T2-VBM is more sensitive to Alzheimer′s disease pathology than conventional T1-VBM

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Introduction: Voxel-based morphometry or VBM (Ashburner and Friston, Neuroimage 2000) is now a well-established neuroimaging analysis tool for detection of morphological alterations in neurodegenerative brain diseases. VBM studies to date have exploited high-resolution, T1-weighted magnetic resonance imaging (MRI) acquisitions, the majority of which used inversion-recovery gradient-echo pulse sequences such as MPRAGE (Mugler and Brookeman, MRM 1990). Atrophy can be detected as grey matter (GM) density reductions in VBM, but other potential histopathological processes involved in neurodegenerative disease states such as dendritic degeneration or accumulation of pathological deposits e.g. β-amyloid cannot be distinguished using T1-weighted scans (T1-VBM). T2 relaxation, in contrast, is strongly dependent on the magnetic field fluctuations caused by magnetic susceptibility differences, not only between tissue types, or between cells and intercellular spaces, but also between paramagnetic iron, in e.g. amyloid deposits, and brain tissue; and may, in theory, be more sensitive to microscopic neurodegenerative processes than T1 relaxation. Furthermore, brain atrophy should also be detectable in T2-weighted scans due to the strong signal intensity contrast between cerebro-spinal fluid and brain tissue. The aim of this study was therefore to test the hypothesis that T2-VBM using the novel T2-weighted SPACE acquisition (Mugler et al., Proc ISMRM 2004) is more sensitive to Alzheimer's disease (AD) histopathology than standard T1-VBM using MPRAGE at identical spatial resolution.

Methods: A cohort of 33 patients diagnosed with incipient AD according to Dubois criteria (Dubois et al., Lancet Neurol 2007) and 21 sex- and age-matched healthy controls were recruited. All subjects were scanned on a Siemens Trio 3T system using a 12-channel phased-array TIM head-coil. The 3D MPRAGE pulse sequence was used with the following scan parameters: TR/TE/TI/flip angle=2300 ms/2.86 ms/900 ms/9°, 144 slices, 192×192 matrix dimensions and 1.25×1.25×1.25 mm^3 voxel size. Receiver bandwidth and echo spacing were 240 Hz/pixel and 6.7 ms, respectively, and scan duration was 7 min 23 s. True-3D SPACE images were acquired as follows: TR/TE/NEX=3200 ms/450 ms/2; matrix, 192×192; 144 slices and isotropic voxel resolution, 1.25×1.25×1.25 mm^3. We allowed for parallel acquisition of independently-reconstructed images using GRAPPA (Griswold et al., MRM 2002) with an acceleration factor of 2 to reduce both specific-absorption rate and scanning time (5 min 9 s). SPM5 (Ashburner and Friston, Neuroimage 2005) was employed with default settings to process and analyse the volumes. Warping procedures need reasonable initial estimates, hence the origin of each image was manually reset to the anterior commissure. Recent studies have shown that prior skull-stripping and r.f. bias correction can improve the performance of warping algorithms (Acosta-Cabronero et al., Neuroimage 2008), hence the following automated pipeline was applied prior to SPM5: first, skull-stripping was performed using the hybrid-watershed algorithm (Segonne et al., Neuroimage 2004) in FreeSurfer. Stripped volumes were then bias corrected using N3 v1.10 (Sled et al., IEEE Trans Med Imaging 1998) with default arguments. Finally, a further fine brain extraction step was performed using the brain-extraction tool (BET2) (Smith, Hum Brain Mapp 2002) with fixed arguments: f=0.2 and g=0. Note that SPACE images were skull-stripped with brain masks generated from pre-processed MPRAGE images, but were not bias-corrected. We assumed that spatial normalisation is optimal using MPRAGE volumes, therefore each SPM5 warp transform was applied to the corresponding (SPACE-derived) GM segment in native space. Prior to this, rigid alignments of SPACE volumes were performed to match the orientation of structural MPRAGE images. The resulting segments were modulated and smoothed using an 8-mm FWHM isotropic Gaussian kernel, and finally, group comparisons (via two-sample T-tests) were performed with a false-discovery rate (FDR) statistical threshold of q<0.005. To explore the hypothesis that GM areas present greater signal changes due to Alzheimer pathology in T2-weighted acquisitions compared to those in T1-weighted images, MR signal intensities from two different regions of interest (ROIs) were extracted. The regions were selected as follows: (i) lesions that were found in T2-VBM, but not in T1-VBM; and (ii) lesions common in T1- and T2-VBM results. In addition, a control occipital cortex region, known to be relatively unaffected by AD, was used to scale the images, thus to match the mean control-ROI signal across subjects. To prove our initial hypothesis, mean z-scores of each AD patient (based on the global mean and standard deviation of the control population) were calculated for each lesion ROI and for each image contrast, hereby an analysis of variance or ANOVA was performed (2×2 factorial design at P<0.001).

