# An integrated resting-state fMRI and DTI based connectivity analysis to understand brain alteration affected by Alzheimer's disease and amnestic mild cognitive impairment

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## Introduction

Integrating multi-modal neuroimaging analyses can provide a more comprehensive understanding of the neuronal connectivity in the brain, e.g. [1]. Resting-state fMRI (rs-fMRI) based correlation analysis [2] gives a measure of functional connectivity between different cortical regions of the brain and diffusion tensor imaging (DTI) based fiber tracking [3] can explore the white matter structural connectivity. In this work, we performed a quantitative analysis of combined functional-structural connectivity and studied the changes in certain cortical regions of the brain affected by Alzheimer's disease (AD) and amnestic mild cognitive impairment (aMCI) compared with an age and education matched healthy normal control (NC) group.

## Methods

Thirty-three subjects (10 AD, 11 aMCI and 12 NC, mean age 75 years) participated in this study. The MRI experiments were conducted on a GE 3T Signa® HDx MRI scanner (GE Healthcare, Waukesha, WI) with an 8-channel head coil. Protocol for rs-fMRI: brain echo-planar imaging (EPI), 7 min scan time, 38 contiguous 3-mm axial slices, 164 volumes of slices, TE/TR= 27.7/2500 ms, flip angle = 80°, FOV = 22 cm, matrix size = 64 × 64, ramp sampling and with the first four data points discarded. Subjects were asked to relax and keep his/her eyes open in a dim-light condition. Protocol for DTI: dual spin-echo EPI, 12 min 6 sec scan time, 48 contiguous 2.4-mm axial slices, FOV = 22 cm, matrix size = 128 × 128, NEX = 2, TE/TR = 77.5 ms / 13.7 s, 25 diffusion directions, b = 1000 s/mm$^2$, parallel imaging acceleration factor = 2. $T_1$-weighted images were acquired using a volumetric inversion recovery fast spoiled gradient-recalled sequence (10 minutes scan time) with cerebrospinal fluid (CSF) suppressed.

The rs-fMRI time courses were processed using AFNI [4] in the following steps: slice timing correction, volume co-registration, spatial blurring (FWHM = 4 mm), removal of nuisance parameters such as motion-introduced artifacts, baseline, linear and quadratic system-induced signal trends, the global mean signal time courses in the brain, CSF and white matter, and band pass filtered in the 0.009 – 0.08 Hz range. The DTI data were processed using FSL [5] as follows: eddy current and motion correction, Bayesian estimate of diffusion parameters (BEDPOSTX in FSL) and probabilistic tracking using PROBTRACKX in FSL. $T_1$ volumes were anatomically parcellated using FreeSurfer [6] and two pairs of regions of interest (ROIs) for both gray and white matter regions were selected. In our example evaluation, we selected the pair of right isthmus of cingulate cortex (rICC) and right anterior cingulate cortex (rACC) where the connectivity is known to be affected by AD/aMCI and the pair of left and right lateral occipital cortices (lLOC and rLOC) as the control regions. For each pair of ROI (i.e. seed-target pair) of each subject, a mean correlation coefficient of the time courses (representing functional connectivity) and a mean of fiber tracking based connection probability (representing structural connectivity) were calculated. Finally, the connectivity values for each subject were shown on 2D scatter plots.

