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Superficial white matter as a novel substrate of age-related cognitive decline

Arash Nazeri [a,b,c], M. Mallar Chakravarty [a,b,d,e,f], Tarek K. Rajji [c,g,h], Daniel Felsky [a,b,h], David J. Rotenberg [a,b], Mikko Mason [a], Li N. Xu [a], Nancy J. Lobaugh [b,c,i], Benoit H. Mulsant [c,g,h], Aristotle N. Voineskos [a,b,c,g,h,*]

[a] Kimel Family Translational Imaging-Genetics Laboratory, Ontario, Canada
[b] Research Imaging Centre, Campbell Family Mental Health Institute, Centre for Addiction and Mental Health, Ontario, Canada
[c] Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
[d] Cerebral Imaging Centre, Douglas Institute, Verdun, Quebec, Canada
[e] Department of Psychiatry, McGill University, Montreal, Quebec, Canada
[f] Department Biomedical Engineering, McGill University, Montreal, Quebec, Canada
[g] Geriatric Mental Health Service, Centre for Addiction and Mental Health, Ontario, Canada
[h] Institute of Medical Science, University of Toronto, Ontario, Canada
[i] Department of Neurology, University of Toronto, Ontario, Canada

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ABSTRACT

Studies of diffusion tensor imaging have focused mainly on the role of deep white matter tract microstructural abnormalities associated with aging and age-related cognitive decline. However, the potential role of superficial white matter (SWM) in aging and, by extension, cognitive-aging, is less clear. Healthy individuals (n = 141; F/M: 66/75 years) across the adult lifespan (18–86 years) underwent diffusion tensor imaging and a battery of cognitive testing. SWM was assessed via a combination of probabilistic tractography and tract-based spatial statistics (TBSS). A widespread inverse relationship of fractional anisotropy (FA) values in SWM with age was observed. SWM-FA adjacent to the precentral gyri was associated with fine-motor-speed, whereas performance in visuomotor-attention/processing speed correlated with SWM-FA in all 4 lobes of the left-hemisphere and in right parieto-occipital SWM-FA (family-wise error corrected $p < 0.05$). Independent of deep white matter-FA, right frontal and right occipital SWM-FA–mediated age effects on motor-speed and visuomotor-attention/processing speed, respectively. Altogether, our results indicate that SWM-FA contributes uniquely to age-related cognitive performance, and should be considered as a novel biomarker of cognitive-aging.

1. Introduction

Normal aging is accompanied by continuous decline in cognitive abilities (Bishop et al., 2010), which may in part be caused by disruption in brain connectivity (Madden et al., 2009). In recent years, diffusion tensor imaging (DTI) studies have shed light on white matter microstructural abnormalities associated with aging (Bennett et al., 2010; Salat et al., 2005; Voineskos et al., 2012; Westlye et al., 2010). DTI exploits random translational motion of water molecules to probe microarchitectural properties of tissues in vivo (Assaf and Pasternak, 2008). Fractional anisotropy (FA), derived from the diffusion tensor model, indexes directionality of water diffusion. FA has been used as a sensitive marker of white matter integrity in aging and other conditions (Ciccarelli et al., 2008).

Almost all DTI studies to date examining cognitive aging have focused on the deep white matter (DWM) tracts that connect distant brain regions (Davis et al., 2009; Voineskos et al., 2012; Ziegler et al., 2010). In contrast, to our knowledge, only one published study has explored the relationship of superficial white matter (SWM) in vivo with age (Phillips et al., 2013). SWM fibers rest just beneath the cortex and mediate local connectivity between adjacent cortical gyri in the form of U-fibers or as longer intralobar fibers (Catani et al., 2012; Yeterian et al., 2012). These superficially located structures were first described in the 19th century (Meynert, 1872). However, their functional and neuropsychological

* Corresponding author at: Centre for Addiction and Mental Health, 250 College Street, Toronto, ON, Canada, M5T 1R8. Tel.: +1 416 535 8501 x4378; fax: + 1 416 979 6936.
E-mail address: Aristotle.Voineskos@camh.ca (A.N. Voineskos).

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correlates in humans remain largely unknown. In particular, the extent to which SWM microstructural integrity, relative to that of DWM, contributes to age-related cognitive decline is also unknown.

Although recent advances in DTI-based tractography methods have improved the capability to map DWM long-range brain connections in the human brain (Jbabdi and Behrens, 2013; Voineskos et al., 2009), group-wise comparisons of SWM structures is difficult with tractography because of high interindividual variability (Oishi et al., 2008). To overcome this limitation we designed a 2-step method that augments probabilistic tractography of SWM via tract-based spatial statistics (TBSS) (Smith et al., 2006). This method permits specific voxel-wise examination of SWM tracts across the brain and enhances between-subject registration of these tracts. Using this approach in a sample of healthy individuals across the adult lifespan, we aimed to: (1) assess the relationship between age and SWM-FA (and other DTI metrics); and (2) determine the contribution of SWM-FA (relative to DWM-FA) to cognitive performance. We hypothesized that we would find (1) widespread age-related SWM-FA decline and (2) regionally specific relationships between SWM microarchitecture and cognitive performance.

