

Distinct longitudinal cortical change in frontotemporal lobar degeneration and Alzheimer's disease

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Introduction: Disease-modifying drugs for neurodegenerative conditions are emerging, with the potential to offset up to billions of dollars in healthcare costs [1]. It has proven difficult to use traditional endpoints in dementia-focused treatment trials because the manifestations of neurodegenerative conditions such as frontotemporal lobar degeneration (FTLD) can be so varied clinically. Longitudinal neuroimaging may be an ideal alternative endpoint for treatment trials because it is quantitative, widely available and relatively cost-effective [2]. Currently, much work has focused on the hippocampus as an imaging-based biomarker [3]. However, there may be distinct advantages to tracking cortical neurodegeneration because neurodegenerative disorders affect different parts of the cortex at different disease stages. Thus, a method that tracks and quantifies cortical atrophy over time can be relevant across the course of a disorder and may also improve the accuracy of disease staging. While some effort at staging Alzheimer's disease (AD) has succeeded [1], longitudinal studies of FTLD are much less common than in AD [4], far less is known about disease staging and the effectiveness of in vivo biomarkers for tracking disease progress in FTLD is poorly understood. In this work, we quantitatively and regionally characterize longitudinal cortical atrophy rates with T1 MRI and illustrate that this focal method improves power for tracking disease in biomarker-confirmed FTLD and AD.

Methods: We employ a novel machine learning-based neuroimaging framework to quantify cortical atrophy rate and identify anatomically distinct longitudinal atrophy patterns in AD (n=35) and FTLD (n=46) that differ from controls (n=22). The cohort is matched for disease duration, age, gender and educational level. Our novel framework is open-source, unbiased [4] and formulated spatiotemporally. This voxel-based framework is designed to accommodate standard confounds of longitudinal data which include intensity inhomogeneity and random noise that occurs over different scanning sessions. Our new system is unbiased, allows accurate quantification, and supports group contrasts it provides an optimal, longitudinally specialized alternative to voxel-based gray matter (GM) morphometry. We apply this framework in a cohort that is diagnosed by autopsy-confirmed cerebrospinal fluid (CSF) values of tau:A β 1-42 ratio. This biofluid biomarker gives high specificity and sensitivity for FTLD and AD [5]. Previous work has suggested that there may be differences in atrophy rate depending on age, and our approach supports regression modeling that can assess the role of age experimentally. Relatedly, disease duration at the time of imaging may have an impact on the rate of longitudinal decline, and our study also assesses this. Because of the potential role that cognitive reserve may have on atrophy, we also assess the role of education on rate of atrophy. Finally, we use power analysis to statistically identify advantages over whole brain measures for tracking FTLD and AD and which translate directly to cost savings in treatment trials.

Results: We extract cortical regions for hypothesis-testing with a statistically powerful automatic cortical parcellation technique based on machine learning. Our unbiased analysis reveals that patients with likely FTD pathology exhibit significant focal atrophy within the inferior orbital frontal and anterior insula cortex (annualized atrophy rate=1.85%). Annualized atrophy rates in these regions in the control group are <0.5%. In contrast, patients with likely AD pathology have a significantly greater atrophy rate in the posterior cingulate/precuneus (annualized atrophy rate=2.0%) and right posterior temporal-occipital cortex (annualized atrophy rate=2.96%). Regression modeling was used to assess the impact of age, disease duration and education on atrophy rates and this impact is quantified as well. Increases in number of years of education, duration or age decrease atrophy rate in both AD and FTLD with age leading to the least amount of reduction. Finally, in FTLD, our method requires only 56% of the subjects needed by whole brain analyses to detect change in atrophy rate at effect size of 0.8 with alpha=0.95. In AD, the reduction in required subjects is 25%.

Conclusion: We conclude that significant rates of anatomically distinct annualized atrophy can be defined with an unbiased analysis in biomarker-defined neurodegenerative disorders, and that this will significantly benefit designs of treatment trials in these conditions.

References: [1]Jack, et al, Lancet Neurology, Jan 2010. [2]Lorenzi, et al, Neurobiol. Aging Aug 2010. [3] Yushkevich, et al, Neuroimage Apr 2010. [4]Rademakers, et al, Lancet Neurology, Oct 2007. [5] Grossman et al, Ann. Neurol, May 2005.