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Baseline Default Mode Network Functional Connectivity as a Predictor of SSRI Treatment Response in Adolescent Major Depressive Disorder

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We use this protocol and it's working

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Abstract

This protocol describes the preprocessing and analytic steps for examining whether baseline resting-state functional connectivity (rsFC) within the default mode network (DMN) predicts treatment response to selective serotonin reuptake inhibitors (SSRIs) in medication-naïve adolescents with major depressive disorder (MDD). Resting-state fMRI data are preprocessed using FreeSurfer 6.0 and AFNI 21.3.09, including removal of initial volumes, motion correction, normalization to MNI152_T1_2009c space, and 4 mm FWHM spatial smoothing. Noise reduction employs ANATICOR with white-matter and ventricular regressors and motion censoring (> 0.2 mm threshold). Functional connectivity maps are computed for three DMN seed regions (vMPFC, dMPFC, PCC). Voxel-wise regression analyses test the association between baseline DMN rsFC and 8-week changes in Children's Depression Rating Scale–Revised scores following escitalopram treatment, controlling for age and sex. Cluster-level correction uses AFNI 3dClustSim (10 000 Monte Carlo iterations; voxel $p < 0.005$, FWE $\alpha < 0.017$). This step-by-step protocol provides a transparent, reproducible workflow for identifying neural predictors of SSRI response in adolescent MDD.

Abstract

- 1 This protocol describes the recruitment, SSRI treatment procedures, and resting-state fMRI preprocessing and analysis steps used to investigate whether baseline default mode network (DMN) functional connectivity predicts SSRI treatment response in adolescents with major depressive disorder (MDD). The study combines a clinical open-label escitalopram trial with voxel-wise seed-based resting-state connectivity analyses using AFNI and FreeSurfer.
- 2 Institutional Review Board (IRB) approval: Seoul National University Hospital (IRB no. 1504-113-668).
Obtain written informed consent from participants and legal guardians.
Ensure MRI scanner access (3T Siemens Tim Trio with 12-channel head coil).
Install software: FreeSurfer v6.0 (Harvard University), AFNI v21.3.09 (National Institute of Mental Health)
- 3 MRI scanner: Siemens Tim Trio 3T
Head coil: 12-channel birdcage
Software: FreeSurfer 6.0, AFNI 21.3.09
Clinical scale: Children's Depression Rating Scale-Revised (CDRS-R)
Antidepressant: Escitalopram (5–30 mg/day)
- 4
 1. Participant recruitment
 - 1) Recruit adolescents aged 12–17 meeting DSM-5 criteria for MDD.
 - 2) Confirm diagnosis using K-SADS-PL by trained psychologists.
 - 3) Apply exclusion criteria (psychosis, developmental disorders, prior antidepressant use, etc.).
 - 4) Obtain written informed consent.
 2. SSRI treatment protocol (8 weeks)
 - 1) Administer escitalopram 5 mg/day during week 1.
 - 2) Increase to 10 mg/day from week 2.
 - 3) Adjust dose at weeks 4 and 6 based on clinical judgment (max 30 mg/day).
 - 4) Assess depressive symptoms using CDRS-R at weeks 0, 2, 4, 6, and 8.
 - 5) Monitor adherence via pill counts; exclude participants <60% adherence.
 3. MRI acquisition (approx. 10 min per scan)
 - 1) Scanner: Siemens Tim Trio 3T
 - 2) Sequence: T2*-weighted echo-planar imaging
 - 3) Parameters: TR = 3000 ms; TE = 40 ms; flip angle = 90°; 35 axial slices; voxel size = 3.4 × 3.4 × 4.0 mm; FOV = 240 mm
 - 4) Instruct participants to keep eyes closed, remain awake, and avoid structured thought.

4. Preprocessing (AFNI + FreeSurfer, 4–6 hours per subject)
 - 1) Discard first 4 volumes for signal stabilization.
 - 2) Perform spike correction, slice-timing correction, and motion correction.
 - 3) Align functional data to base volume with minimal outliers.
 - 4) Co-register to structural T1 image.
 - 5) Nonlinear warp to MNI152_T1_2009c template (AFNI).
 - 6) Apply 4 mm FWHM Gaussian smoothing.
 - 7) Regress out white matter and CSF signals using FreeSurfer-derived masks (eroded).
 - 8) Include 6 motion parameters as nuisance regressors.
 - 9) Censor volumes with >0.2 mm motion or >10% outlier voxels.
 - 10) Apply bandpass filter (0.01–0.1 Hz).

5. ROI definition (10 min)

- 1) Define 10-mm spherical masks for the following DMN seeds:
 - vMPFC (0, 26, –18)
 - dMPFC (0, 52, 26)
 - PCC (–8, –56, 26)
- 2) Extract mean time series for each seed.

6. Functional connectivity analysis (3dRegAna, 1–2 hours per subject)

- 1) Compute voxel-wise correlation maps with each seed's mean time series.
- 2) Convert r-values to z-scores via Fisher's transformation.
- 3) Run regression analyses predicting change in CDRS-R (week 8 – baseline).
- 4) Include age and sex as covariates.
- 5) Correct for multiple comparisons using 3dClustSim (10,000 Monte Carlo iterations).
- 6) Apply voxel-wise $p < 0.005$, cluster-level FWE $\alpha < 0.017$ (Bonferroni correction).

7. Statistical analysis and visualization (SPSS v29, GraphPad Prism)

- 1) Extract z-scores from significant clusters.
- 2) Replicate regression analysis in SPSS to confirm direction and significance.
- 3) Plot scatterplots of baseline rsFC vs. Δ CDRS-R.

- 5 Anticipated Results

1. Stronger baseline DMN–sensorimotor connectivity (vMPFC–postcentral gyrus, vMPFC–insula, dMPFC–supramarginal gyrus, PCC–supramarginal gyrus) predicts greater improvement in depressive symptoms after SSRI treatment.
2. Within-DMN connectivity does not predict treatment response.

- 6 Data Availability

Raw and preprocessed fMRI data are available upon reasonable request from the corresponding author.