Simon Fristed Eskildsen - selected publications

1 Eskildsen, S. F., Coupe, P., Fonov, V. S., Pruessner, J. C., & Collins, D. L. (2014). Structural imaging biomarkers of Alzheimer's disease: predicting disease progression. *Neurobiology of Aging*.
Notes: Optimized magnetic resonance imaging (MRI)-based biomarkers of Alzheimer's disease (AD) may allow earlier detection and refined prediction of the disease. In addition, they could serve as valuable tools when designing therapeutic studies of individuals at risk of AD. In this study, we combine (1) a novel method for grading medial temporal lobe structures with (2) robust cortical thickness measurements to predict AD among subjects with mild cognitive impairment (MCI) from a single T1-weighted MRI scan. Using AD and cognitively normal individuals, we generate a set of features potentially discriminating between MCI subjects who convert to AD and those who remain stable over a period of 3 years. Using mutual information-based feature selection, we identify 5 key features optimizing the classification of MCI converters. These features are the left and right hippocampi gradings and cortical thicknesses of the left precuneus, left superior temporal sulcus, and right anterior part of the parahippocampal gyrus. We show that these features are highly stable in cross-validation and enable a prediction accuracy of 72% using a simple linear discriminant classifier, the highest prediction accuracy obtained on the baseline Alzheimer's Disease Neuroimaging Initiative first phase cohort to date. The proposed structural features are consistent with Braak stages and previously reported atrophic patterns in AD and are easy to transfer to new cohorts and to clinical practice

2 Eskildsen, S. F., Coupe, P., Garcia-Lorenzo, D., Fonov, V., Pruessner, J. C., & Collins, D. L. (2013). Prediction of Alzheimer's disease in subjects with mild cognitive impairment from the ADNI cohort using patterns of cortical thinning. *NeuroImage, 65,* 511-521.
Notes: Predicting Alzheimer's disease (AD) in individuals with some symptoms of cognitive decline may have great influence on treatment choice and disease progression. Structural magnetic resonance imaging (MRI) has the potential of revealing early signs of neurodegeneration in the human brain and may thus aid in predicting and diagnosing AD. Surface-based cortical thickness measurements from T1-weighted MRI have demonstrated high sensitivity to cortical gray matter changes. In this study we investigated the possibility for using patterns of cortical thickness measurements for predicting AD in subjects with mild cognitive impairment (MCI). We used a novel technique for identifying cortical regions potentially discriminative for separating individuals with MCI who progress to probable AD, from individuals with MCI who do not progress to probable AD. Specific patterns of atrophy were identified at four time periods before diagnosis of probable AD and features were selected as regions of interest within these patterns. The selected regions were used for cortical thickness measurements and applied in a classifier for testing the ability to predict AD at the four stages. In the validation, the test subjects were excluded from the feature selection to obtain unbiased results. The accuracy of the prediction improved as the time to conversion from MCI to AD decreased, from 70% at 3 years before the clinical criteria for AD was met, to 76% at 6 months before AD. By inclusion of test subjects in the feature selection process, the prediction accuracies were artificially inflated to a range of 73% to 81%. Two important results emerge from this study. First, prediction accuracies of conversion from MCI to AD can be improved by learning the atrophy patterns that are specific to the different stages of disease progression. This has the potential to guide the further development of imaging biomarkers in AD. Second, the results show that one needs to be careful when designing training, testing and validation schemes to ensure that datasets used to build the predictive models are not used in testing and validation
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3 Eskildsen, S. F., Ostergaard, L. R., Rodell, A. B., Ostergaard, L., Nielsen, J. E., Isaacs, A. M. et al. (2009). Cortical volumes and atrophy rates in FTD-3 CHMP2B mutation carriers and related non-carriers. *NeuroImage, 45,* 713-721.

Notes: Frontotemporal dementia constitutes the third most prevalent neurodegenerative disease with dementia. We compared cortical structural changes in nine presymptomatic CHMP2B frontotemporal dementia mutation positive individuals with seven mutation negative family members. Using serial MRI scans with a mean interval of 16 months and surface based cortical segmentation we measured cortical thickness and volume, and quantified atrophy rates. Cortical thickness and atrophy rates were averaged within major lobes and focal effects were determined by parametric statistical maps. The volumetric atrophy rates in the presymptomatic CHMP2B mutation carriers were statistically significant, though of a lower magnitude than those previously reported in patients of other types of frontotemporal dementia. Cortical thickness measurements revealed cortical thinning in mutation carriers bilaterally in the frontal and occipital lobes, and in the left temporal lobe. Results indicated that cortical thickness has a higher sensitivity for detecting small changes than whole-brain volumetric measures. Comparing mutation carriers with non-carriers revealed increased atrophy rates in mutation carriers bilaterally in the inferio-temporal cortex, the superior frontal cortex, and the insular cortex. These findings indicated impairment of regions involved in both behaviour and language. The symptoms previously reported in clinical CHMP2B frontotemporal dementia patients are associated with the anatomically affected regions here found in the presymptomatic mutation carriers