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RESEARCH ARTICLE

Dorsal White Matter Integrity and Name Retrieval in Midlife

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ARTICLE HISTORY

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Abstract: ***Background*:** Recent findings on retrieval of proper names in cognitively healthy middle-aged persons indicate that Tip-Of-The-Tongue (TOT) states occurring during proper name retrieval implicate inferior frontal (BA 44) and parietal (BA 40) cortical areas. Such findings give rise to the possibility that anatomical connectivity *via* dorsal white matter may be associated with difficulties in name retrieval in midlife.

***Objectives & Method*:** Using Diffusion Tensor Imaging, we examined *in vivo* microstructural properties of white matter in 72 cognitively healthy Middle-Aged (MA) and 59 Young Adults (YA), comparing their naming abilities as well as testing, for possible associations between dorsal white matter integrity and naming abilities in the MA group.

***Results*:** The MA group was better in retrieving correct names ($U = 1525.5$, $p = .006$), but they also retrieved more incorrect names than YA believing they had retrieved the correct ones ($U = 1265.5$, $p < .001$). Furthermore, despite being more familiar with the tested names than YA ($U = 930$, $p < .001$), MA experienced significantly more TOTs relative to YA ($U = 1498.5$, $p = .004$). Tract-based spatial statistics showed significant group differences in values of fractional anisotropy (FA), mean diffusivity, axial diffusivity, radial diffusivity, and mode of anisotropy in a range of white matter tracts. In the MA group, FA values in the right Superior Longitudinal Fasciculus (SLF) were positively correlated with "don't know" scores ($r_s = .287$, $p = .014$).

***Conclusion*:** The association of SLF integrity and name retrieval ability in midlife indicates a need to revisit the models of name retrieval that posit no role for dorsal white matter in proper name retrieval.

Keywords: Diffusion tensor imaging, white matter, name retrieval, tip-of-the-tongue states, superior longitudinal fasciculus, cortical areas.

1. INTRODUCTION

Knowledge of proper names is an aspect of semantic memory that is particularly vulnerable to aging. The susceptibility of proper names to forgetting has been associated with their peculiar nature. Proper names refer to unique entities, such as persons, animals, places, buildings, and so on [1], with each name entailing unique semantics. Thus, they lack lexical meanings characteristic for common nouns, which in contrast refer to categories of objects, *i.e.* non-unique entities. The peculiar nature of proper names has been debated across disciplines, with the major debates revolving around their special status in grammar [1-2], elusiveness of their meaning [3-8], their susceptibility to forgetting and the way they are organized and stored in long-term memory [9-13].

Remembering proper names is the most common memory concern in older neurologically intact people, while a deficit in proper name retrieval accompanies a wide range of neurological conditions. Regardless of age, cognitively healthy people typically find proper names more difficult to retrieve than common nouns [14-16]. Surprisingly, this is the case even in name-occupation homophones (*e.g. Baker-baker*, *Potter-potter*) [11]. Sometimes proper name retrieval is associated with so-called Tip-Of-The-Tongue (TOT) states [10, 17]. TOT states are metacognitive states in which a person cannot retrieve a specific word at a given moment, despite a strong feeling that the word is within reach; crucially, the person is fully aware of this temporary word retrieval failure [10, 18, 19]. In TOT states, we typically remember information about the entity in question, *i.e.* semantic information about that entity is available, but the name eludes us, despite sometimes recalling a part of the name. Put differently, TOT states differ from mere failures to retrieve a name (we can fail to retrieve a name without having the impression that the target name is on the tip-of-the-tongue) and from experiences of retrieving an incorrect name without realizing that the retrieved name does not coincide with the target name. TOTs are complex states, which require multiple cognitive processes and implicate a range of brain areas [20].

Recent evidence suggests that cognitively healthy middle-Aged Adults (MA) have more problems remembering

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familiar proper names than Young Adults (YA) [19]. More specifically, MA individuals experience more TOT states than YA. They also retrieve more incorrect names for which they believe are the correct ones. Furthermore, the higher incidence of TOTs in midlife has been associated with significantly less cortical thickness in left BA 45 (pars triangularis) and right BA 44 (pars opercularis) as well as with less grey matter density in BA 40 (supramarginal gyrus) relative to young adulthood. These findings raise the possibility that the anatomical link between BAs 44 and 40 may have a role in name retrieval processes leading to TOTs [19].

