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Age-related white matter integrity differences in oldest-old without dementia

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ABSTRACT

Aging is known to have deleterious effects on cerebral white matter, yet little is known about these white matter alterations in advanced age. In this study, 94 oldest-old adults without dementia (90–103 years) underwent diffusion tensor imaging to assess relationships between chronological age and multiple measures of integrity in 18 white matter regions across the brain. Results revealed significant age-related declines in integrity in regions previously identified as being sensitive to aging in younger-old adults (corpus callosum, fornix, cingulum, external capsule). For the corpus callosum, the effect of age on genu fractional anisotropy was significantly weaker than the relationship between age and splenium fractional anisotropy. Importantly, age-related declines in white matter integrity did not differ in cognitively normal and cognitively impaired not demented oldest-old, suggesting that they were not solely driven by cognitive dysfunction or preclinical dementia in this advanced age group. Instead, white matter in these regions appears to remain vulnerable to normal aging processes through the 10th decade of life.

1. Introduction

Aging is known to have deleterious effects on cerebral white matter (for reviews see Gunning-Dixon et al., 2009; Raz and Rodrigue, 2006; Salat, 2011). At the macroscopic level, the aging brain is characterized by shrinkage of white matter tissue and development of white matter lesions. These gross structural differences may be driven by age-related effects at the microscopic level, which includes loss or alterations to myelin (demyelination), loss or shrinkage of white matter axons (neuronal degeneration), expansion of perivascular spaces (Virchow–Robin spaces), and proliferation of glial cells (gliosis; Matsusue et al., 2006; Peters, 2007). Because neuropathology studies of normal brain aging have focused on younger-old adults, little is known about these white matter alterations in advanced age groups.

White matter microstructure can be studied in vivo using advanced neuroimaging techniques, such as diffusion tensor imaging (DTI). DTI measures the rate of molecular water diffusion (Beaulieu, 2002; Le Bihan, 2003), which moves more freely along the length of structures within white matter (neuronal cell membranes, myelin sheaths) relative to diffusion perpendicular to these restricting structures. Multiple diffusion indices can be calculated to assess the degree of restricted diffusion (fractional anisotropy, FA), rate of overall diffusion (mean diffusivity, MD), and the rate of diffusion parallel (axial diffusivity, AD) and perpendicular (radial diffusivity, RD) to the primary diffusion direction. These measures are thought to approximate the "integrity" of white matter because they are sensitive to numerous properties of the underlying microstructure (e.g., axonal size and density, degree of myelination, and coherence of fiber orientation) that differ across individuals and with aging.

DTI has been used extensively to assess age-related differences in white matter integrity (for reviews see Bennett and Madden, 2014; Gunning-Dixon et al., 2009; Madden et al., 2009, 2012; Sullivan and Pfefferbaum, 2006). Both longitudinal and cross-sectional studies of normal aging have revealed linear decreases in FA across

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Table 1
Demographic and neuropsychological data

Demographic or neuropsychological measure	All participants ($n = 94$)	Normal ($n = 64$)	CIND ($n = 30$)	Group difference (t or X^2)
Age	94.6 ± 3.3	94.4 ± 3.1 (90–103)	95.0 ± 3.7 (90–103)	−0.9
Sex (female)	68 (72.3 %)	44 (68.8%)	24 (80.0%)	1.3
Education (>high school)	76 (80.9 %)	56 (87.5%)	20 (66.7%)	3.4
MMSE	27.6 ± 2.5	28.5 ± 1.4 (25–30)	25.6 ± 3.0 (19–30)	6.6*
3MS	93.2 ± 7.0	96.2 ± 3.2 (84–100)	86.4 ± 8.5 (68–100)	9.1*

Demographic and neuropsychological test data are presented as mean ± standard deviation (range) or n (%), separately for the full sample and the cognitively normal and cognitively impaired not demented (CIND) subgroups. Group differences were assessed with independent sample t-tests (t) or chi-square tests (X^2), revealing significantly better performance in cognitively normal versus CIND oldest-old on the Mini-Mental State Examination (MMSE) and modified MMSE (3MS; $^*p < 0.001$).

the adult lifespan and quadratic increases in MD starting around age 60 years (e.g., Hsu et al., 2010; Kennedy and Raz, 2009; Michielse et al., 2010). These age-related declines in white matter integrity (decreased FA, increased MD) are most prominent in the genu of the corpus callosum, fornix, and external capsule (e.g., Bennett et al., 2010; Bucur et al., 2008; Burzynska et al., 2010; Davis et al., 2009; Michielse et al., 2010; Pfefferbaum et al., 2000; Sala et al., 2012; Sullivan and Pfefferbaum, 2006). To date, however, very few DTI aging studies have included sizeable samples of individuals over age 80 years (e.g., >10; Kochunov et al., 2012; Westlye et al., 2010) and no studies have assessed oldest-old adults over age 90 years. Here, we hypothesize that if white matter integrity simply continues to decline linearly into advanced age, then similarly large age effects may also be expected in regions previously identified as being vulnerable to healthy aging (e.g., genu of the corpus callosum, fornix, and external capsule) in oldest-old adults without dementia.

