

Building Whole Brain Maps of Atrophy Rate from Multi-Subject Longitudinal Studies Using Free Form Deformations.

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Introduction

Alzheimers disease (AD) and other dementias are associated with slowly progressive neuron loss in the entorhinal cortex, hippocampus and cortical regions leading to local and then global brain atrophy. Numerous studies using manual tracing methods have shown longitudinal changes in AD, but a major problem has been that the error of manual techniques is similar to the magnitude of change/year, making it difficult to accurately quantify regional change. One approach to this problem is to develop high dimensional registration techniques to directly estimate point-wise volume change between longitudinal MRI studies [1,2,3,4]. However, most of these have so far examined specific regions of the brain such as temporal lobe and hippocampus. The goal of this work was to develop a fully automated technique which statistically examines the entire brain in order to determine regional changes which are significant in a population of subjects. Our approach makes use of a development of a Free Form Deformation based registration algorithm, previously employed to recover misregistration from tissue deformation [5,7], and relative imaging distortion [6]. We employed the approach to evaluate whole brain estimates of point-wise volume change between longitudinal scans of a subject and also, to spatially normalise maps of volume change across subject groups. Such an approach allows direct comparison of patterns of atrophy between different groups. We applied the technique to compare point-wise volume loss in subjects with AD and age matched normal controls.

Methods

A total of 10 control and 6 AD subjects were imaged with a 3D T1 MPRAGE sequence (TR=10ms,TE=4ms) using a 1.5T Siemens Magnetom. All images were coronal and had a 1X1 mm in-plane resolution and a 1.5mm slice thickness. We extended our previously reported free form deformation based volume registration [7] to handle much finer deformations. A cubic B-Spline described by a fine 2.4mm isotropic control knot lattice allows us to model small scale changes between longitudinal MRI scans. We used normalised mutual information as a registration criteria, evaluated from a discretely binned joint histogram. To avoid problems of limited statistical support, we adopted a coarse intensity binning strategy but retained contrast between tissue values of interest in the T1 gradient echo MRI. A simple gradient ascent scheme was used to estimate the optimal location of each spline control knot. To minimise computational complexity we employed a kernel based approximation to the partial derivatives of the B-Spline local deformation field.

Within-subject Registration: Localising tissue loss using registration is problematic because we can only infer tissue loss over a uniform MRI region from changes at its borders. We cannot know where, within these regions, actual tissue loss occurred. Therefore we can choose to use a fine-scale transformation-model which localises volume change to points where borders have shifted or, conversely, a coarse-fine strategy which more evenly distributes volume loss over each uniform region of tissue. In this work we have used a fine voxel scale model of tissue loss only, similar to the approach used in finite element and continue model schemes [1,2,3].

Between-subject Registration: The intra-subject spatial normalisation problem is substantially more complex than the intra-subject case. Cortical structures exhibit genetic and developmental variations, while, for the mapping of aging or diseased brains, we have the additional variation in the size of CSF regions. This is particularly a problem when structures around the ventricles appear significantly displaced compared to normal average anatomy. To address this we have employed a rigid, affine and then coarse to fine B-Spline lattice registration scheme in mapping each individual to our reference brain MRI. The starting lattice has a knot separation of 19.2mm while the finest lattice spacing used for this step is identical to that used for the within subject registration (2.4mm).

Results

A reference MRI from a control group in a separate study was selected, having a representative brain shape and ventricle size, for use as a reference space for the comparison. Each subjects longitudinal volume change image, evaluated from the Jacobian of the non-rigid transformation, was normalised by the time interval between the subjects scans (in Years). Figure 1 shows the significant areas of point-wise volume loss (Z score>1.9) in the AD subjects relative to controls, displayed as Z=1.9 contours on the average Alzheimers MRI image volume. Areas in the head of the left (right in the images) hippocampus and the entorhinal cortex are seen to lose tissue significantly with respect to the control group. Other areas of significantly different tissue loss include white matter regions around the ventricles and points within the temporal lobes.



Discussion

Our major accomplishment has been to develop a fully automated approach to the whole brain analyses of groups of longitudinal data, making use of robust, high dimensional spatial registration algorithms. The regions of longitudinal change in the hippocampal and entorhinal cortex regions identified by this method are very similar to those previously reported by other groups using manual methods. In addition, we found significant volume loss in the same anatomical regions using manual and semi-automated techniques in these same subjects (Abstract by Cardenas-Nicolson et al in these Proceedings). We expect that this approach can be improved using an even finer B-spline lattice, and a more sophisticated statistical analysis. In conclusion, the development of a completely automated non-linear registration method which detects longitudinal atrophy should be of considerable value in diagnosis, prognosis, and quantifying the effects of treatment of AD and other dementias.

References

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