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White matter integrity, as measured by diffusion tensor imaging, distinguishes between impaired and unimpaired older adult decision-makers: A preliminary investigation

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Abstract

In the context of normal ageing, some individuals experience cognitive changes that affect their decision-making abilities. We investigated whether such cognitive changes could be related to the integrity of cortical white matter, as measured by diffusion tensor imaging (DTI). Participants were administered a well-validated laboratory decision-making task, and were subsequently grouped as either poor decision-makers (older-impaired, $n = 9$) or strong decision-makers (older-unimpaired, $n = 7$). Participants also underwent magnetic resonance imaging (MRI) that collected high-resolution structural images, including DTI of the brain. The key variable of interest to be contrasted between the groups was fractional anisotropy (FA), as calculated from the tensor images. We hypothesised that FA values would be lower (indicating poorer integrity of tracts) in the older-impaired participants. The results supported our hypothesis, indicating significant differences in FA values between the participant groups for the entire brain as well as several subregions. The results suggest that poorer decision-making abilities are associated with the integrity of cortical white matter across multiple regions of the brain, and support the call for additional research in this area.

Keywords

Decision making; Diffusion tensor imaging; Elderly; Magnetic resonance imaging

Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technology that allows for the visualisation and quantification of the anisotropic diffusion of water. Unimpeded water will diffuse with equal probability in all directions, a concept referred to as Brownian motion (Naismith et al., 2010). However, in the brain, water preferentially diffuses along the longitudinal axis of white matter bundles. As white matter breaks down, or is damaged, the diffusion of water becomes less anisotropic (more isotropic), thereby

providing an opportunity to evaluate the integrity of white matter using fractional anisotropy (FA). FA measures the degree of anisotropic diffusion, with larger FA values representing greater probability of diffusion in one direction (anisotropy) (LeBihan et al., 2001).

In recent years, DTI has been increasingly utilised to study the neurobiology of cognitive changes associated with normal ageing. Unlike structural MRI techniques, which provide measurements of the brain's grey matter, such as thickness of the cortical ribbon (Rosas et al., 2002), DTI allows for an examination of white matter integrity. Several common disease processes, including hypertension, diabetes mellitus, and atherosclerosis, are known to cause microstructural changes in cerebral white matter (Kodl et al., 2008; Kozera et al., 2010). These microstructural changes may disrupt signal transmission leading to cortical disconnection, a disruption in communication between areas of the brain which could lead to cognitive dysfunction in certain tracts while leaving others intact (Charlton et al., 2006; Esposito, Kirkby, van Horn, Ellmore, & Berman, 1999; Westlye, Walhovd, Dale, & Bjornerud, 2010).

Theories abound regarding how the “healthy” brain ages, and some of these go beyond conventional wisdom which holds that ageing is more or less synonymous with memory loss. Although memory does tend to decline with age, many older people experience dramatic declines in nonmemory-related cognitive abilities, such as difficulties with concentration, problem solving, and decision making. Unlike memory, which is strongly linked to the medial temporal region of the brain, these other abilities are closely linked to the frontal lobes. One theory, referred to as the “frontal lobe hypothesis” (West, 1996), proposes that some older people have disproportionate age-related changes of frontal lobe brain structures, and of the associated cognitive abilities. This theory has gained support from several sources of evidence, including neuropsychological, neuroanatomical, and functional neuroimaging studies.

Neuroimaging studies involving positron emission tomography (PET) and DTI have been among the sources of growing evidence supporting the frontal lobe hypothesis. The medial frontal cortices and anterior cingulate cortex show grey matter metabolic decline with age in PET imaging studies (Kalpouzos et al., 2009; Pardo et al., 2007). Others, including diffusion tensor studies, have provided evidence that white matter also undergoes changes with age, and these changes may play a key role in age-related cognitive decline (O'Sullivan et al., 2001; Pfefferbaum, Adalsteinsson, & Sullivan, 2005; Salat, Tuch, Greve, et al., 2005; Ziegler et al., 2010). More specifically, the orbitofrontal cortex, genu of the corpus callosum, forceps major, anterior corona radiata of PFC (Ziegler et al., 2010), and posterior limb of the internal capsule (Salat, Tuch, Greve, et al., 2005) seem to undergo the greatest decline in white matter integrity. Although certain tracts may be targeted, studies suggest overall cerebral FA values decline in parallel with age-related cognitive changes (Charlton et al., 2006; Salat, Tuch, Greve, et al., 2005; Westlye et al., 2010).

