Reliability of Detecting Functional Connectivity Changes in Alzheimer's Disease

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Introduction: Resting-state functional magnetic resonance imaging (RfMRI) has been employed to investigate brain functional changes in a variety of neurological and psychiatric disorders. Understanding the reliability of this technique is essential to its successful application. Numerous studies have focused on the test-retest reliability (i.e., reliability in repeated measurements using the **same cohort**). However, studies focusing on the **between-cohort** reliability are rare. Between-cohort reliability answers the important question of whether the biomarker developed using a limited number of subjects can be applied to the general population. This study will demonstrate the key factors that affect the reliability of detecting functional connectivity changes in studying brain disorders.

Methods: RfMRI data from 65 Alzheimer's disease (AD) and 136 cognitively normal (CN) subjects were included in the study. Data for this work were from the Medical College of Wisconsin (MCW) fMRI Data Bank and the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu).

Experiment 1. Seed-based analysis was employed in this study. Six seed ROIs (left and right hippocampus, posterior cingulate cortex (PCC) and Insula) were chosen, based on prior knowledge in the literature (1–3). The subjects were randomly assigned to a test and validation cohort. The test cohort was employed to define the RfMRI biomarker. The validation cohort was used to validate the biomarker (i.e., functional connectivity index, FCI). When the FCIs were significantly different between the validation AD and CN cohorts, the biomarker is considered reliable and vice versa. The above steps were repeated 100 times. We defined the **RfMRI reliabilities** as the rate of validating the RfMRI biomarker (calculated by dividing the number of reliable outcomes by the number of repetitions). Fig. 1 shows the detailed procedure. This procedure was performed 10 times to obtain the mean and standard deviation of the reliability. To study the effect of the sample size on the reliability, different numbers of subjects in each (test, validation) cohort, ranging from eight to 100, were employed.

Experiment 2. To compare the effects of between-subject variation and between-scan variation, the resting-state data of the testing cohort (used in Experiment 1) were divided to two parts (first and second half of the scans). In Experiment 2, the first half of resting state data was used as the testing data and the second half of the data was used as the validation data. The reliability was then obtained the same way, as described in Experiment 1.

Experiment 3. To characterize the random effect (i.e., false-positive reliability), pseudo groups were created. The pseudo group (pseudo test AD group, for example) contained CN and AD subjects. The "reliability" was then calculated using the pseudo groups.

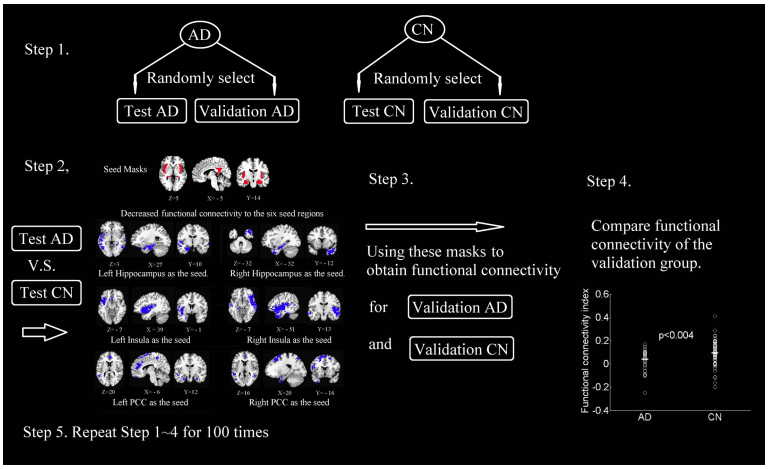

Fig 1. Method flowchart. Procedure used to estimate RfMRI biomarker reliability.

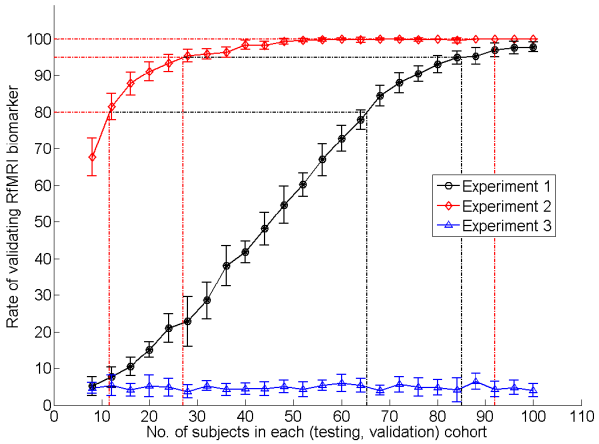

Fig 2. Factors that affect RfMRI biomarker reliability.

Results: RfMRI reliabilities obtained in the three experiments are shown in Fig. 2. The black, red and blue lines correspond to the results from Experiments 1, 2 and 3. In Experiments 1 and 2, the reliability improves with the increasing number of subjects. While the reliability in Experiment 3, it remains near 5%. Also, the reliability of Experiment 2 is significantly higher than that of Experiment 1.

Discussion: We demonstrated that the sample sizes strongly affect the RfMRI reliabilities. When studying brain disorders using RfMRI, the reliabilities improve with the sample size. To obtain a reliable RfMRI biomarker for AD that is applicable to the general population, a large sample size is needed.

Using a small sample size (i.e., 12 subjects in Experiment 1), the reliability of the biomarker is still significantly higher than that obtained by chance (5%). This suggests that a small cohort may be used to explore the feasibility of using RfMRI to study brain disorders. However, the specific biomarkers found in such studies may not be reliable (reliability <10%) when applied to the general population.

Between-subject variation has a much stronger effect on the RfMRI reliabilities compared to the between-scan variation, especially in terms of small sample sizes. Therefore, the sample size requirement should be determined by the type of the studies. For example, the longitudinal studies (to monitor the disease progression or treatment effect of same cohort) may require far fewer subjects than cross-sectional studies (those that require cross-validation).

References: 1. Li SJ, et al., 2002 Radiology, 225:253-9; 2. Greicius MD, et al., 2004. PNAS, 101:4637-42; 3. Xie C, et al., 2012. Neuroimage, 63:320-7; **Acknowledgements:** This work was supported by National Institutes of Health grants: NIH R01 AG20279, NIH R01 DA 10214, NIH-NCRR CTSA program grant 1UL1RR031973. The authors thank Carrie M. O'Connor, M.A., for editorial assistance, Judi Zaferos-Pylant, B.S.M., and Yu Liu, M.S., for MRI technical support.