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IS THE LEFT UNCINATE FASCICULUS ASSOCIATED WITH VERBAL FLUENCY DECLINE IN MILD ALZHEIMER'S DISEASE?

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Abstract

The association between verbal fluency deficit in Alzheimer's disease (AD) and deterioration of specific white matter (WM) tracts is currently not well understood. Using diffusion tensor imaging, we investigated a possible association between the left uncinate fasciculus, which has been implicated in word retrieval, and verbal fluency deficit in AD. A comparison of five properties of WM (fractional anisotropy, mode of anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity) in 28 mild AD patients and 26 age-, gender- and education-matched healthy controls revealed significant group differences in a range of WM tracts. Looking specifically at diffusion parameters' values for the left uncinate fasciculus and verbal fluency scores in the AD group, we observed a positive trend between the letter fluency scores and mode of anisotropy values ($r = 0.36$, $p = 0.55$). Thus, our data suggest more global WM damage in mild AD, which also includes damage to the left uncinate fasciculus. However, damage to this particular tract is not robustly associated with verbal fluency decline at this stage of disease.

Keywords

• Diffusion tensor imaging (DTI) • mild Alzheimer's disease • Uncinate fasciculus • Verbal fluency • White matter

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Verbal fluency tests, involving letter and category fluency, regularly show considerably worse scores in Alzheimer's disease (AD) patients in comparison to cognitively healthy elderly control subjects (HC) [1]. The letter fluency (LF) and category fluency (CF) tests require a subject to produce as many words as possible in 1 minute. In the LF test words need to begin with a specific letter (e.g., S), whereas in the CF test produced words need to belong to a specific category (e.g., animals). Impaired verbal fluency in AD patients has been associated with rapid disease progression, probably reflecting advanced deterioration of the frontal networks [2]. Other brain areas have also been associated with verbal fluency, e.g. inferior parietal lobe, insula, and putamen, among others [3, 4].

While knowledge on grey matter cortical areas supporting verbal fluency is growing, little is known on possible associations between white matter (WM) deterioration and verbal fluency decline in AD. Previous research has suggested that the uncinate fasciculus (UF) is among the most affected WM tracts in manifest AD [5]. The UF connects the temporal pole with the orbitofrontal cortex [6]: it originates and terminates in brain areas already affected by the disease in mild AD. The UF has been associated with retrieval of proper names of famous faces [7], semantic control [8] as well as with word production, word retrieval from semantic memory, and inhibition of competing words from short-term memory [9]. Given the relevance of the anterior temporal area for lexical retrieval [10] and the role of the frontal areas (e.g., pars orbitalis) in language, in the present study we investigated whether there would be an association between the deterioration of this tract in AD and patients' decline of verbal fluency.

Using diffusion tensor imaging (DTI), we examined *in vivo* microstructural properties of WM in 28 mild AD patients and 26 age-, gender-, and education-matched HC, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AxD), radial diffusivity (RD), and mode of anisotropy (MO). These diffusion parameters are sensitive to WM pathology, indicating for instance, abnormalities in crossing fibers tracts (MO), myelin injury (RD) or axonal injury (AxD) [11]. We then conducted a correlation analysis between these indices' values in the left UF and patients' scores on verbal fluency tests.

The participants were selected from the German Center for Neurodegenerative Diseases (DZNE) Rostock database. The patients were diagnosed according to the NINCDS-ADRDA Alzheimer´s criteria. In addition, they had abnormal concentrations of at least one CSF biomarker indicative of AD pathology (decreased β-amyloid, increased total tau and/or phospho-tau) [12]. There were an equal number of male and female subjects within each group. The mean age was 72.6 (± 7.5) years in the AD group and 72.3 (± 5.4) in the HC group. Both groups had a mean of 12.6 years of education (± 2.6 in AD, and ± 2.3 in HC). The two groups differed significantly in their performance on LF ($U = 242$, $p = 0.03$), CF ($U = 48$, $p < .05$), Mini Mental State Examination

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($U = 78$, $p < 0.05$) and Boston naming ($U = 117$, $p < 0.05$), with worse performance in AD than in HC. All tests were two-tailed. All participants signed informed consent. The study was approved by the Ethics Committee of the University Medicine of Rostock.

DTI data were collected on a Siemens MAGNETOM Verio 3 T scanner (single shot echo planar images; TR = 8200 ms; TE = 93 ms; flip angle = 90°; 20 directions; $b0 = 1000$ s/mm^2). FA, MD, AxD, RD, and MO values were generated from a tensor-model fit in FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). Tract-based spatial statistics (TBSS) in FSL (a freely-available comprehensive library of analysis tools for FMRI, MRI and DTI brain imaging data http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL) [13] was used to conduct t-tests and calculate group differences in the five diffusion parameters, correcting for multiple comparisons. In addition, values for the left and right UF defined in the Johns Hopkins University ICBM-DTI-81 white matter labels atlas (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) were extracted from the skeletonized images of all AD patients by using an in-house developed parcellation script in MATLAB (MATLAB and Statistics Toolbox Release 2012b, The MathWorks, Inc., Natick, MA, USA). The values of five diffusion parameters obtained for the left and right UF were entered into SPSS 22 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA, IBM Corp. Released 2013) to calculate correlations between WM properties of this specific tract and patients' scores on two fluency tests using Pearson correlation coefficient.

