

A whole brain approach of multimodal neuroimaging techniques for in vivo investigation of brain tissue changes in Alzheimer's Disease

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Target audience. Researchers and clinicians interested in quantitative MRI methods for the study of gray and white matter alterations due to neurodegenerative pathologies such as Alzheimer's disease (AD).

Purpose. Several MRI studies investigated the differential contribution of gray (GM) and white matter (WM) damages characterizing AD, using morphometric techniques and diffusion tensor imaging (DTI). However, the relationship between the damage of these two tissues is a matter of debate. Only few studies integrated the information provided by volumetric and DTI techniques^(1,2), using an a-priori selection of GM and/or WM structures of interest, based on the literature. We propose a novel approach to investigate the association between the degree of GM atrophy and the WM microstructural damage in AD, without a-priori hypothesis but at a whole-brain level.

Methods. Twenty-two mild to moderate Alzheimer's Disease patients (MMSE range=18-23) and 23 elderly healthy controls (HC) (age≥65 years; MMSE≥28) were recruited. The following MRI sequences were acquired with a 1.5T Siemens scanner: diffusion weighted (DW) single shot spin-echo (TR/TE=7100/94 ms, 50 axial slices, 128x96 matrix, FOV=320x240 mm², slice thickness=2.5 mm) and 3D T1-weighted magnetization prepared rapid gradient echo (TR=1,900 ms; TE=3.37 ms; TI=1,100 ms; flip angle=15°; 176 contiguous, 1mm thick axial slices; matrix size=192x256; FOV=192x256 mm²). DW images were corrected for eddy current distortion with FSL (<http://www.fmrib.ox.ac.uk/fsl/>); the tensor and the fractional anisotropy (FA) were then calculated for each voxel using Diffusion Toolkit v0.4.3 (<http://www.trackvis.org>). Tract-based spatial statistic (TBSS) analysis³ was run using FSL, with the following steps: non-linear registration of all the FA to the FMRIB58_FA template (MNI space, 1x1x1 mm resolution), skeletonization of the coregistered FA mean image, projection of all coregistered FA to the thresholded skeleton (FA threshold=0.2). Voxel-based morphometry (VBM) was performed with the standard approach described in FSL-VBM guidelines, with the creation of study-specific GM template using non-linear registrations and selecting a Gaussian kernel of sigma =3 mm. The voxel-wise statistical analysis of HC vs AD were assessed with general linear model (GLM), including age and sex as covariates, via permutation non-parametric testing (5000 permutations), for both TBSS and VBM. The threshold-free cluster enhancement (TFCE) analysis was used in order to obtain significant clusters; Family-wise Error (FWE) correction across space was used for handling multiple comparisons (p_{FWE}<0.05 was considered significant). The TBSS results were mapped to the JHU DTI atlas of FSL⁴, then the mean FA value was computed, for each subject and for each significant region. The FA of each significant region was used to test the topographic correlation with GM volume in AD patients.

Results. VBM results showed that patients with AD were significantly more atrophic than HC in several brain regions (Figure 1) including medial temporal lobe structures, anterior and postero-inferior areas of temporal lobes, precuneus, anterior/posterior cingulate, basal ganglia, frontal lobes and cerebellum. TBSS results showed a significant FA reduction in AD compared to HC in: corpus callosum (genu, body, splenium); anterior limb of internal and external capsules; corona radiata (all the subportions); bilateral posterior thalamic radiations, bilateral cinguli; right superior and inferior longitudinal fasciculus and superior and inferior fronto-occipital fasciculus. The principal significant GM loss correlated with FA reduction are illustrated in Figure 2.

Discussion and Conclusion. The VBM conventional analysis confirmed the well-known pattern of GM atrophy in AD compared to HC, which starts from medial-temporal regions then spreads to medial-parietal cortex and orbito-frontal regions and finally to other neocortical association areas⁵. Moreover, the results of TBSS analysis are similar to previous works⁶ and are in line with the disconnection mechanism hypothesis¹, i.e. clinical manifestations of AD are also associated with regional WM damage. Interestingly, the integration of VBM and TBSS results showed a positive correlation between GM loss and WM FA reduction in anatomically close regions, without an a-priori selection of the areas. It remains unclear whether the WM damage occurs in parallel, is secondary to GM loss, or vice versa. Only longitudinal studies with the combined analyses of multimodal neuroimaging techniques as proposed here will allow for the investigation *in vivo* of pathophysiological brain tissue changes across the AD clinical evolution.

References.

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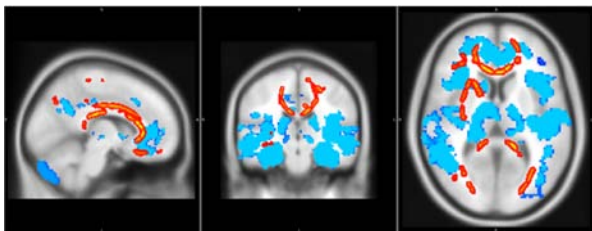


Fig.1. VBM and TBSS results showing areas of atrophy and of FA decrement in Alzheimer's Disease patients compared to healthy controls. VBM results are displayed at p_{FWE}<0.001 in light-blue, TBSS results are displayed at p_{FWE}<0.05 in yellow.

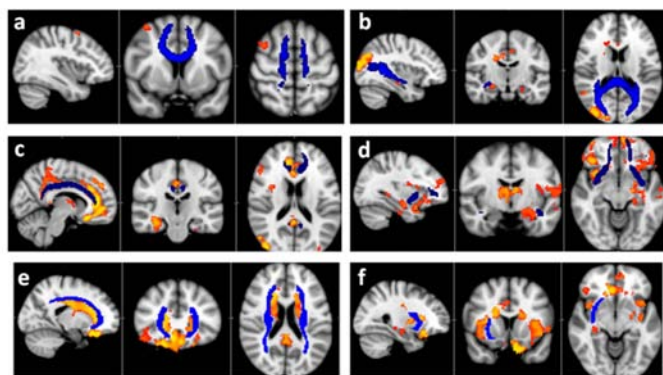


Fig.2. VBM results showing areas of atrophy correlated with FA reductions in white matter bundles [corpus callosum body (a) and splenium (b); cinguli (c); uncinate fasciculus (d); corona radiata (e) and external capsule (f)]. VBM results are displayed at p_{FWE}<0.05, Red-Yellow scale. The bundles (blue) are superimposed for a better interpretation of VBM results, but the FA used for the correlations were computed only in the areas resulted from TBSS (HC>AD).