

The diffusivity pattern of white matter degeneration in semantic dementia is spatially and qualitatively different from Alzheimer's disease

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Introduction: Semantic dementia (SD) is a variant of frontotemporal dementia characterised by the loss of semantic memory. SD patients have severe temporal lobe atrophy and hypometabolism, yet, unlike Alzheimer's disease (AD), SD does not display posterior cingulate hypometabolism¹. In AD, there is compelling evidence that there is concomitant degeneration of nodes in a functionally and anatomically connected system²⁻⁴. However, empirical evidence that SD is a network disorder is still scarce. Therefore, the aim of this study was to directly search for evidence of network degeneration in SD using whole-brain diffusion tensor imaging (DTI) analysis.

Methods: Ten SD patients according to consensus criteria^{5,6}, 33 patients diagnosed with early-stage probable AD according to Dubois criteria⁷ and 21 sex-, age- and education-matched healthy controls were explored in this study. MRI scans were performed on a Siemens Trio 3T system with gradient coils capable of 45 mT/m and 200 T/m/s slew rate. A 12-channel TIM head-coil was used with twice-refocused single-shot EPI: TR/TE=7800/90 ms; matrix, 96 x 96; 63 axial slices and voxel resolution of 2x2x2 mm³. The diffusion tensor was acquired with diffusion gradients along 63 non-collinear directions ($b \sim 1000$ s/mm²), and one scan without diffusion weighting ($b=0$ s/mm², b_0); the total scan time was 8'44". The FMRIB's diffusion toolbox was used to correct for eddy currents, fit the diffusion tensor and compute diagonal elements (λ_1 or axial diffusivity, λ_2 and λ_3), mean diffusivity (MD) and fractional anisotropy (FA) at each brain voxel. $(\lambda_2 + \lambda_3)/2$, known as radial diffusivity (RD), were also calculated. Warping errors due to atrophy and anatomical discrepancies were minimised by taking advantage of the tract-based spatial statistics (TBSS) approach⁸; this method allows voxel-wise statistics to be applied only at the centre of each major fibre bundle defined by a study-specific white matter tract skeleton. T -tests of reduced/increased DTI indices in SD patients compared to both the control and AD groups were performed using permutation-based nonparametric inference⁹; we generated 10,000 permutations of the data to test against. Results were corrected for multiple testing at a family-wise error rate of 0.05. Cluster-like structures were enhanced using the threshold-free cluster enhancement¹⁰ (TFCE) algorithm.

Results and Discussion: The left-side panels in the figure below illustrate TBSS abnormalities (increased diffusivities and reduced FA) in SD patients compared to the control population. The results are in agreement with prior knowledge that SD is predominantly associated with inferior anterior temporal lobe atrophy. However, white matter abnormalities in SD appear to be more lateralised –left worse than right– than in AD (see [4] for TBSS in early AD); particularly white matter of the superior temporal gyrus. An interesting result is that there is also involvement of the connection to the orbito-frontal region through what we assume is the uncinate bundle (see bottom sagittal cross-section in bottom left-side panel). Overall, radial diffusivity differences were more extensive than those for λ_1 –unlike in AD, where λ_1 differences were the most widespread⁴–; this suggests that there may be a stronger local effect of axonal loss and/or demyelination in SD than in AD. Besides, the strong RD abnormalities in SD made FA a lot more sensitive to changes than in AD. The right-side panels represent the SD versus AD comparisons using TBSS (dark blue for AD worse than SD and other colours for SD worse than AD). These results show that the temporal poles in AD are relatively preserved, which in addition to the uncinate bundle, are the characteristic white matter abnormalities in SD. In contrast, the AD group, which only appears statistically different to the SD population in the λ_1 contrast, presents key involvement of the limbic-diencephalic neuronal network: including white matter of the parahippocampal gyrus continuing along the posterior cingulum bundle, extending into posterior temporo-parietal areas with preferential degeneration of interhemispheric connections passing through the splenium and fibres connecting the mesial temporal lobe and diencephalon via the fornix. This distribution of abnormalities is almost identical to that seen when comparing AD to controls⁴.

Conclusions: This study showed that temporal white matter degeneration in SD is predominantly left sided with greater localised inferior and anterior involvement than in AD. Abnormal connections to the orbito-frontal region may support the hypothesis that SD is a network disorder. Therefore, on the basis of the tensor differences observed in this study, we can speculate not only that SD and AD may be vulnerable to different networks of degeneration, but also that the nature of the neurodegenerative processes—as measured by differential patterns of absolute diffusivities—in those networks may also be different

References: [1] Nestor *et al.* Neuroimage **30**:1010 (2006); [2] Nestor *et al.* Ann Neurol **54**:343 (2003); [3] Seeley *et al.* Neuron **62**:42 (2009); [4] Acosta-Cabrero *et al.* Brain (in press; doi:10.1093/brain/awp257); [5] Hodges *et al.* Brain, **115**:1783 (1992); [6] Neary *et al.* Neurology, **51**:1546 (1998); [7] Dubois *et al.* Lancet Neurol **6**:734 (2007); [8] Smith *et al.* Neuroimage **31**:1487 (2006); [9] Nichols *et al.* Hum Brain Mapp **15**:1 (2002); [10] Smith *et al.* Neuroimage **44**:83 (2009).