This hypothesis deserves attention, because the white matter tract connecting inferior frontal and inferior parietal areas, *i.e.* the Superior Longitudinal Fasciculus (SLF) is implicated in the control of phonological processing [21]. This is relevant because TOTs in cognitively healthy people have been interpreted in terms of an interrupted access to phonological processing. In addition, this complex system of fibers, whose functionality is yet to be fully described, may play a role in higher cognitive processes [22], including those that support awareness about failures to retrieve the target word and possibly with the generation of alternative strategies for word retrieval. This tract could therefore contribute to name retrieval and associated TOT experiences in more than one way.

So far, proper name retrieval has been typically associated with white matter tracts supporting the ventral processing stream for language, in particular, the left Uncinate Fasciculus (UF) [23-25]. An alternative proposal, however, suggests that the uncinate fasciculus is redundant for language [26, 27]: together with the inferior longitudinal fasciculus, it represents only a back-up pathway for the inferior fronto-occipital fasciculus, which is the main ventral tract for language. Possible further modifications of the model of white matter supporting name retrieval pertain to the role of dorsal white matter.

In the present study, we investigated whether dorsal white matter would be relevant for proper name retrieval and whether there would be differences in the ability to retrieve proper names as well as in white matter integrity in middle-aged cognitively healthy subjects relative to young controls. Testing the hypothesis on the relevance of anatomical connectivity between right BAs 44 and 40 for proper name retrieval [19], we investigated whether the microstructural integrity of the right Superior Longitudinal Fasciculus (SLF) would be associated with middle-aged subjects' ability to retrieve proper names. Previous research has suggested that anatomical connections between pars opercularis (BA 44) and the supramarginal gyrus (BA 40) *via* one component of the Superior Longitudinal Fasciculus (SLF III) may have a role in phonological processing [21, 22], while the anatomical connections between the orbitofrontal and anterior temporal areas *via* uncinate fasciculus is implicated in semantic/ conceptual knowledge. Thus, the anatomical links implicated in proper name retrieval go beyond the uncinate fasciculus. If SLF is implicated in proper name retrieval, and possibly related to TOTs, we would find significant associations between the indices of white matter integrity of this tract and the ability to retrieve proper names, and possibly TOTs in the MA group.

To test this hypothesis, we used Diffusion Tensor Imaging (DTI) and assessed white matter microstructural integrity in 131 cognitively healthy individuals, including 72 middle-aged and 59 young adults. This *in vivo* MR imaging technique quantifies integrity of white matter microstructure through diffusion parameters, based on micron-scale displacement of water molecules [28]. DTI indices of white matter microstructural integrity are defined based on the directional variability of water diffusion in white matter. Importantly, they are more sensitive indicators of age-related differences in white matter microstructure than white matter lesions [29, 30]. Thus, we examined *in vivo* the following indices of microstructural integrity of white matter: Fractional Anisotropy (FA), Mean Diffusivity (MD), axial diffusivity (AD), Radial Diffusivity (RD), and Mode of Anisotropy (MO).

These diffusion parameters are sensitive to age-related changes of white matter and white matter pathology, indicating for instance abnormalities in crossing fibers regions (MO), myelin injury or glial cell damage (RD), axonal injury or changes in intracellular space (AD) [29, 31]. Normally, water molecules spread in parallel to the axon and myelin sheath, leading to anisotropic diffusion. However, abnormalities in fiber tracts lead to a more heterogeneous diffusion. For example, lower FA values and higher MD values in white matter tracts in Alzheimer's disease patients indicate tracts' deterioration due to Alzheimer's pathology [32, 33]. Still, these indices are far from being unambiguous. As an example, changes in FA values may indicate changes in myelination, axon density and diameter, to intravoxel incoherence of fiber deterioration [34]. Thus, simultaneously assessing multiple indices of white matter microstructural integrity is more informative regarding the possible effects of aging than focusing on only one of them [35].

