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Differential aging of cerebral white matter in middle-aged and older adults: A seven-year follow-up

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ABSTRACT

The few extant reports of longitudinal white matter (WM) changes in healthy aging, using diffusion tensor imaging (DTI), reveal substantial differences in change across brain regions and DTI indices. According to the "last-in-first-out" hypothesis of brain aging late-developing WM tracts may be particularly vulnerable to advanced age. To test this hypothesis we compared age-related changes in association, commissural and projection WM fiber regions using a skeletonized, region of interest DTI approach. Using linear mixed effect models, we evaluated the influences of age and vascular risk at baseline on seven-year changes in three indices of WM integrity and organization (axial diffusivity, AD, radial diffusivity, RD, and fractional anisotropy, FA) in healthy middle-aged and older adults (mean age = 65.4, SD = 9.0 years). Association fibers showed the most pronounced declines over time. Advanced age was associated with greater longitudinal changes in RD and FA, independent of fiber type. Furthermore, older age was associated with longitudinal RD increases in late-developing, but not early-developing projection fibers. These findings demonstrate the increased vulnerability of later developing WM regions and support the "last-in-first-out" hypothesis of brain aging.

Introduction

Healthy aging is associated with changes in brain structure and function. Although the evidence of differential age-associated regional brain shrinkage is consistent across multiple studies (see Raz and Rodrigue, 2006; Raz and Kennedy, 2009; Fjell et al., 2014 for reviews), considerably less is known about age-related changes in microstructural properties of cerebral white matter (WM). The invention of diffusion tensor imaging (DTI; Basser et al., 1994) enabled investigations of WM microstructure and organization through fitting brain water diffusion data to a tensor and quantifying diffusion properties in three principal directions by indices computed from the diffusion tensor eigenvalues: fractional anisotropy (FA), axial diffusivity (AD) and radial diffusivity (RD). In the past decade, numerous studies reported age-related differences in all DTI-derived indices (see Madden et al, 2012 for a review).

Cross-sectional studies in humans and postmortem examination of age-related WM differences in the brains of non-human primates suggest that WM deterioration occurs in late adulthood (Peters, 2002). The pattern and magnitude of such age differences vary across brain regions and among DTI indices and are consistent with the notion of differential vulnerability (Hasan et al., 2009a; Hasan et al., 2009b; Kochunov et al., 2012; Lebel and Beaulieu, 2011; Lebel et al., 2012). The reasons for differential predilection of some WM regions to decline in aging remain unclear. Because the molecular composition of normal cerebral WM does not vary across the brain (Paus et al., 2014), it is unlikely that the observed pattern of WM age differences reflects differential sensitivity of cellular and molecular processes involved in WM maintenance.

Whereas the cellular structure of WM is uniform throughout the brain, its local organization varies across the brain regions and tracts. Neuroanatomists identify three major classes of the cerebral WM: intracortical (incorporated in the layers of the gray matter), "superficial" (e.g., U-fibers) and long-range bundles of fibers or tracts (Paus et al., 2014). By considering the origins and targets of the long range tracts, WM fibers may be further classified into three major groups: projection, commissural, or association tracts (Catani, 2006). Significant heterochrony of WM development has been suggested by postmortem studies that report early emergence of the projection fibers and protracted maturation of the association tracts (Flechsig, 1901; Hermoye et al., 2006). Longitudinal DTI studies of infants and children are consistent with heterochronic development of the long-range WM tracts, although it remains unclear which processes (myelination, axon expansion or changes in cytoskeleton density) determine maturational

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WM changes observed on MRI (Simmonds et al., 2014; Giorgio et al., 2010; Paus, 2010; Lebel and Beaulieu, 2011; Bava et al., 2010).

Observations on differences and changes in WM across the lifespan prompted several hypotheses linking heterochronic age-related decrements in WM microstructure to common patterns of WM development. Specifically, the last-in-first-out hypothesis (Raz, 2000, 2001) postulates that tracts that are late to mature, and particularly late-myelinating fibers, are more vulnerable to insult and decline in later life (Gao et al., 2011; Lu et al., 2011). A stronger retrogenesis hypothesis posits a more specific mirroring of developmental progression by age-related course of decline (Reisberg et al., 1999; Brickman et al., 2011).

Testing of such hypotheses of WM aging is hampered by reliance on cross-sectional designs, which may inform about age-related differences, but are poorly suited for evaluating individual differences in change and may underestimate the rate of age-related longitudinal WM decline (Hofer and Sliwinski, 2001; Lindenberger et al., 2011). Longitudinal studies of other putative measures of brain health, such as regional volumes, have shown poor agreement with cross-sectional investigations (Raz et al., 2005, 2010; Pfefferbaum and Sullivan, 2015), but similar comparisons of WM measures are still scarce. To date, only a handful of studies have examined trajectories of WM change in healthy adults through application of DTI-derived indices of brain microstructure and organization (Barrick et al., 2010; Bender and Raz, 2015; Lövdén et al., 2014; Sullivan et al., 2010a; Sexton et al., 2014; Teipel et al., 2010). Notably, these studies were restricted to only two measurement occasions and hence could not elucidate the trajectories of WM aging. Only two studies to date have evaluated change over three or more occasions (Pfefferbaum et al., 2014; Vik et al., 2015). Moreover, these investigations (with exception of Bender and Raz, 2015 and Lövdén et al., 2014) did not attempt to examine individual differences in the rate of change, and did not take into account the influence of prevalent age-related risk factors (except Bender and Raz, 2015) and pathological WM changes (except Sexton et al., 2014; Bender and Raz, 2015).

