Comparing Automatic Deformation-Based Techniques Against Manual Volumetry in a Mouse Model of Alzheimer's Disease: A Longitudinal *In Vivo* Study

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Background:
Magnetic Resonance Imaging (MRI) of transgenic mice can provide valuable insight into the complex mechanisms underlying Alzheimer's disease (AD). Quantification of underlying pathological changes is often performed using manual segmentation [1,2]. These methods are prone to intra- and inter-rater variability as well as single-painter bias, and are extremely labour-intensive. Nevertheless, they provide a quantitative measure of volumetric differences, which if segmented properly, lend themselves to group-wise and longitudinal comparisons. Deformation-based morphometry (DBM) has previously been proposed as a means of detecting anatomical differences between populations [3], and has since been applied to detect group-wise phenotypic differences in mice [4], as well as in a four-dimensional (4D) study of atrophy [5]. In addition, a framework for statistical analysis has been devised [6].

Objectives:
We hypothesize that automated DBM analysis can reproduce known patterns of 4D AD progression in the mouse model, as well as elucidate other morphometrically affected brain regions for which changes have not yet been well-characterized.

Materials and Methods:
Five wild-type (WT) and five AD mice were scanned *in vivo* at 2.5, 4.5, 6.5 and 9 months of age on a 9.4 T magnet (Bruker Biospec Avance 94/30) at 156 µm isotropic resolution. A model-independent average for each group was created across timepoints [7]. The combined average was back-transformed into the space of each subject scan. The scaled Jacobian (a measure of local volumetric expansion or contraction) was calculated from the deformation fields and significant differences were localized using regression analysis. Results were compared against manual tracings of the ventricles, hippocampus, and previously reported findings.

Results:
Using automated DBM analysis, significant local volumetric growth was found over time in the lateral and third ventricles in the AD group but not in the WT group (Figure 1). Longitudinal hippocampal growth was noted in both AD and WT groups at different rates. Group-wise differences have also been found across timepoints in a region of the cingulate and motor cortex (Figure 2).

Discussion:
Dynamic morphometric changes localized using automated methods support findings using manual volumetry in the hippocampus and ventricles of this AD mouse model [1,2]. The discoveries using automated pipeline analysis can serve as longitudinal *in vivo* biomarkers for preclinical therapies. Moreover, DBM analysis may help to elucidate morphometric differences that have not been as well studied, such as the suggested structural phenotypic differences between groups in the cingulate and motor areas.

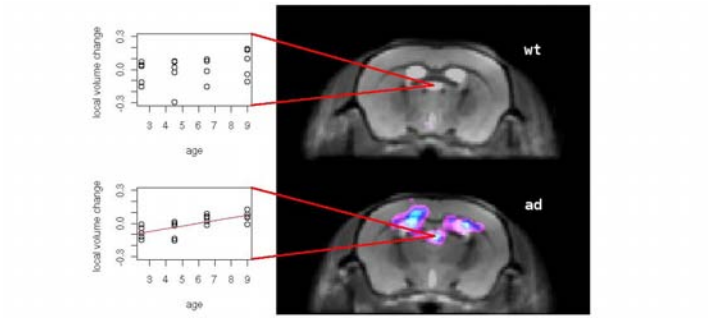

Figure 1. No significant volumetric change was found in the WT population (top). In contrast, significant volumetric expansion was found in the ventricles over time in the AD population (bottom). The t-value was thresholded to be greater than 3.5.

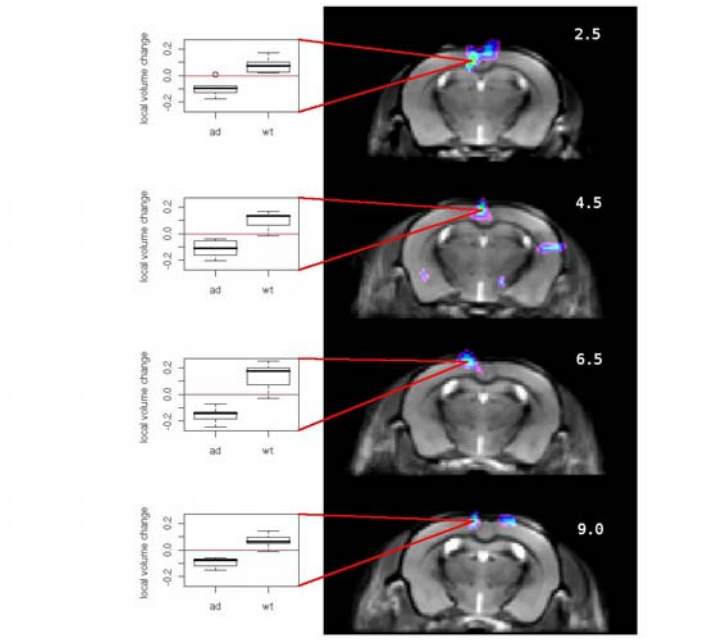

Figure 2. Group-wise differences in cingulate and motor cortex for 2.5, 4.5, 6.5 and 9 months from top to bottom. The t-value was thresholded to be greater than 3.5. Manual tracing of the cortex yielded a percent decrease in AD cortical volume at 2.5 months and 9 months to 91% and 93% of WT respectively.

References:

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