Few studies have attempted to examine DTI data in relation to decision-making ability. The few that have are rather equivocal in their findings. To illustrate, Moeller and colleagues (2007) found no reliable differences in FA values when comparing regions of the corpus callosum in younger adult MDMA (known colloquially as ecstasy) users that did poorly on a

laboratory decision-making task, the Iowa Gambling Task (IGT), relative to nondrug normal comparisons, but did show a difference in the longitudinal component of diffusion. By contrast, Lane and colleagues (2010) evaluated younger adult cocaine-dependent individuals who performed poorly on the IGT, as compared to normal comparisons, and showed decreased FA values in frontal, parietal, and corpus callosum regions.

The IGT has been used as a measure of decision-making ability in several different populations. Individuals known to have decision-making deficits in the real world, including patients with ventral medial prefrontal cortex lesions (Bechara, Tranel, & Damasio, 2000), substance-dependent individuals such as cocaine addicts (Cunha, Bechara, de Andrade, & Necastrì, 2010), and adolescents that have alcohol-related problems (Xiao et al., 2009), all do poorer on the IGT. Another participant sample that has performed poorly on the IGT is a subset of older adults that are otherwise healthy and independent in their functioning, and for whom other aspects of cognition are fully intact (e.g., memory and language) (Denburg, Tranel, & Bechara, 2005). Such individuals may be at an increased risk for making poor real-world decisions, for instance in the domains of medical and financial decision making, or may be at increased risk of falling prey to fraudulent advertisers, telemarketers, and door-to-door salespeople who all too often target older adults. Detection of these individuals and an understanding of the neurobiological processes that contribute to the decision-making deficits could allow for interventions and possibly lead to treatments. To help better understanding of the neurobiology behind older adult decision making, we utilised DTI in a group of cognitively well-characterised older adults to examine whether FA values were related to decision-making abilities.

In the present study, we grouped participants based on their performance on a well-validated laboratory task of decision making (the Iowa Gambling Task or IGT; Bechara, 2007). Roughly half of our participants were deemed poor decision-makers (hereafter referred to as older-impaired, $n = 9$); the remaining half were deemed strong decision-makers (hereafter referred to as older-unimpaired, $n = 7$). We hypothesised that FA values would significantly differ between the older-unimpaired and older-impaired decision-makers, such that the FA values would be smaller in the older-impaired participants.

METHODS

Participants

We studied 16 healthy community-dwelling older adults, aged 65–90 years. All participants had a negative psychiatric and neurological history per clinical interview (as in Tranel, Benton, & Olson, 1997), and all performed at or above expectations on an extensive neuropsychological screening procedure.

The screening procedure involved a 3-hour comprehensive battery of clinical neuropsychological instruments designed to ensure that participants' cognitive and emotional status was fully intact and in order to ascertain that our participant groups did not differ in such a way so as to confound interpretation of our neuroimaging results. Specifically, participants were administered the Mini Mental Status Examination (Folstein, Folstein, & McHugh, 1975), a cognitive screening instrument [MMSE]; the Wechsler

Abbreviated Scale of Intelligence (Wechsler, 1999), a four-subtest measure of intellectual functioning [Full Scale IQ]; the Digit Span subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1997), a measure of attention and concentration [Verbal Working Memory]; the Benton Visual Retention Test (Sivan, 1992), designed to assess visual attention and short-term retention [Visual Working Memory]; the Benton Facial Discrimination Test (Benton, Sivan, Hamsher, Varney, & Spreen, 1994), a measure of visual perceptual discrimination [Visual Perception]; the Rey Auditory-Verbal Learning Test, a verbal list-learning [Verbal Learning] and delayed memory test [Verbal Memory] (Rey, 1941); the Rey-Osterrieth Complex Figure Test, a nonverbal visual construction and delayed memory test (Osterrieth, 1944; see also Corwin & Bylsma, 1993) [Visual Memory]; the Controlled Oral Word Association Test (Benton & Hamsher, 1989), a speeded verbal fluency (word finding) task [Verbal Fluency]; a short form of the Boston Naming Test (Goodglass, Kaplan, & Barresi, 2000), a measure of confrontation naming [Verbal Naming]; Trail Making Tests A and B (Reitan & Wolfson, 1985), tests of visuomotor tracking [Psychomotor Speed] and set-shifting [Simple Executive Functioning]; and the Beck Depression Inventory—second edition (Beck, Steer, & Brown, 1996), a self-report mood instrument [Depression].