2. Methods

2.1. Study participants

One hundred forty-one healthy participants across the adult lifespan (18–86 years of age; 66 female; 75 male) were recruited at the Centre for Addiction and Mental Health n Toronto, Canada, via referrals, study registries, and advertisements. All participants completed the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, Edition IV Disorders, the Mini Mental Status examination, and a urine toxicology screen. All participants were fluent English speakers. Exclusion criteria included any history of a mental disorder (including a dementia, current substance abuse, or a lifetime substance dependence) except for simple phobias; positive urine toxicology, a first-degree relative with a history of psychotic mental disorder; or a history of head trauma with loss of consciousness, seizure, or another neurological disorder. Participants were characterized with the Wechsler Test for Adult Reading Intelligence Quotient; Edinburgh handedness inventory (Oldfield, 1971); Hollingshead index; Clinical Illness Rating Scale for Geriatrics (CIRS-G) (Miller et al., 1992); and weight, height, and blood pressure (see Table 1). None of the participants had severe osteoarthritis (CIRS-G score ≥3 on the MSK section), whereas 7 participants had a history of mild-to-moderate osteoarthritis (CIRS-G scores 1–2 on the MSK section). The study was approved by the Research Ethics Board of the Centers for Addiction and Mental Health, and all participants provided written informed consent.

Table 1
Demographic and clinical characteristics of participants

	Age group 1 (n = 57)	Age group 2 (n = 43)	Age group 3 (n = 41)
Age, y	18–34	35–59	60–86
Sex, F/M	28/29	16/27	22/19
Handedness, R/L	55/2	41/1	40/1
Education, y, mean (SD)	15.7 (1.8)	15.1 (2.08)	15.0 (2.2)
WTAR IQ, mean (SD)	118.3 (7.9)	114.4 (8.6)	120.7 (5.5)
Systolic BP, mmHg, mean (SD)	115.5 (12.1)	124.9 (11.9)	133.2 (15.2)
Diastolic BP, mmHg, mean (SD)	71.1 (8.5)	79.0 (9.2)	76.8 (11.3)
BMI: mean (SD)	23.7 (5.2)	26.9 (5.11)	26.8 (4.19)
CIRS-G (ratio score): mean (SD)	0.82 (0.72)	0.81 (0.55)	1.25 (0.46)

Key: BMI, body mass index; BP, blood pressure; CIRS-G, Clinical Information Rating Scale; F, female; L, left; M, male; R, right; SD, standard deviation; WTAR IQ, Wechsler Test for Adult Reading Intelligence Quotient.

2.2. Cognitive battery

A comprehensive battery of well-established standardized cognitive tests was administered to participants over approximately 1.5 hours. This battery assessed a wide range of cognitive tasks: letter-number span (working memory) (Wechsler, 2008), letter cancellation test (Geldmacher et al., 2000) (visuospatial processing speed/scanning), finger tapping (Halstead, 1948) (fine motor speed), grooved pegboard (Matthews and Klove, 1964) (visuomotor coordination), letter fluency (Ruff et al., 1989) (semantic fluency), Stroop test (Trenerry et al., 1989) (set shifting/response suppression), Trail-making test B (Reitan and Wolfson, 1985) (flexibility), along with subtests from Repeatable Battery for the Assessment of Neuropsychological Status (Gold et al., 1999; Hobart et al., 1999) (i.e., list learning [verbal memory/encoding], story memory [verbal memory/encoding], line orientation [visuospatial/constructional], category fluency [language], digit span [attention], symbol digit coding [processing speed], list recall [delayed memory], story recall [delayed memory], and figure recall [delayed memory/visuospatial]).

2.3. Magnetic resonance imaging

2.3.1. T1-weighted imaging

High-resolution, T1-weighted scans were acquired using an 8-channel head coil on a 1.5 T GE Echospeed system (General Electric Medical Systems, Milwaukee, WI, USA). Axial 3D inversion recovery prepared spoiled gradient recall images were acquired using the following parameters: time of repetition (TR): 12.3 ms; echo time (TE): 5.3 ms; inversion time: 300 ms; flip angle: 20°; number of excitations: 1; 124 contiguous images, and 1.5-mm slice thickness.

2.3.2. Diffusion tensor imaging

Acquisition of DTI was conducted via the use of a single-shot echo planar sequence with diffusion gradients (b =1000 s/mm^2) applied in 23 noncollinear directions along with 2 b=0 images. Fifty-seven axial-oblique slices (parallel to anterior commissure–posterior commissure plane) were acquired for whole brain coverage. Slice thickness was 2.6 mm, and voxels were isotropic. The field of view was 330 mm and the size of the acquisition matrix was 128 × 128 mm^2, with TR/TE = 15,000/85.5 ms. The DTI sequence was repeated 3 times to improve the signal-to-noise ratio.

2.4. Image analysis

Diffusion volumes from all repetitions were concatenated and corrected for motion, and eddy current distortions with the FMRIB Diffusion Toolbox, part of FSL v4.1.9 toolkit (http://www.fmrib.ox.ac.uk/fsl) (Jenkinson et al., 2012). After averaging the corrected diffusion data across the repetitions, FA maps were generated by fitting the diffusion tensor model in each voxel using FSL's *dtifit* function. The general framework proposed here for investigating SWM-FA relationship with aging and cognition is outlined in Fig. 1.

2.4.1. SWM tractography and creation of SWM-mask

Probabilistic tractography was performed for each individual within the native diffusion space. To constrain tractography within the superficial white matter, the following steps were carried out:

1. Cortical reconstruction and subcortical segmentation were performed on the structural T1-weighted scans with the FreeSurfer v5.1.0 software (average lobar cortical thickness and surface area also were recorded for each individual) (https://surfer.nmr.mgh.harvard.edu/) (Fischl, 2012). Next, the gray matter–white matter