Neurobiology of Aging 43 (2016) 79–88

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Age-dependent differences in brain tissue microstructure assessed with neurite orientation dispersion and density imaging

Andrew P. Merluzzi [a,b], Douglas C. Dean III [c], Nagesh Adluru [c], Gaurav S. Suryawanshi [c], Ozioma C. Okonkwo [a,d], Jennifer M. Oh [a], Bruce P. Hermann [d], Mark A. Sager [d], Sanjay Asthana [a,e], Hui Zhang [f], Sterling C. Johnson [a,d,e], Andrew L. Alexander [c,g,h], Barbara B. Bendlin [a,d,*]

[a] Department of Medicine, Wisconsin Alzheimer's Disease Research Center, University of Wisconsin, Madison, WI, USA
[b] Neuroscience and Public Policy Program, University of Wisconsin, Madison, WI, USA
[c] Waisman Laboratory for Brain Imaging and Behavior, Madison, WI, USA
[d] Wisconsin Alzheimer's Institute, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
[e] Geriatric Research Education and Clinical Center, William S. Middleton Memorial Veteran's Hospital, Madison, WI, USA
[f] Department of Computer Science & Centre for Medical Image Computing, University College London, UK
[g] Department of Medical Physics, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
[h] Department of Psychiatry, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

ARTICLE INFO

Article history:
Received 24 September 2015
Received in revised form 17 March 2016
Accepted 26 March 2016
Available online 6 April 2016

Keywords:
Aging
Diffusion-weighted imaging
MRI
Neurites
Cognition
Microstructure

ABSTRACT

Human aging is accompanied by progressive changes in executive function and memory, but the biological mechanisms underlying these phenomena are not fully understood. Using neurite orientation dispersion and density imaging, we sought to examine the relationship between age, cellular microstructure, and neuropsychological scores in 116 late middle-aged, cognitively asymptomatic participants. Results revealed widespread increases in the volume fraction of isotropic diffusion and localized decreases in neurite density in frontal white matter regions with increasing age. In addition, several of these microstructural alterations were associated with poorer performance on tests of memory and executive function. These results suggest that neurite orientation dispersion and density imaging is capable of measuring age-related brain changes and the neural correlates of poorer performance on tests of cognitive functioning, largely in accordance with published histological findings and brain-imaging studies of people of this age range. Ultimately, this study sheds light on the processes underlying normal brain development in adulthood, knowledge that is critical for differentiating healthy aging from changes associated with dementia.

1. Introduction

Human aging involves progressive changes in neural architecture, including a loss of cortical dendritic spines, axonal alterations, and demyelination (Pannese, 2011). Although gray matter (GM) changes, such as cortical thinning (Salat et al., 2004) or reduced dendritic branching (Uylings and de Brabander, 2002), have been well documented, white matter (WM) changes are also implicated in the aging process. Age-related changes have been observed in myelin (Aboitiz et al., 1996), including a decline in the overall number and length of myelinated fibers (Marner et al., 2003), as well as decreased myelin volume in older compared to younger participants (Tang et al., 1997). These findings have been documented in postmortem histological studies (as the 3 preceding references demonstrate) and in studies using a common in vivo technique, diffusion-tensor imaging (DTI) (Salat et al., 2005).

Diffusion-tensor imaging provides markers that include fractional anisotropy (FA) and mean diffusivity (MD), which serve as surrogates of tissue microstructure. The technique is sensitive to Brownian diffusion of water molecules, and microstructural features can be inferred given the relative coherence of myelinated axons in fiber tract bundles. Though DTI has proved invaluable for assessing changes in WM regions with age and determining the neural correlates of cognitive function (Bendlin et al., 2010; Charlton et al., 2006; Madden et al., 2004; Nazeri et al., 2015a; Salat et al., 2005; Sullivan and Pfefferbaum, 2006), it is inherently a nonspecific technique; a change in FA could reflect changes in

* Corresponding author at: Department of Medicine, Wisconsin Alzheimer's Disease Research Center, University of Wisconsin – Madison, Madison, WI 53705. Tel.: (608) 265 2483; fax: (608) 265 3091.
E-mail address: bbb@medicine.wisc.edu (B.B. Bendlin).

0197-4580/$ – see front matter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2016.03.026

myelination, axon diameter, axon packing density, or increased membrane permeability (Jones et al., 2013). Further, DTI is insensitive to microstructural nuances within a particular voxel, such as regions in which WM tracts intersect, fan, or bend (Zhang et al., 2012). This is particularly important given the abundance of crossing fibers in white matter (Jeurissen et al., 2013). However, recent advances in diffusion-weighted imaging have allowed for a much closer inspection of cellular microstructure in humans.

One such technique is Hybrid Diffusion Imaging (HYDI) (Wu and Alexander, 2007) modeled with Neurite Orientation Dispersion and Density Imaging (NODDI) (Zhang et al., 2012). HYDI acquires DTI and diffusion spectrum imaging data simultaneously, allowing for collection of more diffusion directions and including higher b-values in a clinically reasonable scan time (Wu and Alexander, 2007; Zhang et al., 2012). NODDI is capable of differentiating between 3 microstructural features: intraneurite diffusion (within axons and dendrites), extraneurite diffusion, and the volume fraction within a voxel occupied by isotropic water diffusion. It does this by modeling neurite orientation with a Watson distribution, which allows for a more accurate assessment of microstructure, including in regions with highly complex arborization such as in the cortex (Zhang et al., 2012).

