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Supplementary Material

Article Title: A Supervised Exercise Intervention for Youth at Risk for Psychosis: An Open-Label Pilot Study

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List of Supplementary Material for the article

1. **Criteria to determine ultrahigh risk and training of clinical interviewers**
2. **Detailed methods of the structural and fcMRI analysis**

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SUPPLEMENTAL MATERIAL

Clinical Interviews

The Structured Interview for Prodromal Syndromes (SIPS)[1, 2] was administered to diagnose a prodromal syndrome. Participants in the present study met SIPS criteria for a prodromal or high-risk syndrome, defined by moderate to severe but not psychotic levels of positive symptoms (rated from 3 to 5 on a six point scale) and/or a decline in global functioning accompanying the presence of schizotypal personality disorder and/or a family history of schizophrenia.[3] The SIPS gauges distinct categories of prodromal symptoms including positive and negative domains. A total sum score for each domain is used as an indicator of the respective dimensions of symptomatology. Family history of psychosis was attained by asking participants if any first-degree family members had been diagnosed with a psychotic disorder. In most cases, family history was corroborated with another family member of the participant.

The Structured Clinical Interview for Axis-I DSM-IV Disorders (SCID)[4] was also administered to rule out a psychotic disorder diagnosis. This measure has been demonstrated to have excellent inter-rater reliability in adolescent populations[5] and has been used in several previous studies focusing on adolescent populations with schizophrenia spectrum disorders.[6] Training of advanced doctoral student interviewers was conducted over a 2-month period, and inter-rater reliabilities exceeded the minimum study criterion of Kappa $\geq .80$. Interviewers were kept blind to the prescribed exercise condition for each participant.

Structural Magnetic Resonance Imaging acquisition and data processing

A T1-weighted three-dimensional (3D) magnetization prepared rapid gradient multiecho sequence (MPRAGE; sagittal plane; repetition time [TR]=2530 ms; echo times [TE]=1.64 ms, 5.36 ms, 7.22 ms, 9.08 ms; GRAPPA parallel imaging factor of 2; 1 mm^3 isomorphic voxels, 192 interleaved slices; FOV=256 mm; flip angle=7^o; time=6.03 min) covering the whole brain was acquired for anatomic segmentation. A turbo spin echo proton density (PD)/T2-weighted acquisition (TSE; axial oblique aligned with anterior commissure-posterior commissure line (AC-PC line); TR=3720ms; TE=89ms; GRAPPA parallel imaging factor of 2; .9 x .9 mm voxels; FOV=240mm; flip angle 120^o; 77 interleaved 1.5mm slices; time=5:14) was acquired to check for incidental pathology.

The processing stream involved motion correction, removal of non-brain tissue using a hybrid watershed/surface deformation procedure,[7] automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter structures,[8, 9] intensity normalization,[10] tessellation of the gray matter/white matter boundary, automated topology correction,[11] and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class.[12]

Hippocampal target structures were segmented from the MPRAGE using the FreeSurfer suite of automated tools.[13, 14] The processing stream involved motion correction, removal of non-brain tissue using a hybrid watershed/surface deformation procedure,[7] automated Talairach transformation, segmentation of the subcortical white

matter and deep gray matter structures,[8, 9] intensity normalization,[10] tessellation of the gray matter/white matter boundary, automated topology correction,[11] and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class.[12] FreeSurfer also calculates values for each participant's total intracranial volume (TICV; i.e., the sum of whole-brain gray matter + white matter + cerebrospinal fluid), and each structure's volume was divided by the TICV to control for whole brain volume.

Resting state functional connectivity processing

A 5 minute 34 second functional resting state blood-oxygen-level-dependent scan was acquired with a T2*-weighted echo-planar functional protocol (number of volumes =165; TR = 2,000 ms; TE = 29 ms; matrix size = 64 x 64 x 33; FA = 75°; 3.8 x 3.8 x 3.5 mm voxels; 33 slices; FOV = 240mm). During the resting state scan, participants were instructed to relax and close their eyes. A turbo spin echo proton density (PD)/ T2-weighted acquisition (TSE; axial oblique aligned with anterior commissure-posterior commissure line; TR= 3720ms; TE=89ms; GRAPPA parallel imaging factor of 2; FOV=240mm; flip angle: 120°; .9 x .9 mm voxels; 77 interleaved 1.5mm slices) was acquired to check for incidental pathology. The fcMRI scan was kept relatively short in order to minimize anxiety and the possibility of within-scan movement. This fcMRI scan duration has been shown to yield equivalent power as longer scans.[15]

Data were preprocessed in FSL (v.5; http://fsl.fmrib.ox.ac.uk/fsl), which involved motion correction (MCFLIRT), brain extraction (BET), high-pass filtering (100 s), and spatial smoothing (6 mm FWHM). Functional images were aligned to the MNI152-T1 2-

mm brain template with a two-step procedure. First, the resting state scan was aligned to the high-resolution MPRAGE using a linear boundary-based registration method, which relies on gray/white matter boundaries.[13, 16, 17] Second, the MPRAGE was nonlinearly aligned to the template, and the two registrations were then combined in order to align the functional resting state scan to the template.

Recent papers have demonstrated the importance of properly correcting for motion by not only regressing out motion parameters, but also regressing out or eliminating specific frames with motion outliers.[18] To accomplish this, we used the Artifact Rejection Toolbox (ART; http://www.nitrc.org/projects/artifact_detect/) to create confound regressors for motion parameters (3 translation and 3 rotation parameters), and additional confound regressors for specific image frames with outliers based on brain activation and head movement. In order to identify outliers in brain activation, the mean global brain activity (i.e., the mean signal across all voxels) was calculated as a function of time, and was then Z-normalized. Outliers were defined as any frames where the global mean signal exceeded 3 SD. Similarly, frame-wise measures of motion (composite measure of total motion across translation and rotation) were used to identify any motion outliers (i.e., motion spikes). Motion outliers were defined as any frame where the motion exceeded 1 mm. From the motion translation parameters we also calculated mean displacement, and used this measure as well as the number of motion and mean signal outliers in order to control for the degree of head movement.

fcMRI analysis was performed in the Conn toolbox v.15b.[19, 20] The data were band-pass filtered from 0.008 to 0.09 Hz. Seed regions-of-interest (ROIs) within the left and right, hippocampus were defined using FSL Harvard-Oxford subcortical structural

atlas.[21] The mean time-series, averaged across all voxels within each ROI, was used as a predictor regressor. Anatomical images were segmented into gray matter, white matter, and CSF with SPM8 (www.fil.ion.ucl.ac.uk/spm) in order to create masks for signal extraction. The Conn toolbox uses principal component analysis to extract 5 temporal components from the segmented CSF and white matter, which were entered as confound regressors in the subject-level GLM. This approach corrects for confounds of motion and physiological noise without regressing out global signal. We used state of the art methods to account for subject motion, as well as outliers, as suggested by Power and colleagues.[18] Accordingly, the GLM also included confound regressors for subject motion (6 parameters for translation and rotation) and frame-wise outliers identified with the ART toolbox.

Connectivity between the seed ROI was calculated with all other voxels in the brain at each time point. The *conn* toolbox used a GLM approach with connectivity measures calculated as bivariate correlations. All comparisons were defined as within-subject *T*-contrasts. Data in tables and statistical maps were first thresholded at the voxel-level at $p_{uncorr} < .001$ and then corrected at the cluster-level to a false-discovery rate (FDR) of $p < .05$.[22]

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