Comparison of Brain Metabolism and Atrophy in Prodromal Alzheimer's Disease

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INTRODUCTION: Understanding the relationship between atrophy and reduced metabolism may help elucidate the mechanisms underlying Alzheimer's Disease (AD) progression and may help to identify sensitive biomarkers for early detection and monitoring. Using a large subset of the baseline data from the AD Neuroimaging Initiative (ADNI) cohort, we applied high-throughput analysis methods that provide quantitative estimates of PET activity within subject-specific anatomical ROIs derived from each individual subject's MRI enabling us to directly compare metabolic and structural changes in subject-specific ROIs. Here, we have evaluated these changes in mild AD, mild cognitive impairment (MCI), and single-domain, amnestic MCI (SMCI).

METHODS: PET and MRI data were obtained for 304 subjects from the ADNI: 80 normal controls, 68 with AD, 156 with MCI and 69 of whom met criteria for SMCI. ROIs were derived from co-registered MRI images using high-throughput, subject-specific, FreeSurfer-based procedures. These procedures produce continuous surface maps of cortical thickness and activity as well as quantification of structural and activity measures within specific, pre-defined ROIs. We evaluated metabolic and structural differences between groups for 45 predefined ROIs. In all analyses, PET activity was normalized to the brainstem. Analysis of covariance (ANCOVA) was performed to examine group differences while controlling for age and gender. Estimated intracranial volume was included as a covariate for structural volume measures to control for individual differences in head size. Cohen's *d* effect sizes were computed to determine regions showing significant metabolic differences between diagnostic groups, and then differences in cortical thickness were evaluated in these same regions. To determine the significance of regional differences between atrophy and hypometabolism, paired t-tests were performed on the mean MRI and PET Z-scores for each region. Z-scores were computed after regressing out the effects of age and gender. For PET measures, morphometric effects were also regressed out to avoid confounding the effects of atrophy with metabolism. Z-scores were calculated as: (patient individual value-control mean)/control standard deviation.

RESULTS: Evaluation of the AD-NC continuous surface maps demonstrates overlapping metabolic and structural changes with greater structural changes in mesial temporal areas, while in association and cingulate cortices, metabolic changes were greater (Figure 1). The MCI-NC comparisons were generally similar: The mesial temporal ROIs such as the entorhinal cortex, parahippocampal cortex and hippocampus have greater structural changes (1.4, 1.5 and 2.6 fold, respectively), while association ROIs such as the inferior parietal and precuneus cortices exhibit greater metabolic reductions (2 and 1.4 fold, respectively) (Figure 1 and ANCOVA analyses, not shown). While significant metabolic reductions were seen in the posterior cingulate cortex (-4.4 %, $p<.001$, Cohen's *d* 0.5), the thickness changes were not statistically significant. The ROI exhibiting the overall greatest effect size is the hippocampal structural measure (-8.5%, $p<.001$, Cohen's *d* 1.9) while the greatest effect size in activity measures was the entorhinal cortex (-6.1%, $p<.001$, Cohen's *d* 0.7). Similar to the MCI-NC comparisons, SMCI-NC comparisons showed that mesial temporal ROIs exhibited structural reductions that were greater than metabolic changes (1.4-2.4 fold). The hippocampal structural measure again exhibited the greatest effect size (-9.5%, $p<.001$, Cohen's *d* 0.9) while the greatest effect size in activity measures was the entorhinal cortex (-4.2%, $p<.001$, Cohen's *d* 0.5). Similar to the MCI-NC comparisons, there was no significant thickness reduction in the posterior cingulate cortex, whereas significant activity reduction was noted (-3.3%, $p<.04$, Cohen's *d* 0.4). Paired t-tests performed on the mean MRI and PET Z-scores showed that the differences between atrophy and metabolism were significant (p's$<.01$) for the posterior cingulate cortex in both MCI-NC and SMCI-NC comparisons.

Figure 2 shows plots of the adjusted means from omnibus 3-group ANCOVAs controlling for the effects of age and gender for ROIs. These plots show that changes in mesial temporal ROIs across groups is qualitatively similar with significant reductions in activity and thickness occurring between NC and SMCI groups. In contrast, in some association and cingulate ROIs, no reductions are observed in SMCI, except for the posterior cingulate cortex where metabolic reductions are observed, without concomitant structural changes at the earliest stages of the disease.

CONCLUSIONS: While previous studies have focused on mild AD and multi-domain MCI, this report is one of the first to directly compare atrophy and metabolism in single domain, amnestic MCI. Our data support a model in which initial structural changes in mesial temporal regions lead to metabolic reductions and modest atrophy in downstream association cortices with disease progression. These results suggest that structural changes in mesial temporal ROIs such as the hippocampus and metabolic reductions in the posterior cingulate cortex may be effective biomarkers for the detection of prodromal AD.

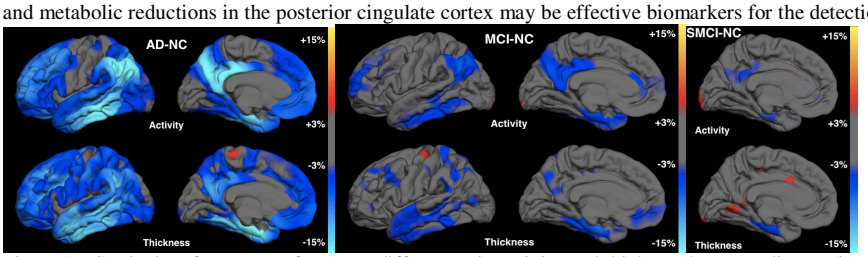

Figure 1: Cortical surface maps of average differences in activity and thickness between diagnostic groups.

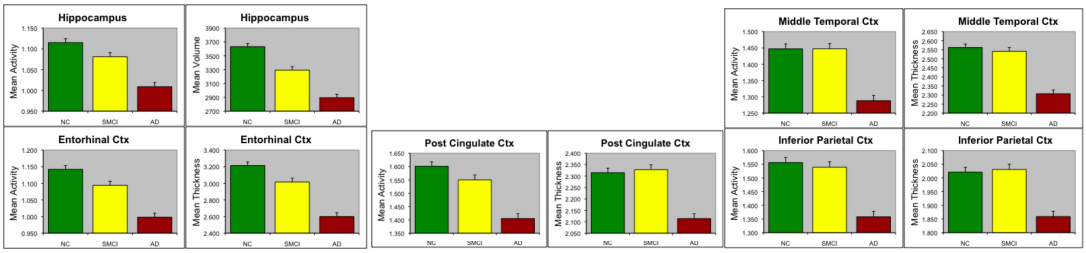

Figure 2: ROI means for activity and thickness or volume: Error bars: +/- 1 SE. Y-axis scaled to data.