NODDI provides 3 parameters of interest: (1) neurite density index (NDI), which estimates the volume fraction within neurites and ranges in value from 0 (complete extraneurite diffusion) to 1 (complete intraneurite diffusion); (2) orientation dispersion index (ODI), which estimates the degree of fiber coherence, with values ranging from 0 (complete directional coherence) to 1 (fully dispersed neurites); and (3) volume within a voxel occupied by isotropic water diffusion (V_{iso}) similar to freely moving cerebrospinal fluid (CSF), with values from 0 (no CSF-like fluid) to 1 (complete CSF-like fluid). NODDI has been used to examine both normal brain development and disease conditions (Adluru et al., 2014; Billiet et al., 2014; Eaton-Rosen et al., 2015; Figini et al., 2014; Grussu et al., 2015; Jelescu et al., 2015; Kunz et al., 2014; Lemkaddem et al., 2014; Magnollay et al., 2014; Stikov et al., 2015; Timmers et al., 2015; Wen et al., 2015; Winston et al., 2014). Such studies provide a more detailed analysis of the microstructural subtleties and underlying mechanisms associated with these illnesses and processes.

With regard to human aging, NODDI has been used in several studies investigating changes in WM and GM microstructure including a recent study by Nazeri et al. (2015b). In this analysis of 45 cognitively healthy participants between 21 and 84 years, widespread decreases in ODI were observed with age throughout the cortex. This effect was particularly pronounced within fronto-parietal regions, possibly indicating reduced dendritic complexity or a regression of dendritic arborization (Nazeri et al., 2015b). Importantly, this result is largely in accordance with histological findings in monkeys (for a review, see Dickstein et al., 2013) and humans showing age-related differences in dendritic complexity and density (Anderson and Rutledge, 1996). This group demonstrated no significant changes in NDI with age, possibly because analyses were limited to GM regions in which NDI values are lower than those in WM (Zhang et al., 2012). Several other studies have investigated age-related NODDI changes in WM in cohorts of healthy, relatively young individuals. One study, Billiet et al. (2015), examined 59 participants (aged 17–70 years) and observed widespread cerebral V_{iso} increases in WM and more localized NDI and ODI increases. Similarly, Chang et al. (2015) observed increases in NDI and ODI in WM in a group of 66 healthy participants aged 7–63, though tending to over represent younger adults and therefore perhaps better modeling early-life development rather than aging through adulthood. Finally, Kodiweera et al. (2015) used the HYDI acquisition protocol and examined changes specific to WM in 47 adults aged 18–55, finding increased ODI and no age-related changes in NDI. Perhaps most importantly, each of these studies found increases in ODI with increasing age, a microstructural phenomenon which may lend mechanistic insight into the increased FA seen in early development (Lebel and Beaulieu, 2011). By extension, Chang et al. (2015) speculated that WM FA reductions often observed in older populations of participants may be due to either accelerated increases in ODI or slowing increases or reductions in NDI. There are known biological mechanisms to support this hypothesis, including the accumulation of water in myelin sheaths (Feldman and Peters, 1998), reduced packing density, or overall loss of myelinated fibers (Marner et al., 2003; Sandell and Peters, 2001;), and the present study may be able to shed light on this question by examining age-related differences in NDI and ODI in an older population.

Although these prior studies provide important observations on age-related brain changes, each used relatively small sample sizes with wide age ranges, resulting in a sparse sampling across different ages. In the present study, we sought to determine the effect of age on NODDI metrics in a large sample of well-characterized middle- to older-aged adults. Given these previous studies and prior histological observations, we hypothesized: (1) age would be associated with a decrease in ODI and NDI in GM, given potential age-related losses in neurite arborization; (2) ODI in WM would increase with age, reflecting greater dispersion of axons; (3) NDI would decrease with age in WM, reflecting reduced packing density; (4) V_{iso} would show age-dependent increases throughout the cerebrum, reflecting cell shrinkage with increasing age; (5) age-associated changes in NODDI measures would be observed within regions known to degenerate first in healthy aging, such as prefrontal WM (Reisberg et al., 1999); and (6) greater age-associated changes in microstructure would be associated with lower memory and executive function.

2. Methods

2.1. Participants

One hundred and sixteen cognitively healthy participants (mean age = 61.7; standard deviation [SD] = 6.1; range 45.4–72.0; 62% female) were recruited from the Wisconsin Registry for Alzheimer's Prevention (Sager et al., 2005) and the Wisconsin Alzheimer's Disease Research Center. The cohorts are composed of healthy middle to older-aged adults with and without parents with late onset AD. The current sample was enriched for AD risk via a parental history (72%) and included participants positive for the known AD genetic risk factor Apolipoprotein E ε4 (*APOE* ε4; 40%). Participants were defined as having a parental history of AD if one or both parents were determined to have the disease by a validated interview (Kawas et al., 1994) or were confirmed AD positive by an autopsy reviewed by a multidisciplinary diagnostic consensus panel. Detailed medical history and phone interviews were conducted to confirm parental history negative participants. Absence of parental history of AD required that the participant's father survive to at least age 70 years and the mother to age 75 years without diagnosis of dementia or cognitive decline (McKhann et al., 2011). Exclusion criteria included any significant neurological disease, magnetic resonance imaging (MRI) contraindications, major psychiatric disorders, or significant mental illness. Although age was analyzed as a continuous variable, demographic characteristics and cognitive performance scores are listed in Table 1 by 3-age strata. The University of Wisconsin's institutional review board approved all portions of this study, and each participant provided written informed consent before all procedures.