Since microstructural integrity of white matter tracts deteriorates differentially due to aging [35] and given that aging differentially affects associations between DTI parameters of white matter integrity and cognitive functions [36, 37], in addition to comparing the two groups' values in the five DTI parameters described above we conducted a correlation analysis, testing for possible associations between these parameters' values in the tract under study (SLF) and MA group's naming scores.

2. MATERIALS AND METHODS

Data used in the preparation of this work were obtained from the Cambridge Center for Ageing and Neuroscience (Cam-Can) data repository [38, 39]. The protocol for the CamCan study has been approved by their institution's ethics committee (reference: 10/H0308/50), as stated in [39]. We obtained permission to use the data in December of 2016, within a data sharing initiative launched by the Center earlier that year. For more information about the CamCan study, see http://www.mrc-cbu.cam.ac.uk/datasets/camcan/.

2.1. Participants

The sample in the present study (N = 131) consisted of a group of Middle-Aged Adults (MA) (n = 72), who were between 45 and 55 years old, and a group of Young Adults (YA) (n = 59), who were between 18 and 30 years old (Table **1**). All participants were cognitively healthy individuals,

Table 1. Demographics and behavioral scores of two groups.

	MA (n = 72)	YA (n = 59)	*Test value*	*p*-value
Age (Mean, SD)	49.7 ±3.3	25.5 ±3.4	t (129) = 40.882	< .001
Age range	45-55	18-30	-	-
Gender (m/f)	36/36	24/36	χ^2 (1) = 1.135	= .29, n.s.
Know-correct	20.1 ±10.2	15.3 ±9.4	U = 1525.5	= .006
Know-incorrect	5.2 ±3.6	2.9 ±2.5	U = 1265.5	< .001
Don't know	10.7 ±9.4	22 ±11.1	U = 930	< .001
TOT	12.2 ±6.5	8.8 ±5.2	U = 1498.5	= .004

with a Mini Mental State Exam score of 24 or better, with no history of substance abuse, dementia, stroke, motor neuron disease, multiple sclerosis, encephalitis, epilepsy or other neurological or psychiatric (schizophrenia, bipolar disorder, psychosis) problems that could affect cognition [39].

2.2. Behavioral data

For the present study, we retrieved behavioral data on a picture-naming task. In this task, pictures of 50 famous people such as actors, musicians, and politicians were presented to participants, who were required to look at one picture at a time and name the person on it. Each picture appeared after a fixation cross, which was presented for 1000 milliseconds, and it remained on the screen for 5000 milliseconds. Participants named a person on the picture if they could, they responded as "don't know" if they did not know the name of the person, or said that they were experiences a TOT state if they knew the name, but could not recall it. For analysis, the correct responses were divided into "know-correct" and "know-incorrect" responses (*i.e*. the retrieved name was correct *vs*. incorrect) [39].

2.3. DTI Data Acquisition and Preprocessing

DTI data retrieved for the present study were collected on a single Siemens TIM Trio 3 T scanner with a 32 channel head coil and twice-refocused spin echo sequence. The data included b = 1000/ 2000 scans (TR = 9100 ms; TE = 104 ms; Field Of View (FOV) = 192x192; voxel size: 2 x 2 x 2; 30 directions), and a set of b = 0 scans with the same parameters, but without applying the diffusion-coding gradients, as described in [38].

We also retrieved high-resolution structural T1-weighted images for anatomical reference in data processing and analysis. These images were obtained using a Magnetization Prepared RApid Gradient Echo (MPRAGE) sequence, with TR = 2250 ms, TE = 2.99 ms, flip angle = 9 degrees, FOV = 256 x 240 x 192 mm, voxel size 1 x 1 x 1 mm, GRAPPA acceleration factor = 2, acquisition time = 4 minutes and 32 seconds [38].

