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Non-Gaussian water diffusion in aging white matter

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ABSTRACT

Age-associated white matter degeneration has been well documented and is likely an important mechanism contributing to cognitive decline in older adults. Recent work has explored a range of noninvasive neuroimaging procedures to differentially highlight alterations in the tissue microenvironment. Diffusional kurtosis imaging (DKI) is an extension of diffusion tensor imaging (DTI) that accounts for non-Gaussian water diffusion and can reflect alterations in the distribution and diffusion properties of tissue compartments. We used DKI to produce whole-brain voxel-based maps of mean, axial, and radial diffusional kurtoses, quantitative indices of the tissue microstructure's diffusional heterogeneity, in 111 participants ranging from the age of 33 to 91 years. As suggested from prior DTI studies, greater age was associated with alterations in white-matter tissue microstructure, which was reflected by a reduction in all 3 DKI metrics. Prominent effects were found in prefrontal and association white matter compared with relatively preserved primary motor and visual areas. Although DKI metrics co-varied with DTI metrics on a global level, DKI provided unique regional sensitivity to the effects of age not available with DTI. DKI metrics were additionally useful in combination with DTI metrics for the classification of regions according to their multivariate "diffusion footprint", or pattern of relative age effect sizes. It is possible that the specific multivariate patterns of age-associated changes measured are representative of different types of microstructural pathology. These results suggest that DKI provides important complementary indices of brain microstructure for the study of brain aging and neurologic disease.

1. Introduction

Diffusion-weighted magnetic resonance imaging has been applied across several studies as a means to investigate the microstructural properties of white matter as well as changes associated with age and disease (Abe et al., 2002; Basser and Pierpaoli, 1996; Basser et al., 1994; Le Bihan et al., 2001; Pfefferbaum et al., 2000; Salat et al., 2005). The usage of techniques such as diffusion tensor imaging (DTI) comes from the fact that a range of microstructural properties can be obtained from a standard acquisition and that different metrics show differential sensitivity to effects in group comparisons. Fractional anisotropy (FA) and mean diffusivity (MD) are 2 common metrics calculated in DTI studies that are sensitive to changes with development and disease (Dong et al., 2004; Le Bihan, 2003; Sundgren et al., 2004). FA is a measure of the directional dominance of water diffusion in tissue and has been loosely interpreted as an indirect quantitative metric of the density of nerve fibers and their myelin sheaths (Beaulieu, 2002; Moseley, 2002). In contrast, MD is a measure of the overall (direction-independent) degree of water diffusion within the tissue, and has been used as an important marker of ischemia, edema, and cell death (Chenevert et al., 2000; Sotak, 2002). In the context of healthy aging, decreases in FA and increases in MD have been reported throughout much of the cerebral white matter (Pfefferbaum et al., 2000; Salat et al., 2005). More recently, the directional components of diffusivity, such as axial diffusivity (AD) and radial (RD) diffusivity have been shown to have spatially specific and differential sensitivities to the effects of aging (Bennett et al., 2010; Madden et al., 2009). The idea that different pathologies affect specific diffusional properties preferentially (Song et al., 2002, 2003) has potential value in the diagnosis and tracking of specific disease processes as opposed to more generic tracking of cumulative white matter damage without

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specific etiology. To date, however, little if any work has attempted to differentiate between various types of age-associated white matter changes based on multivariate diffusion properties.

Although DTI provides multiple indices of diffusional behavior, it is possible that composite information across a wider range of diffusional processes beyond what DTI provides would enable better classification of differing patterns of white matter damage with aging and disease. The physical model widely used to extract DTI parameters assumes that water molecules diffuse according to a Gaussian distribution, which corresponds to free, unrestricted diffusion in a homogenous environment. However, given the structural complexity of neural tissue, this assumption can only be an approximation, and appreciable differences in diffusivity are expected among tissue compartments (e.g., intra- and extra-cellular) within a same volume element. In theory, these differences are better characterized using higher-order diffusion statistics. By acquiring images with multiple diffusion weightings (b values), thus allowing for a better estimation of the water molecules' displacement distribution, the excess kurtosis of the distribution can be calculated, which is a unitless index of its non-Gaussianity (Liu et al., 2004). Diffusional kurtosis imaging (DKI) was developed recently with the goal of characterizing the diffusional heterogeneity arising from multiple tissue compartments with different diffusivities (Jensen et al., 2005). Diffusional heterogeneity can be described by how variable the diffusivity index varies across different cellular compartments within a voxel, and cannot be measured with diffusion tensor imaging which only provides the average diffusivity over a given voxel. DKI therefore provides a novel set of in vivo diffusion properties that describe tissue microstructure beyond the scope of traditional DTI (De Santis et al., 2011b); these properties are quantified through the mean, axial, and radial diffusional kurtoses (MK, AK, and RK, respectively). MK corresponds to the mean of the excess kurtosis for all diffusion directions, and represents a direction-independent index of diffusional heterogeneity. Analogous to diffusivity, diffusional heterogeneity or kurtosis also varies depending on the direction of diffusion weighting. AK and RK represent respectively the diffusional kurtosis in the principal diffusion direction and averaged over its perpendicular directions, based on the diffusion tensor orientation. Several multi-compartment models have been proposed to describe the biophysical and biological nature of diffusional kurtosis (Jensen and Helpern, 2010; Jensen et al., 2005), particularly in the white matter (De Santis et al., 2011a; Fieremans et al., 2011). Quantitative measures from DKI may be sensitive to developmental or disease-associated conditions in which there is a differential alteration in diffusion and permeability properties across cellular compartments. For instance, MK is known to vary with developmental stage in the rat brain (Blockx et al., 2011; Cheung et al., 2009) and human brain (Falangola et al., 2008; Helpern et al., 2011; Latt et al., 2013), suggesting a maturational increase and subsequent decline in white matter integrity during aging. These prior studies demonstrated coarse changes in MK with development and aging and suggested that DKI metrics may be sensitive to subtle microstructural changes related to age.