Results and Discussion: The analyses confirmed the prior hypothesis that T2-VBM is more sensitive than the conventional T1-VBM method in detecting GM abnormalities at a group level in AD (Fig. 1). The main regions of significant abnormality in the T1-VBM results were the hippocampi, with some additional involvement of adjacent parahippocampal and inferior temporal regions. The statistical map obtained with T2 volumes showed significant change in these same areas, but with greater sensitivity, particularly for extra-hippocampal involvement. In addition, the T2-VBM analysis identified further new areas of significant involvement in the posterior cingulate and the ventro-mesial frontal lobe, along with confluent changes in the lateral posterior temporal association cortex and intense insular involvement, which were not identified by T1-VBM. The key question therefore is: what is T2-VBM detecting that T1-VBM does not? Here the results offer what we believe is a compelling case that this may be amyloid deposition (Fig. 2). Turning the attention to the regional analysis, we found a significant difference in MR signal change due to AD pathology between areas abnormal in T2-VBM only, possibly amyloid areas, and abnormal areas common to T1- and T2-VBM, where atrophy is present. We also found a significant effect on contrast (T1 vs. T2), and a significant interaction that reflects the significant difference across image contrasts and that the effect on the lesioned regions depends on the type of image contrast used. The results also showed that there were not significant T1-weighted signal changes on pathological tissue, and therefore confirmed that T1-VBM is only sensitive to cortical atrophy.

Conclusion: This study demonstrated, for the first time, that T2-VBM is viable and shows greater sensitivity to cortical signal change than conventional T1-VBM.
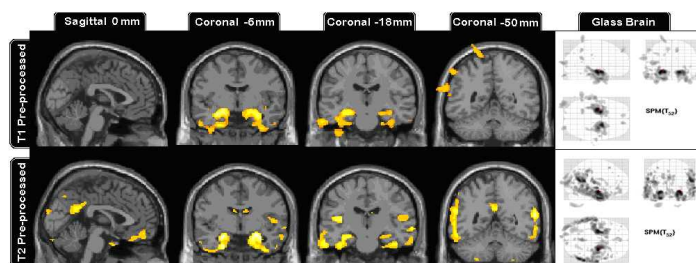
Fig 1 Group statistical comparisons using T1- and T2-VBM of 33 AD patients compared with 21 controls (FDR, q<0.005)
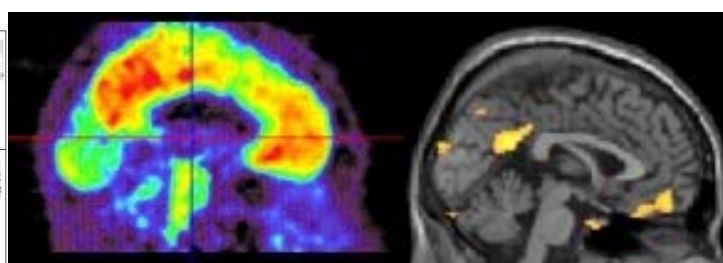
Fig 2 T2-VBM result (right) compared to a mild AD patient imaged with the amyloid PET ligand ^{11}C-Pittsburgh compound-B (left). Both highlight posterior cingulate and ventro-mesial frontal regions.