Relative to younger-old adults, however, oldest-old adults are disproportionately affected by dementia (Corrada et al., 2008; Gardner et al., 2013; Yang et al., 2013). Alzheimer's disease, in particular, has been linked to a number of white matter alterations that would directly influence measures of white matter integrity (demyelination, neuronal degeneration, and gliosis; Brun and Englund, 1986; Sachdev et al., 2013; Zhan et al., 2014). Consistent with this view, DTI studies in younger-old adults diagnosed with mild cognitive impairment and Alzheimer's disease have reported integrity declines in the fornix, cingulum, and splenium of the corpus callosum (Stebbins and Murphy, 2009). Importantly, similar dementia-related differences in white matter integrity have also been observed in cognitively normal younger-old adults at increased risk for Alzheimer's disease (Gold et al., 2012; Rieckmann et al., 2016). Thus, any examination of white matter aging in the oldest-old will need to account for the potential contribution of preclinical dementia in this advanced age group. Here, we hypothesize that if white matter integrity declines in advanced age are primarily attributed to the increased prevalence of dementia-related pathology in this age group, then age effects in regions previously identified as being vulnerable to dementia (e.g., fornix, cingulum, and splenium of the corpus callosum) may differ as a function of cognitive status in oldest-old adults without dementia.

The current study is the first to assess age-related differences in white matter integrity in the oldest-old and the degree to which they may be driven by cognitive dysfunction associated with preclinical dementia. Ninety-four oldest-old adults without dementia (age 90–103 years) underwent DTI to assess relationships between chronological age and multiple measures of integrity (FA, MD, AD, RD) from 18 white matter regions across the brain. The effect of preclinical dementia was assessed by controlling for cognitive status and by comparing age effects in cognitively normal and cognitively impaired not demented (CIND) oldest-old, the latter of whom are at increased risk of progressing to dementia, with incidence rates greater than 30% per year relative to only 8% for cognitively normal oldest-old (Peltz et al., 2011).

2. Methods

2.1. Participants

One hundred one oldest-old adults were recruited as part of a new neuroimaging component of The 90+ Study, a longitudinal study of aging and dementia in the oldest-old (see Kawas and Corrada, 2006 for additional details). Participants' cognitive status was assessed by trained examiners who evaluated their neurologic, physical, and neuropsychological performance, the latter of which included the Mini-Mental State Examination (MMSE; Folstein et al., 1975) and modified MMSE (3MS; Teng and Chui, 1987). Seven participants who demonstrated cognitive and functional impairments consistent with Diagnostic and Statistical Manual of Mental Disorders, 4th edition (Association, 1994) criteria for dementia were excluded from further analysis. Thirty participants who did not meet Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria for dementia, but who demonstrated some degree of cognitive impairment (i.e., performed below age-specific norms in one or more cognitive domains), were diagnosed as CIND and remained in the study. Demographic and neuropsychological data on the full sample of 94 oldest-old adults without dementia, and the cognitively normal and CIND subgroups, are provided in Table 1.

Prior to participation, individuals were screened for contraindications that would make it unsafe for them to undergo magnetic resonance imaging scanning (e.g., having ferrous metal implants). Each participant provided informed consent, and the University of California, Irvine Institutional Review Board approved the experimental procedures. Participants were compensated for their time.

2.2. Imaging data acquisition

Participants were scanned using a GE Signa HD 3.0 Tesla magnetic resonance imaging system. Fitted padding was used to minimize head movements.

One diffusion weighted echo planar imaging sequence was acquired using the following parameters: repetition time/echo time (TR/TE) = 12,850/72 ms, field of view (FOV) = 256 × 256 mm, 59 axial slices, and 1.4 × 1.4 × 2.7 mm spatial resolution. Gradients (b = 1000 s/mm^2) were applied in 30 orthogonal directions, with 5 images having no diffusion weighting (b = 0).

A high-resolution T1-weighted fast-spoiled gradient recalled echo (TR/TE/IT = 7/3/400 ms, FOV = 256 × 256 mm, 160 sagittal slices, and 1.0 mm^3 spatial resolution) and a fluid attenuation inversion recovery (FLAIR) sequence (TR/TE/IT = 11,000/151/2250 ms,