Two groups of healthy older adults were defined for our study, based on their performance on the Iowa Gambling Task (IGT; Bechara, 2007), a well-validated laboratory test of decision-making under uncertainty. These groups were derived by applying the binomial theorem to IGT performance, with one group performing at or below chance (at the .05 level; Siegel, 1956), and the other group performing above chance, on the IGT (at the .05 level; Siegel, 1956; see Denburg et al., 2005, for an explication of that classification scheme). The disadvantageously performing subpopulation was termed older-impaired ($n = 9$), and the advantageously performing population was termed older-unimpaired ($n = 7$). Figure 1 shows that the two groups start at a roughly similar performance but diverge considerably, with the impaired group showing a lack of learning over the five trial blocks, culminating in a negative net score.

Procedures

All 16 participants underwent high resolution anatomical and diffusion tensor imaging using a Siemens Avanto 1.5T scanner (Erlangen, Germany). Diffusion tensor imaging data were gathered on 70 slices with a slice thickness/gap of 2.0/0.0 mm in a 256 mm $\times$ 256 mm field of view. The acquisition matrix was 128 $\times$ 128, using 30 unique directions and a b-value of 1000. TR/TE = 8800/83 ms, flip angle was 90 degrees, pixel bandwidth was 1860 Hz, and the imaging frequency was 63.672214 MHz. Total scan time per person was 283 s. Processing of the images was performed using BRAINS2 (Brain Research: Analysis of Images, Networks, and Systems) software (Magnotta et al., 2002). The diffusion tensor data were analysed using GTRACT software (Cheng et al., 2006). The diffusion tensor images were coregistered to eliminate motion. Once the images were co-registered, the diffusion tensor decomposition was performed and fractional anisotropy (FA) maps were generated. The FA maps were then aligned with the participant's anatomical scan. Region measures of FA were then obtained in the white matter by warping the FA maps to the anatomical image in Talairach atlas space. A threshold of FA above 0.1 was used to designate areas of white matter (Magnotta et al., 2002).

Figure 2 shows a prototype tissue-classified image generated using information from T1- and T2-weighted images. The white matter regions have been colour coded to represent the different regions assessed such that pink represents sub-cortical structure white matter; blue represents temporal lobe white matter; yellow represents frontal lobe white matter; red represents parietal lobe white matter; and green represents occipital lobe white matter.

RESULTS

Table 1 indicates that the older-impaired and older-unimpaired participant groups did not differ reliably with respect to demographic and neuropsychological characteristics. Importantly, age, sex, handedness, level of educational attainment, mental status screening, intellect, attention, working memory, visual perception, verbal learning and memory, visual memory, language, psychomotor speed, simple executive functioning, and self-reported depression did not differ between the two subgroups of older adults. Thus, we were able to contrast our DTI findings between the older-impaired and older-unimpaired participants without concerns about confounding demographic or neuropsychological factors.

We statistically analysed the IGT data using 2×5 ANOVA using group (older-impaired vs. older-unimpaired) as a between-subjects factor and trial block (Blocks 1–5) as a within-subjects factor. This analysis yielded a significant main effect of group, $F(1, 14) = 56.68$, $p < .0001$, and two-way interaction, $F(4, 56) = 5.73$, $p < .01$, substantiating the trends evident in Figure 1.

We contrasted the DTI findings in our two groups of decision-makers (unimpaired vs. impaired) using independent samples *t*-tests. As predicted, the older-impaired participants demonstrated lower FA values than the older-unimpaired participants in several brain regions. These brain regions involved whole brain (which includes cerebellum, $p = .04$); left brainstem ($p = .03$); right cerebrum (which does not include cerebellum, $p = .03$); right temporal ($p < .05$); subcortical ($p = .03$, driven primarily by the right subcortical, $p = .01$); frontal (at the level of a trend, $p = .06$); and right parietal (again, at the level of a trend, $p = .06$).

Pearson correlations between the FA values and the demographic (i.e., age, sex, educational attainment) and neuropsychological (i.e., intellect, attention, working memory, visual perception, anterograde memory, language, psychomotor speed, simple executive functions, and mood) variables revealed no relationships (all $ps > .05$), suggesting that the decision-making finding had notable specificity in relation to DTI.

DISCUSSION

Consistent with our hypothesis, the older-impaired participants demonstrated lower FA values in cerebral white matter when compared to the older-unimpaired participants. This implies that white matter integrity may be a contributing factor to relatively poorer decision-making abilities among otherwise healthy older adults. The neuropathological aetiology for the FA findings is as yet unknown; however, possibilities include accelerated age-related alterations of myelin-related processes and/or neuronal loss with axonal degeneration (Salat, Tuch, Hevelone, et al., 2005).