Significantly decreased FA values but increased MD, RD, and AxD values in AD patients in comparison to HC were found in the inferior and superior longitudinal fasciculi, inferior fronto-occipital fasciculus, uncinate fasciculus, and anterior thalamic radiation bilaterally (Fig. 1). In addition, increased RD, MD and MO values in patients compared to HC were found in the corpus callosum, and increased RD values in the posterior thalamic radiation and corticospinal tract bilaterally. Decreased MO values in the AD group compared to HC were found in the left corticospinal tract.

Looking specifically at the left UF and its possible association with the verbal fluency tasks, we found a positive trend between the LF scores and MO values ($r = 0.367$, $p = 0.055$), but no significant or close to significant ($p < 0.05$) associations between the patients' verbal fluency scores and right UF diffusion parameters (e.g.: LF-MO: $r = 0.109$, $p = 0.29$).

Studies of patients with the semantic type of primary progressive aphasia have shown associations between UF changes and single word comprehension and naming, but not with verbal fluency [14]. Awake intraoperative electrostimulation studies involving patients undergoing a tumor resection in either anterior temporal or orbitofrontal region suggest that the UF may be redundant for language [15]. However, in slow-growing tumors, the slow

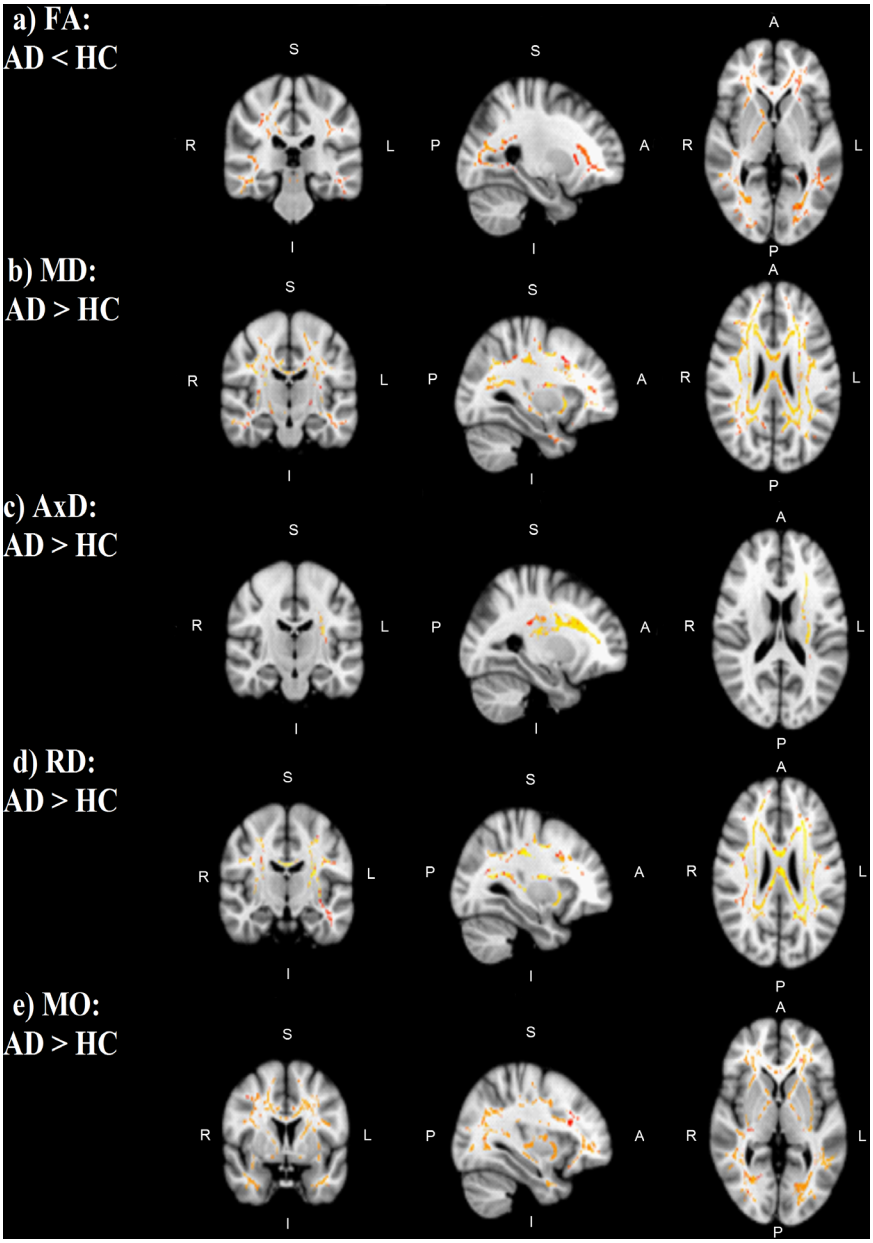

Figure 1. Tracts with significant ($p < 0.05$, TFCE-corrected) AD-HC differences. A, anterior; AD, mild Alzheimer's disease; AxD, axial diffusivity; FA, fractional anisotropy; HC, healthy controls; I, inferior; L, left; MD, mean diffusivity; MO, mode of anisotropy; P, posterior; R, right; RD, radial diffusivity; S, superior; TFCE, threshold-free cluster enhancement.

rate of lesion growth may afford network reorganization of the affected region, rendering the UF redundant in the face of spared function.

In conclusion, our data agree with previous studies in suggesting more global WM damage in mild AD, which also includes damage to the left UF. However, damage to this particular tract is not robustly associated with verbal fluency decline at this stage of disease.

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