## Results and discussion

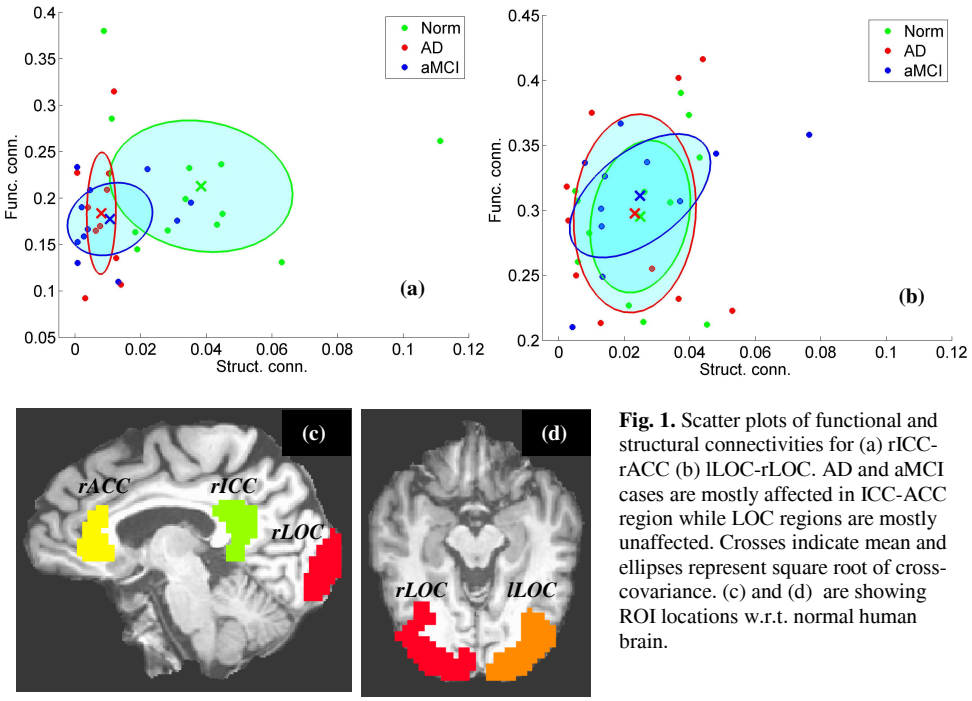


**Fig. 1.** Scatter plots of functional and structural connectivities for (a) rICC-rACC (b) lLOC-rLOC. AD and aMCI cases are mostly affected in ICC-ACC region while LOC regions are mostly unaffected. Crosses indicate mean and ellipses represent square root of cross-covariance. (c) and (d) are showing ROI locations w.r.t. normal human brain.

Fig. 1 shows the 2D scatter plots of subject-wise functional-structural connectivity metrics. It is clearly visible in the figure that rICC-rACC pair shows visible difference in the distribution of the connectivity metrics affected by AD and aMCI, which is also shown in previous studies [7]. The LOC regions remain mostly unaffected and thus do not show a visible difference in the connectivity metrics. The difference in functional connectivity is less than the structural connectivity for rICC-rACC which could be due to spatial averaging of the correlation coefficients. Analysis on more ROI pairs would further help reveal the reduction in the neuronal connectivity in the brain by AD.

The purpose of this 2D representation of connectivity metrics is to provide an integrated view of the overall neuronal connectivity between two brain regions in terms of mean and covariance. This 2D distribution can be further used to compute Bayesian posterior probability of integrated connectivity metric which combines both structural and functional connectivity. Functional connectivity is not affected by distance while DTI-based structural connectivity is affected. A distance correction can be included to address this issue. Also, ROIs should be selected to have known white matter connection otherwise structural connectivity values would be too low to be meaningful.

**References**:

[1] Douaud G, Filippini, N, *et. al. Brain* 2011; 134: 3470–3479, [2] Fox MD, Raichle ME. *Nat Rev Neurosci* 2007; 8:700–11, [3] Behrens TE, *et. al.*, *NeuroImage* 2007; 34: 144–55, [4] Cox RW. *Comput Biomed Res*. 1996; 29(3):162-73 [5] Jenkinson M, Beckmann CF, *NeuroImage,* 2012; 62:782-90, [6] Desikan RS, *et. al. Neuroimage* 2006; 31: 968–980 [7] Greicius MD, Srivastava G, Reiss AL, *et. al.*, *Proc Natl Acad Sci U S A* 2004;101:4637–42.