DTI data preprocessing was performed following the standard FSL protocol (http://www.fmrib.ox.ac.uk/fsl), including correction for head motion and eddy currents, removal of non-brain voxels with the Brain Extraction Tool, and fitting of diffusion tensors to the data with DTIfit [40]. A tensor model fit in FSL was used to calculate quantities of FA, MD, AD, RD, and MO.

2.4. Statistical Analyses

We used Tract-Based Spatial Statistics (TBSS) in FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL) (Smith *et al*., 2006) to calculate group differences in the five diffusion parameters separately, correcting for multiple comparisons ($p < .05$, TFCE) at the cluster level. Furthermore, we extracted the values for the right SLF from the skeletonized images of all MA participants using the Johns Hopkins University white matter atlas (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). In the next step, these values were entered into SPSS 22 to test for significant associations between the microstructural properties of this tract and the naming scores in the MA group, using Spearman test of correlation. An alpha level of .05 was set for all tests. All tests were two-tailed.

3. RESULTS

3.1. Demographics and Behavioral Tests' Results

The two groups differed statistically in age, with the MA group being significantly older than the YA group, as shown in Table **1**. There were no statistically significant differences in gender distribution across the groups. The two groups differed in their behavioral scores. We summarize subjects' characteristics and behavioral data in Table **1**.

The MA group had significantly more "know-correct" scores and significantly less "don't-know" scores relative to the YA group, indicating that they were more familiar with the tested names than the young adults. However, MA also had significantly more "know-incorrect" answers and experienced considerably more TOT states than YA, as shown in Fig. (**1**).

3.2. Results of TBSS Analysis

Statistically significant group differences were found in a range of tracts supporting cognition, including the superior longitudinal fasciculus, the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and uncinate fasciculus bilaterally, alongside anterior thalamic radiation and cortico-spinal tracts, among others (Fig. **2**).

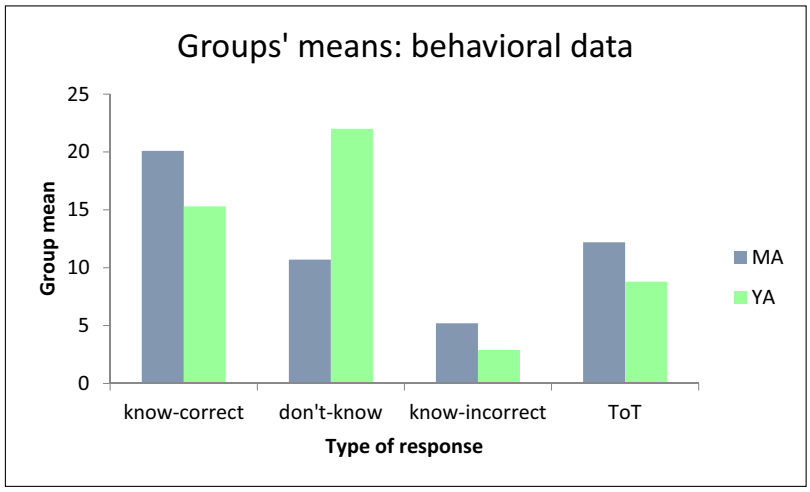

Fig. (1). Groups' means in behavioral task responses. MA – middle-aged adults; YA – young adults.

More specifically, compared to YA, the MA group had significantly lower FA values in a range of tracts, including the right superior longitudinal fasciculus (Fig. **2a**). The MA group also had lower MO values in the superior longitudinal fasciculus, uncinate fasciculus, inferior fronto-occipital fasciculus, and inferior longitudinal fasciculus bilaterally (Fig. **2e**). In contrast, they had higher RD values than the YA group in the superior longitudinal fasciculus, involving the portion that links inferior frontal lobe to the supramarginal gyrus (Fig. **2d**), as well as higher MD values in this tract and in the major ventral language tracts bilaterally, including the uncinate fasciculus, inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus (Fig. **2b**). Finally, lower AD values in the MA group relative to the YA group were found in the superior longitudinal fasciculus, uncinate fasciculus and inferior longitudinal fasciculus (Fig. **2c**). Thus, the results of TBSS analysis suggest significant group differences in the microstructural integrity of a range of white matter tracts, including the tract of interest (SLF).

