A Combined Functional-Structural Connectivity Analysis of Major Depression Using Joint Independent Components Analysis

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Introduction

Resting state functional connectivity (FC) and fractional anisotropy (FA) data are powerful measures for assessing neural networks in clinical populations. We integrated these data in a joint independent component analysis (jICA) [(1)] to better characterize connectivity of the subgenual cingulate cortex (sACC) in major depression [(2,3)].

Methods

A. Subject: Nine subjects with no history of psychiatry or neurological disorder and four subjects with major depressive disorder (MDD) participated in accordance with Institutional Review Board policy.

B. Image Acquisition: MRI data were acquired on a 3T Siemens Trio scanner (Siemens Medical Solutions, Malvern, PA) using a TX/RX birdcage head coil. T1 images were collected in 128 sagittal slices using an MPRAGE sequence with following parameters: TR/TE=2600/3ms; voxel resolution=1*1*1mm; number of slices=176; matrix=224*256. DTI data were collected using a diffusion weighted single-shot spin-echo planar imaging sequence with the following parameters: b=1000sec/mm2; voxel resolution=1.72*1.72*2.5mm; number of slices=34; matrix=128*128, 12 directions with 6 averages for each direction; TR/TE=6500/90ms. Resting state FMRI data were acquired using a Z-SAGA[(4)] sequence (to recover areas affected by susceptibility artifact) with following parameters: 210 measurements; voxel resolution=3.4*3.4*4mm; matrix=64*64, TR/TE=2000/35ms. Patients were instructed to keep their eyes open and to let their minds wander.

C. T1 image processing: White matter and grey matter masks were generated from T1 images through simultaneous segmentation and normalization to MNI space using SPM5.

D. Resting state fMRI data processing: Functional datasets underwent slice-timing correction, motion correction, coregistration to the respective T1, normalization to MNI space using the transformation generated in the T1 normalization process, and spatial smoothing with a 7mm FWHM Gaussian filter using the SPM5 toolbox in MATLAB. A seed was defined as a 6mm radius sphere located at the center of sACC. FC analysis was performed using AFNI software. The ROI was masked by a subject's grey matter mask to ensure that the seed was fully located in grey matter. The mean time course was extracted from the seed and used as a contrast of interest along with the global mean time course, and six motion correction time courses as confounders, in a general linear model analysis to derive FC maps.

E. Diffusion data processing: Diffusion data underwent brain extraction, eddy current correction, and local DTI fitting using FSL software. FA maps were normalized to MNI space using SPM5, B0 images were coregistered to T1 images and this transformation matrix was applied to the FA maps.

F. Joint ICA: jICA was implemented using the Ranking and Averaging Independent Component Analysis by Reproducibility (RAICAR) toolbox [(5)] in MATLAB. Both FC and FA maps were mean centered and scaled to unit variance using the z-score transformation and then reduced using grey and white matter masks respectively. Additionally the sign of FA values was flipped on alternate voxels in order to preserve positivity in the analysis. This process was reversed after ICA decomposition. FC and FA maps for each subject were then concatenated and simultaneously decomposed into statistically independent spatial patterns and a weighting matrix using ICA. This was performed 3000 times with randomly determined initial values and the spatial patterns were ranked based on their reproducibility across the iterations. Two sample t-tests were performed on the weighting matrix values for the top 5 spatial patterns to determine if any discriminated MDD from healthy controls. The resulting spatial patterns were converted to an absolute value (FC: positive, FA: Negative) for display on one image.

Results & Discussion

Results from jICA analysis of FC and FA data are presented in Figure 1. The weighting matrix scores for the component with the highest reproducibility score (from RAICAR) demonstrated a significant difference between controls and MDD (Figure 2; $p < 0.043$). Only one component had a significant difference between major depression and controls subjects. The FC differences incorporate regions previously identified in a seed PLS analysis of a similar population, and suggest altered strength of connectivity between sACC and perigenual ACC (Brodmann Area [BA] 24a), anterior midcingulate cortex (BA24b), caudate, thalamus, medial frontal cortex (BA10, amygdala, hippocampus, insula, and lateral temporal lobe. Interestingly, FA differences are spatially concordant with these functionally connected areas suggesting that white matter tracts connecting these regions may be different in depressed versus control subjects. These results indicate that disease related alterations in functional connectivity may be mediated by white matter structural abnormalities. Despite the small sample size, these preliminary results support the use of joint ICA for integrating functional and structural connectivity measures in the study of neuropathology. We are currently validating these findings in a larger cohort of depressed and control subjects.

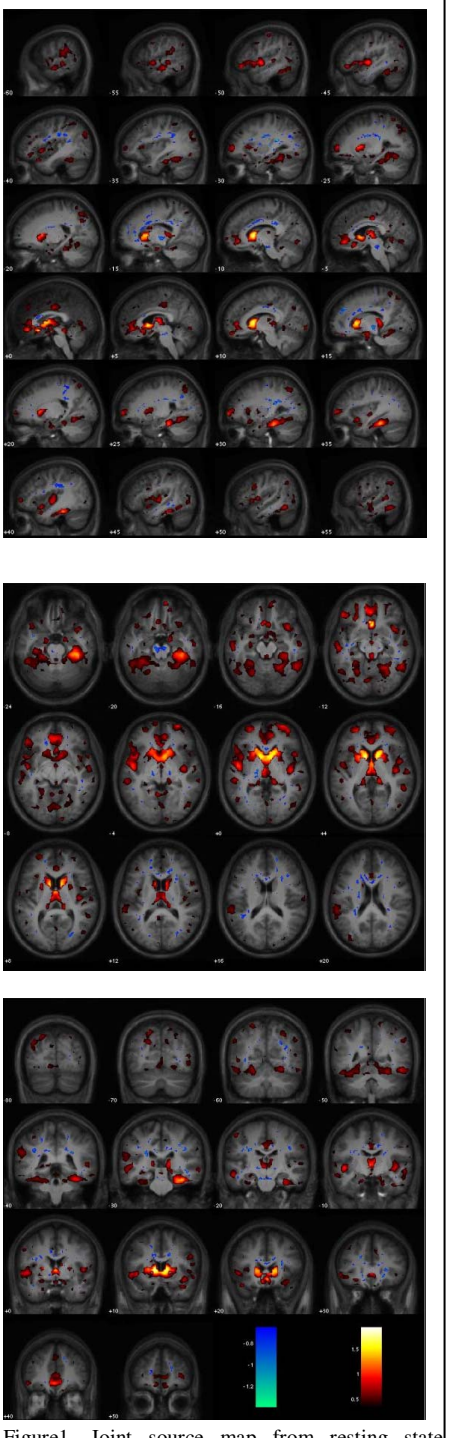

Figure1. Joint source map from resting state functional (Red) and FA connectivity (Blue) with Cg25 seed regions.

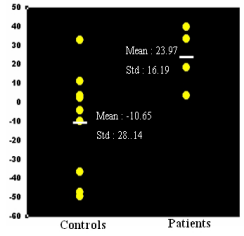

Figure2. Loading (mixing) parameters (t-test : $p < 0.043$)

References

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