The major goals of this study were 2-fold: first, to examine the regional age trajectories of white-matter microstructural alterations observed through DKI metrics in a large cross-sectional sample of generally healthy adults, and second, to determine whether DKI provides additional, unique information compared with DTI for studying healthy aging. The results demonstrate that although both DKI and DTI metrics show substantial age-associated patterns of change throughout the cerebral white matter, DTI and DKI measures demonstrate differential age effects and complement one another in the identification of different types of microstructural changes. This work suggests a novel framework for understanding alterations in microstructural properties with aging and disease.

2. Methods

2.1. Participants

A total of 111 healthy adults between the age of 33 and 91 years (62 women, 49 men) were recruited through the Massachusetts General Hospital and local community. The sample included healthy individuals as well as older adults with some mild forms of vascular risk, including hypertension, hyperlipidemia, hypercholesterolemia, and diabetes. Individuals were excluded for signs of major neurologic or psychiatric illness including dementia, high cerebrovascular disease risk or overt disease (large vessel stroke or hemorrhage), cancer of the central nervous system, major head trauma, and/or other neurologic or psychiatric, or therapeutic conditions that may influence cognition or imaging measures. Participants were nondemented, as assessed by a minimum score of 24 on the Mini Mental State Examination (Folstein et al., 1975). Twelve participants in the sample had some degree of depression according to the BDI-II score (Beck and Beamesderfer, 1974). Fourteen participants were either left-handed or ambidextrous. However, the exclusion of all depressed and left-handed or ambidextrous participants did not alter our findings (see Supplementary Fig. 1). One hundred four participants were Caucasian and 7 participants were African-Americans. Characteristics of the study group are provided in Table 1. All participants gave informed consent and the study protocol was approved by the Partners Healthcare Institutional Review Board.

2.2. Magnetic resonance imaging data acquisition

All participants were imaged on a Siemens 3T Trio system (Siemens Medical Solutions, Erlangen, Germany) with a 32-channel head coil. Whole-brain diffusion-weighted scans were acquired (repetition time = 9250 ms, echo time = 103 ms, slice thickness = 2 mm isotropic, 64 slices total, acquisition matrix 128 × 128 [field of view = 256 mm × 256 mm], 6/8 partial Fourier, bandwidth = 1396 Hz/pixel, 24 noncollinear directions with b values of 700, 1400, and 2100 s/mm^2, single average, and 10 T_2-weighted (b_0) images with b value = 0 s/mm^2). The b values were chosen to be optimal for both DTI and DKI analysis (b values < 2500 mm/s^2 adequate for DKI) and the number of directions to accommodate scan time while ensuring proper estimation of the model. The DKI acquisition sequence used a twice-refocused balanced spin echo to reduce eddy current distortions (Reese et al., 2003). Head motion

Table 1
Demographics for all participants

Group	Age (y)	Education (y)	MMSE[a]	Systolic BP[b] (mm Hg)	Diastolic BP[b] (mm Hg)
All (111)	60.5 ± 11.5	16.4 ± 2.7	28.7 ± 1.5	123.3 ± 13.3	76.4 ± 8.7
Men (49)	59.1 ± 12.6	16.3 ± 2.8	28.7 ± 1.5	125.6 ± 9.6	76.1 ± 8.0
Women (62)	61.7 ± 10.4	16.5 ± 2.7	28.6 ± 1.5	121.8 ± 15.2	76.6 ± 9.2

Key: BP, blood pressure; MMSE, Mini-Mental State Examination.
[a] Information not available for the youngest participant.
[b] Information not available for 19 participants.