At first glance, the observed FA reduction among the older-impaired participants in multiple brain regions appears to indicate diffuse white matter involvement in higher order real-world decision making (rather than a region-specific finding, say in the prefrontal cortex, as one might suspect given the frontal lobe hypothesis of ageing). However, we raise the caveat that the present study did not evaluate the data for focal or track-based changes in FA. Therefore, although we found a global reduction in FA in the older-impaired as compared to the older-unimpaired participants, we cannot rule out the possibility that focal reductions in FA exist. For example, the frontal lobe is notably prone to susceptibility-related signal loss (Frahm, Merboldt, & Hanicke, 1988; Ojemann et al., 1997). The analysis performed in this study should minimise the impact of susceptibility-related signal loss. The large regions of white matter evaluated and the measurement of FA within white matter identified by both the anatomical as well as diffusion tensor images minimise the impact of these artefacts on the resulting measurements.

Our findings are promising and suggest that further work relating DTI to higher order cognitive abilities among older adults would be informative. Often, DTI effects are rather subtle, and thus we are pleased that, with a relatively small sample of participants, we were able to observe group differences in FA. However, along with our small sample size comes a limitation of power which could be masking the effects of unknown variables or variables we found to be nonsignificant. With an increase in power, we may see variables come into play, adding complexity to the relationship between decision-making capabilities and white matter integrity. Hence, our findings support the need for further research but the power of our study doesn't allow us to suggest causation. In the future we hope to extend our results by increasing power with additional research participants and further processing the data using tractography methods (Davis et al., 2009), in order to distinguish with finer resolution the locations of the cortical white matter integrity differences between our older adult groups. Tractography uses diffusion-directional information obtained from an Eigen analysis of the diffusion tensor to piece together white matter pathways, allowing us to differentiate with greater certainty which white matter bundles are involved in older-impaired participants' disadvantageous decision-making abilities.

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Figure 1.

Decision-making performance on the IGT (good deck selections minus bad deck selections) for older-impaired and older-unimpaired participants, graphed as a function of trial block (card choices 1–20, 21–40, 41–60, 61–80, and 81–100) $\pm$ standard error of the mean (SEM).

Figure 2.

Tissue-classified image generated using information from T1 - and T2-weighted images with white matter regions masked by colour. Colour-coded to represent the different white matter regions assessed. Pink represents subcortical structure white matter; blue represents temporal lobe white matter; yellow represents frontal lobe white matter; red represents parietal lobe white matter; and green represents occipital lobe white matter. [To view this figure in colour, please visit the online version of this Journal.]

TABLE 1

Comparison of the demographic and neuropsychological characteristics of the older-impaired and older-unimpaired participants

Characteristic	Statistic	Participants		Significance
		Older-impaired (n = 9)	Older-unimpaired (n = 7)	
Age	<i>M (SD)</i>	76.7 (7.0)	76.4 (4.0)	<i>ns</i>
Sex	% female	66%	29%	<i>ns</i>
Handedness	% RH	77%	100%	<i>ns</i>
Education	% beyond high school	56%	85%	<i>ns</i>
MMSE	<i>M (SD)</i>	29.3 (0.9)	29.9 (0.4)	<i>ns</i>
Full scale IQ	<i>M (SD)</i>	115.6 (13.6)	125.8 (10.4)	<i>ns</i>
Verbal working memory	<i>M (SD)</i>	10.1 (2.0)	8.9 (2.8)	<i>ns</i>
Visual working memory	<i>M (SD)</i>	7.1 (2.0)	7.8 (1.1)	<i>ns</i>
Visual perception	<i>M (SD)</i>	44.6 (4.8)	48.9 (4.1)	<i>ns</i>
Verbal learning	<i>M (SD)</i>	49.6 (6.4)	49.1 (6.8)	<i>ns</i>
Verbal memory	<i>M (SD)</i>	10.2 (2.3)	9.1 (3.4)	<i>ns</i>
Visual memory	<i>M (SD)</i>	17.5 (4.6)	16.2 (3.6)	<i>ns</i>
Verbal fluency	<i>M (SD)</i>	40.4 (12.9)	50.6 (8.2)	<i>ns</i>
Verbal naming	<i>M (SD)</i>	19.1 (0.9)	19.1 (0.9)	<i>ns</i>
Psychomotor speed (time)	<i>M (SD)</i>	31.8 (7.8)	37.6 (7.9)	<i>ns</i>
Simple executive functioning (time)	<i>M (SD)</i>	84.6 (31.3)	90.1 (13.8)	<i>ns</i>
Depression	<i>M (SD)</i>	6.1 (5.4)	4.3 (3.4)	<i>ns</i>

ns = nonsignificant.