The association between the burden of white matter hyperintensities (WMH) that are observed on T2-weighted MRI scans and reflect multiple age-related pathological processes (Erten-Lyons et al., 2013), and DTI indices of WM diffusion have been demonstrated in cross-sectional (Vernooij et al., 2008, 2009) and longitudinal (Sexton et al., 2014) studies. WMH reflect a diverse set of interrelated metabolic, inflammatory and vascular risk factors that affect the brain in ostensibly healthy adults (Jagust, 2013; Raz and Rodrigue, 2006; Kennedy and Raz, 2015). Elevated blood pressure and hypertension (even treated and reasonably well-controlled) are associated with differences in DTI-derived indices even in selective healthy samples (Artero et al., 2004; Bender and Raz, 2015; Burgmans et al., 2010; Kennedy and Raz, 2009; Raz et al., 2007; Raz et al., 2012). It is important, therefore, to include such factors in analyzing the trajectories of brain aging, especially in samples with significant proportion of older participants.

To address some of the outlined limitations of the extant studies, we sought to characterize the longitudinal changes in WM diffusion properties in a sample of healthy middle-aged and older adults, who were measured at one to four occasions over seven years. We hypothesized that the rate of change in diffusion properties of normal appearing WM over that period would differ by fiber tract type, and by the region. Specifically, in accordance with the "last in-first out" hypothesis, we expected the greatest longitudinal decline in association fibers, lesser change in the commissural regions and relative stability of diffusion properties in the projection fibers. Furthermore, based on prior findings (Bender and Raz, 2015; Lövdén et al., 2014; Sexton et al., 2014), we hypothesized that advanced aging would be associated with greater declines in FA and increase in radial diffusivity (RD) compared to less pronounced changes in axial diffusivity (AD).

Methods

Participants

Participants were paid volunteers recruited from a major metropolitan area in the Midwestern United States by print media advertisements, flyers, and word of mouth. This sample overlaps with previously reported samples that were assessed at baseline (Kennedy and Raz, 2009) or on three occasions, with other brain indices (Raz et al., 2012). The sample analyzed here includes those who were at least 50 years of age at first DTI assessment, and had one to four longitudinal assessments.

At each measurement occasion, all participants provided written informed consent, in accord with the guidelines for human subject research established by the University Institutional Review Board and the Declaration of Helsinki. Participants were screened via self-report questionnaire for history of neurological and psychiatric disorders, cardiovascular disease other than physician diagnosed and medically treated essential hypertension, diagnosis or treatment for endocrine disorders, head injury accompanied by loss of consciousness for more than five min, use of anxiolytic, antidepressant, or antiepileptic medications, or consumption of more than three alcoholic beverages per day. In addition, participants were screened in the laboratory for cognitive impairment with the Mini Mental Status Examination (Folstein et al., 1975; baseline cutoff = 26), and for symptoms of depression with the Geriatric Depression Questionnaire (CES-D; Radloff, 1977; cut-off = 15). All participants reported right-hand dominance with scores >75% on the Edinburgh Handedness Inventory (Oldfield, 1971).

The sample included 38 healthy adults (55% women), who were 50 to 84 years of age at first DTI assessment (mean age = 65.4, SD = 9.0 years). Men and women did not differ in age, MMSE scores, or blood pressure (Table 1). The mean education exceeded four years of college (mean education = 16.8, SD = 2.5 years), and there was only a nonsignificant trend for men to report more years of formal schooling compared to women. Furthermore, proportion of self-reported smoking, regular exercise or frequency thereof, and diagnosed hypertension did not differ as a function of participant sex. Eleven participants who developed additional health problems between the third and the fourth measurement occasions, did not differ from the remainder of the sample in baseline demographics, health characteristics, or rates of WM change (see Supplementary Materials 1.1 and Supplementary Table 1 for a complete description).

Although MRI scans were administered at four separate occasions (i.e., T1, T2, T3, and T4), because the DTI sequence was introduced to the protocol midway through the first wave (T1), the first 22 out of the 38 participants did not have DTI scans at T1. Thus, T2 occasion served as the baseline for those 22 participants. Across the sample, the mean intervals between consecutive occasions of measurement were: mean T1–T2 delay = 14.93 months (SD = 1.38; n = 13); mean T2–T3 delay = 15.58 months (SD = 2.65; n = 31); and mean T3–T4 delay = 58.06 months (SD = 5.28; n = 19). In addition two participants

Table 1
Participant characteristics.

Baseline variables	Women Mean (SD)	Men Mean (SD)	t or χ^{2a}	p
Age (years)	63.85 (8.91)	67.31 (8.98)	1.19	.244
MMSE	28.43 (1.08)	28.71 (1.36)	0.70	.487
Education (years)	16.14 (2.67)	17.71 (2.20)	1.99	.054
Systolic BP (mm Hg)	128.00 (10.82)	131.52 (12.29)	0.94	.355
Diastolic BP (mm Hg)	78.71 (7.45)	75.97 (7.67)	1.11	.272
% Smokers	0.0%	11.77%	2.61[1]	.106
% Exercise	80.95%	64.71%	1.28	.258
Days exercise/week	3.41 (2.46)	2.79 (2.42)	0.77	.449
% Hypertension Dx	28.57%	35.29%	0.20	.658

Notes: SD = standard deviation; 1: [a] = single degree of freedom chi-square test; BP = blood pressure; Dx = diagnosis

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