There was a significant direct correlation between MA group's FA values in the right SLF and their "don't know" responses (r_s = .287, p = .014). No significant correlations were found between their TOT scores and this tract's DTI values.

4. DISCUSSION

A recent study on proper name retrieval in cognitively healthy subjects reported more TOT states associated with proper name retrieval in midlife relative to young adulthood as well as an association between reduced grey matter density in the right supramarginal gyrus (BA 40) as well as cortical thinning in right pars opercularis (BA 44) and TOT states [19]. Assuming that the right hemisphere becomes more involved in name retrieval with increased age [41], in the present study we tested the hypothesis on a possible involvement of the right SLF in retrieval of proper names in midlife. The SLF is a complex fiber system, whose one component connects inferior frontal and inferior parietal areas [21, 22]. Previous research has emphasized the role of the uncinate fasciculus in proper name retrieval [23, 24], which is consistent with the evidence on the role of the anterior temporal lobe in naming [12], given the fact that the uncinate fasciculus links the temporal pole with orbitofrontal areas [27, 42, 43]. Thus, a possible association of the SLF and naming would provide evidence for the relevance of the dorsal white matter to name retrieval.

Consistent with previous work on proper name retrieval in midlife [19], our behavioral data revealed that, relative to young participants, the middle-aged participants retrieved considerably more incorrect names while believing that those were the corrects names, and experienced more TOT states during proper name retrieval. Taken together, these results suggest that certain aspects of name retrieval are already affected by midlife.

Furthermore, we found statistically significant age-related differences in the integrity of white matter microstructure across a range of white matter tracts. Overall, the differences in DTI parameters between midlife and young adulthood observed across the major tracts supporting cognition (Fig. **2**) are consistent with previous findings, indicating a negative effect of age on white matter microstructural integrity [30, 44-46]. Importantly, our data indicate that the age-related differences in microstructural integrity of the right SLF are associated with the ability of MA adults to retrieve proper names. More specifically, we found a significant association between the inability to retrieve proper names and the FA values in this tract in the MA group.

However, we did not find a significant relation between the DTI parameters' values and TOT scores in MA. One could argue that testing more narrowly for an association between SLF III segment, which presumably connects BAs 44 and 40 [22], and TOT states could have resulted in different findings. While this objection is merited, one should keep in mind that multiple tracts run through the white matter underlying the supramarginal gyrus (SLF II, SLF III, middle longitudinal fasciculus, frontooccipital fasciculus) and that DTI data from this region "like gross dissection, cannot resolve the specific fiber bundles that mingle with each other" [47]. In fact, the difficulty of teasing apart fibers from different cerebral white matter fasciculi [48] and inaccuracies of DTI in mapping the fiber architecture of the areas with intersecting fibers' trajectories are so pronounced that they have apparently motivated a renewed interest in sophisticated fiber dissection techniques [49].

