

Automated segmentation of cortical and subcortical gray matter structures for evaluation of Alzheimer's disease and Frontotemporal Dementia

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Introduction:

As therapeutic interventions become available for degenerative dementias (1) there is a need for automated imaging methodologies which can provide *in vivo* surrogate markers of brain pathological changes. The aim of the present study was to assess the ability of combined MR cortical structure volumetry and DTI to automatically detect regional brain changes in patients with a clinical and neuropsychological diagnosis of Alzheimer disease (AD) and Frontotemporal dementia (FTD).

Methods

Subjects. As part of an on-going study, patients were recruited from the Ospedale S. Orsola, Bologna, with a clinical/radiological diagnosis of AD or FTD, along with healthy controls of similar ages. All subjects gave written informed consent. Subject characteristics: AD: 9 patients (2 M), ages 67±8 yrs (mean±s.d.); FTD : 7 patients (3 M), ages 64±5 yrs; 7 controls (4 M), ages 66±11 yrs. **MR acquisition.** All MRI studies were performed on a 1.5 T GE Signa Horizon LX scanner. A conventional T1-weighted (T1W) axial volumetric image was acquired using the FSPGR sequence TI=600 ms; TE=5.1 ms; TR=12.5 ms; 25.6 cm square FOV, 1 mm slice thickness; in-plane resolution=256x256. A DTI SE-EPI image, was also acquired, encoded in 25 directions at b=900 s.mm⁻² and one T₂-weighted image; TE=89.2 ms; TR=10 s; 32 cm square FOV, 4 mm inter-slice distance; in-plane resolution=192x192; NEX=1. DTI parameter maps of mean diffusivity (MD) were generated using DTIFIT (FSL; 2). **Data analysis.** Automatic segmentation of the volumetric image was performed using FIRST (2) to bilaterally define seven subcortical gray matter structures (thalamus, putamen, caudate, pallidus, accumbens, hippocampus and amygdala). In addition, five cortical regions (frontal, parietal, temporal and occipital lobes and cerebellum) were defined using an MNI (3) template. Within these regions gray matter was defined using a three-class segmentation of the T1W images All structures were registered onto the DTI maps in two steps using flirt (2), following a previously published method (4). White matter partial volume on DTI images was masked by registering the MNI FA template onto subjects' own FA map using non-linear registration. Deep gray structures were identified by warping the Harvard-Oxford sub-cortical structure atlas (also defined in MNI coordinate space). A mask excluding CSF was generated from a three-class segmentation of the T₂-weighted image volume. ROIs of all deep gray and cortical structures was defined in the DTI space by fusing registered FIRST, Harvard-Oxford, and CSF and WM exclusion masks. Volumes and median MD values were calculated. **Statistics.** Cortical and subcortical volumes were separately corrected for subject age and total brain volume, MD values for age only. Each set of corrected values was then analysed by a full factorial ANOVA including structure and patient group as factors. In addition particular structures of interest (frontal, parietal and temporal lobes and hippocampus) were analysed by one-way ANOVA.

Results: Results of the ANOVA analysis were significant (p<0.001) for cortical volume, subcortical volume, cortical MD and subcortical MD, using structure and patient group as factors. However patient group was not a significant factor for subcortical volume. Cross terms (group * structure) were not significant, indicating that group differences did not vary between structures. Differences between groups are summarised in the Table. One way ANOVA revealed a reduction in gray matter volume in patients, in the hippocampus, and the parietal but not frontal or temporal lobes. Individual structures and cortical lobes did not reveal elevated MD.

Table. Subject group comparisons for cortical/subcortical volume/MD. Mean ±S.E. * Sig. diff from controls at p<0.05

Group	Volume (mL)				MD (x10 ⁻³ mm ² .s ⁻¹)			
	Cortex		Subcortical		Cortex		Subcortical	
	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.
Controls	203.1	3.0	6.1	0.1	0.802	0.005	0.801	0.006
AD	195.3	2.9 *	6.0	0.1	0.824	0.005 *	0.835	0.006 *
FTD	186.4	3.2 *	5.8	0.1	0.829	0.006 *	0.831	0.006 *

Discussion:

Volumetric structural imaging and DTI are two MR imaging modalities which offer the potential of improving the radiological diagnosis and grading of neurodegenerative diseases, but to achieve this potential in a clinical setting automated methods of image segmentation and analysis are required. In the current study, for both AD and FTD, a highly automated method of image segmentation, combining information from both volumetric and diffusion imaging was able to differentiate patient groups from normal subjects of similar ages. The changes related to diffuse reductions in cortical volume, and diffuse increases in MD in both cortex and subcortical structures. Alterations were much less apparent on examination of individual structures, even those known to be involved in the degenerative pathology. This may be both to the limited number of cases studied so far, and the heterogeneity of the disorder, at least for FTD (5). Even in this limited group of patients this automated segmentation method revealed differences between control subjects and patients. These are expected to increase with the number of subjects in the study database.

References: [1] Brunden KR, Trojanowski JQ, Lee VM. Nat Rev Drug Discov. 2009 Oct;8(10):783-93. [2] www.fmrib.ox.ac.uk/fsl [3] Montreal Neurological Institute, Quebec, Canada. [4] Malucelli E, Manners DN, Testa C, et al. ISMRM 17th Annual Meeting p.1219. [5] Whitwell JL, Przybelski SA, Weigand SD et al., Brain. 2009;132(11):2932-46.