Joint Contribution of Structural and Perfusion MR Images for the Classification of Alzheimer's Disease

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Introduction: It is generally assumed that structural MRI of brain tissue loss and physiological imaging of regional cerebral blood flow (CBF) provide complimentary information for the characterization of brain diseases, such as Alzheimer's disease (AD). Yet thorough investigations into gains in predictive power for AD using structural and CBF imaging jointly has been limited. Our aim in this study was to determine the joint contribution of structural and CBF imaging for the classification of AD in a cross-sectional study using an integrated multimodality MRI processing framework and a cortical surface-based analysis approach.

Methods: Studied data set was comprised of 38 healthy elderly (65.70 ± 8.25 years old, with 29.44 ± 0.86 MMSE) and 24 Alzheimer's disease patients, (66.29 ± 9.99 years old, with 21.76 ± 5.80 MMSE). Subjects were recruited from the Memory and Aging Center of the University of California, San Francisco. All subjects were diagnosed based upon information obtained from an extensive clinical history and physical examination. All scans were performed on a 4 Tesla (Bruker /Siemens) MRI system with a birdcage transmit and 8 channel receive coil. Structural MRI included T1-weighted images using a 3D volumetric magnetization prepared rapid gradient echo (MPRAGE) sequence, TR/TE/TI = 2300/3/950 ms, timing; 7° flip angle; isotropic 1.0 mm^3 resolution. T2-weighted images were acquired with variable flip (VFL) angle turbo spin-echo sequence with TR/TE = 4000/30 ms and with the same resolution matrix and field of view of MPRAGE. CBF images were acquired using a continuous arterial spin labeling (cASL-MRI) sequence with single-shot echo-planar imaging (EPI), yielding five 5 mm thick slices with 24% gaps, with an in-plane resolution of 3.75×3.75 mm^2, oriented 10° up from the anterior-posterior commissural line and covered the volume above this line. The other acquisition parameters were as follows: TR/TE = 5,200/9 ms and 1,590 ms post labeling delay. The key integrated multimodality image processing steps are as follows: (1) Expectation maximization segmentation was performed on each brain image volume to estimate the volume fractions of cerebral white matter (WM), gray matter (GM), and sulcal cerebrospinal fluid (CSF). Each individual's cortical surface was extracted using a cortical reconstruction method using implicit surface evolution technique [1]. (2) Cortical thickness at each point in the cortical GM tissue mantle was defined as the sum of the distances from this point to the GM/WM and GM/CSF tissue boundaries following Laplace's equation's flow field, which guarantees a one-to-one, symmetric, and continuous correspondence between the two tissue boundaries [2]. Voxel-based estimated cortical thickness values were mapped onto the corresponding central cortical surface using trilinear interpolation at each mesh vertex. (3) Processing of the cASL images involved a sequence of processing steps including normalization by the arterial water density, differential intensity scaling, affine alignment followed by the fluid-flow warping [3] based nonlinear geometry distortion correction to establish anatomical correspondence between structural T2 and perfusion images, and partial volume correction was applied to estimate CBF. (4) Cortical surface mapping of CBF was computed by integrating the volumetric CBF values over the curvilinear Laplace's equation's flow field computed for thickness computation. (5) To account for inter- and intra-subject variability associated with various sources of physiological and non-physiological noise, each subject's CBF was proportionally scaled to the subject's sensorimotor CBF. (6) Finally, an image analysis technique known as surface-based cortical spatial normalization was used to match anatomically homologous cortical features across subjects before performing cross-subject comparisons [4]. Logistic regression analysis was used to determine sequentially the predictive value of (I) CBF, (II) cortical thickness, and (III) CBF and cortical thickness jointly for AD. In all logistic regressions, sex and age were included as covariates. Differences in predictive values were compared using non-parametric permutation tests augmented by adjustments for multiple comparison at p=0.01 using the concept of false discovery rate. All statistical computations were carried out using the statistical package R.

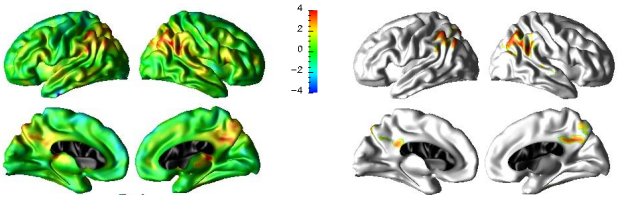

Fig.I: Logistic regression analysis to determine whether CBF is predictive of having AD (left: coefficient; right: significance)

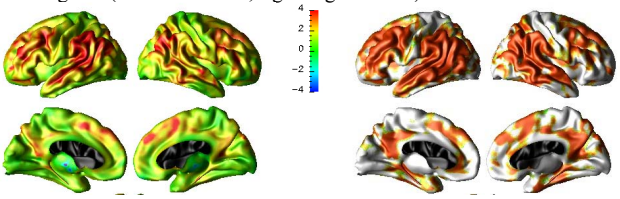

Fig.II: Logistic regression analysis to determine whether cortical thickness is predictive of having AD (left: coefficient; right: significance).

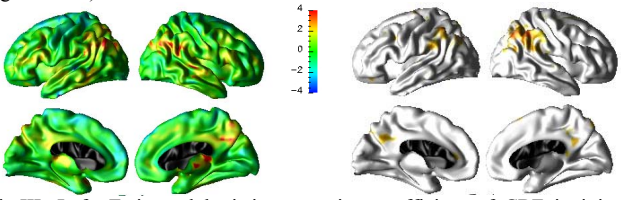

Fig.III: Left: Estimated logistic regression coefficient of CBF in joint analysis of CBF and cortical atrophy; Right: Testing for the indirect effect of CBF on AD diagnosis through cortical atrophy to measure significant reduction in predictive power of CBF.

Results: Findings from each logistic regression is as follows: (I) Using cASL-MRI alone, CBF reduction in bilateral inferior parietal lobules, right precuneus, bilateral posterior cingulate cortices had the highest predictive value for AD. AD diagnosis was also associated with hypoperfusion in the medial temporal cortex bilaterally (Fig.I). (II) Using structural MRI alone, cortical atrophy in the temporo-parietal, posterior cingulated, superior frontal, hippocampal gyrus, and middle frontal cortices bilaterally had the best predictive values for AD (Fig.II). (III) Using cortical atrophy and CBF jointly showed that CBF made no longer a significant contribution to the prediction for AD compared to the prediction of cortical atrophy throughout the brain in brain regions where significant predictive power of CBF was observed in unimodal analysis (Figs. I and III). This statistically significant reduction on effects of hypoperfusion on diagnosis of AD versus controls after accounting for cortical atrophy was quantified using z-score based Sobel's significance test (Fig. III). No significant change in predictive power of cortical thickness was observed in joint analysis model.

Discussion: From the joint analysis of CBF and cortical atrophy measures, we infer that cortical atrophy dominates the prediction of AD while CBF adds no significant value. One interpretation of the results is that CBF is diminished proportionately to brain tissue loss and therefore provides no additional information to structural alterations. However, in early stages of AD as well as in MCI, results may differ as the relationship between CBF and tissue loss changes (for example elevated CBF in presence of atrophy has been reported in MCI [5]). Further studies on early stage AD and MCI patients are required to further elucidate these findings. From computation medicine perspective, we described a novel integrated multimodality image processing framework coupled with surface based cortical analysis.

Reference:

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