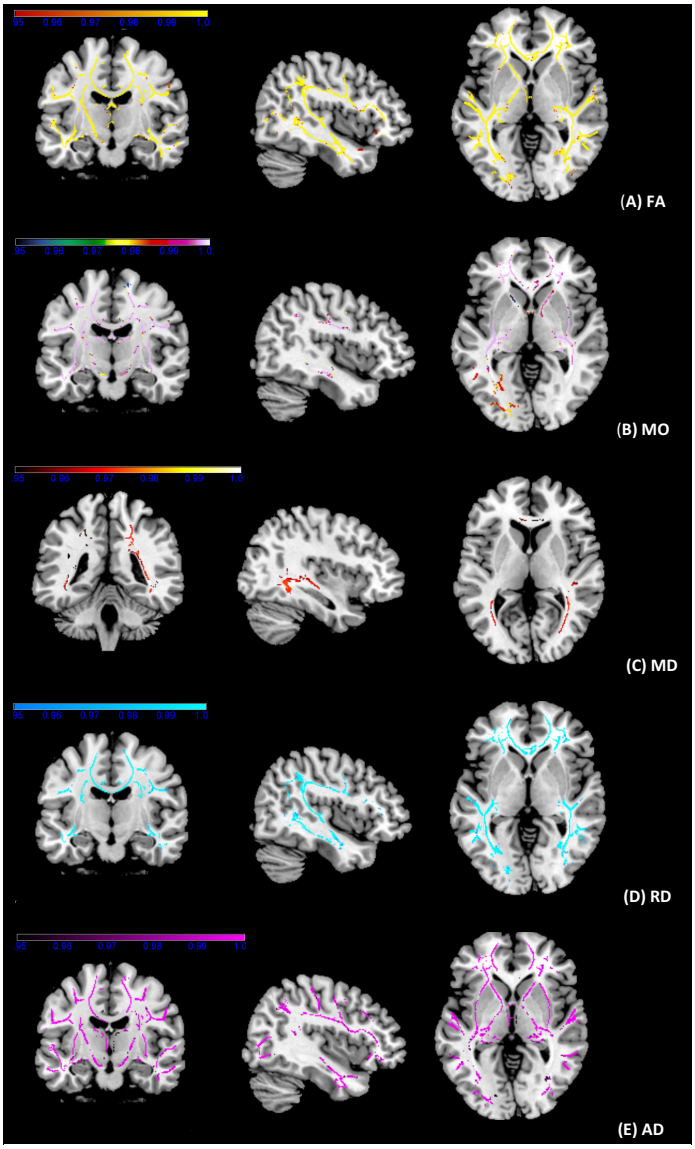

Fig. (2). Statistically significant ($p < .05$, TFCE corrected) group differences in fractional anisotropy (**A**), mode of anisotropy (**B**), mean diffusivity (**C**), radial diffusivity (**D**) and axial diffusivity (**E**). Image orientation: radiological (right side of the image corresponds to the left side of the brain).

A related issue is whether the two dorsal tracts for language, the arcuate fasciculus and the superior longitudinal fasciculus, can be reliably separated [47, 50, 51]. Since axons from the arcuate fasciculus "mingle with those of SLF II and SLF III in the white matter of supramarginal gyrus", establishing their respective terminations using current DTI methodology would be challenging, even though evidence from the macaque monkey shows that SLF III terminates in BA 44 [21, p.38]. This uncertainty is further exacerbated by lack of consensus on a model of dorsal language tracts. According to the traditional view, the left arcuate fasciculus is the classical language pathway, connecting Broca's and Wernicke's areas. On the other hand, according to one currently prominent view, the superior longitudinal fasciculus is a complex fiber system [52], consisting of four components in the human brain (see [43] for a review). In this multicomponent system view, the arcuate fasciculus is a part of the superior longitudinal fasciculus system [21, 22]. Thus, search for a possible role of a more narrowly defined portion of the SLF in name retrieval may be problematic for methodological and theoretical reasons.

Finally, among frequently observed limitations of DTI [53] there is also the limitation that this technique allows only indirect measures of the white matter properties. We need to keep in mind this lack of direct mappings between the differences in signal intensities measured by this technique, on the one hand, and neurocognitive processes, on the other, when interpreting our findings.

CONCLUSION

In conclusion, the present data indicate significant age-related group differences in proper name retrieval, with more pronounced naming difficulties in midlife relative to young adulthood, as also found in [19]. Furthermore, significant age-related differences were found in the microstructural integrity in a range of white matter tracts, consistent with previously observed effects of aging on the integrity of white

matter microstructure [35, 29]. In addition, we have identified an association between the right SLF FA values and the retrieval of proper names in middle-aged subjects. Thus, although we did not observe specifically an association between white matter deterioration and TOT states in MA, the present data suggest the relevance of the anatomical connections between the right inferior frontal (BA 44) and inferior parietal areas (BA 40) to proper name retrieval in midlfie, as hypothesized by Kljajevic & Erramuzpe [19].

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The protocol for the CamCan study has been approved by their Institution's Ethics Committee (Reference: 10/H0308/50), as stated in [39].

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Data collection and sharing for this project was provided by the Cambridge Centre for Ageing and Neuroscience (CamCAN).

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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