphometry, which attempts to identify selective regions throughout the brain where older groups differ from younger ones (reviewed by Sullivan and Pfefferbaum (2007)). Regardless of approach, the general consensus is that with advancing age, anisotropy in white matter declines and is accompanied by an increase in diffusivity (Chun et al., 2000; Head et al., 2004; Madden et al., 2004; Nusbaum et al., 2001; O'Sullivan et al., 2001; Pfefferbaum and Sullivan, 2003; Pfefferbaum et al., 2000b; Salat et al., 2005; Stebbins et al., 2001; but see Chepuri et al., 2002; Helenius et al., 2002). The age effects are regionally diverse and typically show an anterior-posterior gradient of anisotropy decline (Ardekani et al., 2007; Bhagat and Beaulieu, 2004; Bucur et al., 2007; Foong et al., 2000; Grieve et al., 2007; Head et al., 2004; Hsu et al., 2008; Kochunov et al., 2007; Madden et al., 2004, 2007; Nusbaum et al., 2001; O'Sullivan et al., 2001; Pfefferbaum et al., 2000b, 2005; Pfefferbaum and Sullivan, 2003; Salat et al., 2005; Sullivan et al., 2001; Takahashi et al., 2004; Yoon et al., 2007) and diffusivity rise (Chen et al., 2001; Engelter et al., 2000; Head et al., 2004; Helenius et al., 2002; Hsu et al., 2008; Naganawa et al., 2003; Pfefferbaum et al., 2005; Pfefferbaum and Sullivan, 2003) with age that was confirmed in a monkey model of aging (Makris et al., 2007). With a few exceptions (Hsu et al., 2008), this aging pattern is similar in men and women (Sullivan et al., 2001). A study of elderly twin men revealed that anterior regions of callosal white matter are under proportionately greater environmental than genetic control than are posterior regions (Pfefferbaum et al., 2001). Taken together, these studies indicate the relevance in comparing DTI metrics in multiple white matter fiber systems, separately in men and women, to reveal a complete picture of the pattern of sparing and loss of tissue integrity related to normal aging.

In addition to assessment of regional samples of white matter, DTI can provide visual depictions of white matter fiber systems (Lehericy et al., 2004; Stieltjes et al., 2001; Xu et al., 2002) and can be used to quantify FA and diffusivity along the length of identified fiber bundles (Gerig et al., 2005; Sullivan et al., 2006). This approach, referred to as quantitative fiber tracking, does not actually identify anatomically specific fibers or fiber bundles as detected histologically. Rather, it is a statistical representation of the voxel-to-voxel coherence of DTI-detectable water diffusion in white matter that is, nonetheless, increasingly being shown as representative of the underlying anatomy (Schmahmann et al., 2007). Whereas FA is a measure of the orientation of diffusion derived from the tensor's eigenvectors on an intravoxel basis, coherence-based measures, including tractography, provide an orientational measure on an intervoxel basis, that is, the degree to which the diffusion orientation of a voxel is similar to its neighbors (Pfefferbaum et al., 2000a), and serves the conceptual basis for quantitative fiber tracking (Fillard and Gerig, 2003; Gerig et al., 2005). Although the connectivity and coherence between different brain regions on vector and fiber tracking maps are readily apparent on visual inspection, these displays are not commonly quantified.

Quantitative fiber tracking has recently been used to characterize the developing brain in normal children and premature neonates (Barnea-Goraly et al., 2005; Gilmore et al., 2007), yet few studies have applied it to normal aging in adulthood. Recently, we observed lower FA, higher diffusivity, and fewer imaging-defined fibers in the anterior but not posterior segments of the corpus callosum in 10 elderly compared with 10 young, healthy men and women (Sullivan et al., 2006). Also observed were correlations between callosal fiber tracking metrics and performance on the Stroop color-word reading test. In a later study, which examined only the genu and splenium and based on DTI data from the 120 healthy adults in the current report, we observed a decline in FA and increase in diffusivity with age over a six-decade span that was greater in the genu than splenium of the corpus callosum (Pfefferbaum et al., 2007). A study focused on the fornix and cingulum, two fiber bundles connecting nodes of the limbic system, found age-related decline in FA and number of fibers and increase in diffusivity in the fornix but not the cingulum in 38 healthy individuals, age 18–88 years (Stadlbauer et al., 2008).

The functional ramifications of the DTI metrics have been regularly verified with observations of correlations between regionally-specific low FA or high diffusivity and poor cognitive (Bucur et al., 2007; Charlton et al., 2007; Grieve et al., 2007; Madden et al., 2007; O'Sullivan et al., 2001; Shenkin et al., 2003; Stebbins et al., 2001; Sullivan et al., 2006) or motor (Sullivan et al., 2001) test performance in humans and also a monkey model of aging (Makris et al., 2007). A recent study reported that decreased frontostriatal transverse diffusivity, suggestive of increasing myelination, correlated with speeded reaction time in a cognitive control (GO/NOGO) task engaged in by 21 individuals, age 7–31 years (Liston et al., 2006) and lending functional relevance to fiber tracking methods.

The purpose of the present analysis was to examine in a large group of healthy men and women, spanning the adult