The Prospectively Validated RfMRI Biomarkers for Mild Cognitive Impairment

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Introduction: Resting-state functional magnetic resonance imaging (RfMRI) has been employed to produce imaging biomarkers (1, 2) for mild cognitive impairment (MCI). However, like most pioneer work, these studies only used small sample sizes, so the statistical power is limited. Using larger sample sizes will help reducing individual effects on the imaging biomarkers and will allow us to develop reliable and applicable biomarkers for MCI. In the current study, the RfMRI data were collected through an international collaboration effort across 17 imaging sites. The goal is to answer the crucial question: whether the imaging biomarkers developed for MCI can be applied to the prospective population. This question must be rigorously answered first, before the imaging biomarkers can be applied to assist physicians in disease assessment, prediction of disease progression and monitoring the efficacy of disease modifying therapies.

Methods: One hundred and seven MCI and 110 cognitively normal (CN) subjects' RfMRI data were included in the study as the training set. Another set of RfMRI data from 107 MCI and 110 CN disjoint subjects were included in the study as the prospective validation set. As a result, a total of 434 individual subjects' RfMRI data were collected through an international collaboration effort across 17 imaging sites.

RfMRI biomarkers: The seed-based analysis was employed in this study. Ninety seed regions of interest (ROI) (3) were chosen. The regions that had decreased or increased functional connectivity to the seed ROIs in MCI were identified. Specifically, using the training cohort, seed functional connectivity was calculated from the preprocessed RfMRI time courses (2, 4) using Pearson product-moment correlation coefficient (r) followed by Fisher transformation: $m=0.5\ln[(1+r)/(1-r)]$. The decreased and increased functional connectivity patterns were found using one-tailed two sample t-test, family-wise error corrected using AlphaSim. The results were 90 decreased functional connectivity (hypo FC) patterns and 90 increased functional connectivity (hyper FC) patterns. These patterns, as the RfMRI biomarkers, were validated using the prospective validation data set.

RfMRI biomarker validation: The individual subject's functional connectivity indices were calculated using the validation cohort. The regional hypo FC index was obtained from the seed RfMRI time course (preprocessed RfMRI time courses averaged over the voxels within the seed ROI) and the corresponding hypo FC pattern RfMRI time course (preprocessed RfMRI time courses averaged over the voxels within the hypo FC pattern) using Pearson product-moment correlation coefficient followed by Fisher transformation. Then the regional hypo FC indices were averaged to produce a single hypo FC index for each subject. Similarly, a single hyper FC index was produced for each subject as well. The hypo and hyper FC indices of the validation MCI and CN subjects were then compared using one-tailed two-sample t-test.

Results:

Figs. 1 and 2 show the hypo and hyper FC patterns of a representative ROI (Left Hippocampus). Figs. 3 and 4 show the individual hypo and hyper FC indices of the validation MCI and CN subjects. The RfMRI biomarkers were validated on the prospective data set ($p<0.004$ for the hypo FC biomarker and $p<0.0006$ for the hyper FC biomarker).

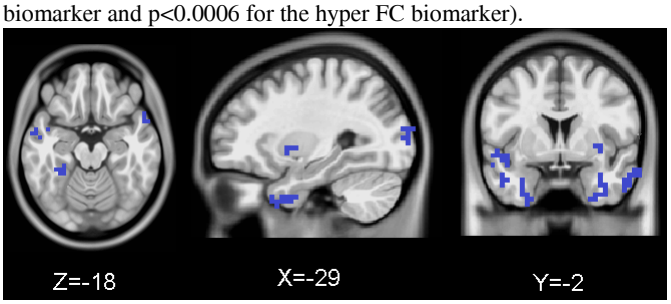

Fig1. Hypo FC pattern of a representative ROI (Left Hippocampus)

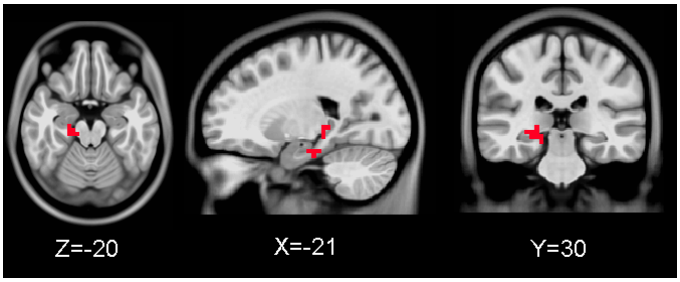

Fig 2. Hyper pattern of a representative ROI (Left Hippocampus)

Discussion:

In this study, we show that RfMRI biomarkers developed for MCI can be reliably applied to the prospective population when a large sample size is employed. Further study may be needed to indentify the optimum sample size, imaging parameters and/or methodologies required to produce the most reliable RfMRI biomarkers.

References:

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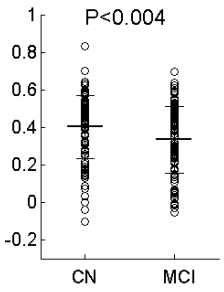

Fig 3. Individual hypo FC indices of the validation MCI and CN subjects. The mean and standard deviation of each group are also shown.

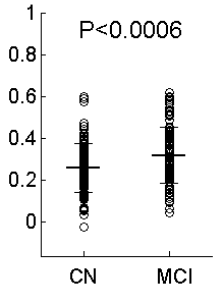

Fig 4. Individual hyper FC indices of the validation MCI and CN subjects. The mean and standard deviation of each group are also shown.

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