Altered Intrinsic Functional Brain Architecture in Children at Familial Risk of Major Depression

Supplementary Information

Participant Recruitment

Participants were recruited from among participants in longitudinal studies of offspring at risk, conducted in the Clinical and Research Program in Pediatric Psychopharmacology at the Massachusetts General Hospital, supplemented with participants responding to advertisements to the community. Six of the 30 control children were from a prior study with an identical protocol (1). The prior studies from which we recruited had been approved by the Institutional Review Board at the Massachusetts General Hospital, and the present study was approved by the Institutional Review Boards at the Massachusetts General Hospital and at the Massachusetts Institute of Technology. Eligible participants were right-handed, had normal or corrected-to-normal visual acuity, and had a working command of the English language. Exclusion criteria included the presence of acute psychosis or suicidality in a parent or a child; the presence at any point in the lifespan of bipolar disorder in the parent, autism in the child, or a lifetime history of a traumatic brain injury or neurological disorder in the child. Children were also excluded if they had conditions incompatible with MRI (e.g., metal implants, braces, electronically, magnetically, or mechanically activated devices such as cochlear implants, or claustrophobia).

Six participants from the at-risk group and 12 participants from the control group were excluded from analysis due to excessive head movement during the functional scan (greater than 3 mm displacement in x, y or z direction, or had more than 1/3 of the time points identified as outliers, see below). Two participants from the at-risk group and two participants from the control group did not complete the functional scan. From the at-risk group, one child with previous history of depression that had remitted, and two children with current clinical-range scores from the Child Behavior Checklist (CBCL), (see below) internalizing scores were

excluded in the analysis so that all remaining children in this group had no history of depression. The final sample included 27 at-risk and 16 control participants.

Child Behavior Checklist

The CBCL records, in standardized format, behavioral problems and competencies of children ages 6 to 18 years. Normed on a nationally representative sample of 1,753 youths, it includes a total problems score, as well as scores reflecting internalizing (affective and anxiety) and externalizing symptoms (attentional problems and disruptive behavior).

Child Depression Inventory (CDI)

This 27-item self-report questionnaire measures total depression, and five factors: negative mood, interpersonal problems, ineffectiveness, anhedonia, and negative self- esteem. Because this was a non-clinical sample including young children, we omitted the item asking about suicidal ideation.

Online Prospective Acquisition Correction (PACE)

PACE tracks the head of the participant, and updates the position of the field-of-view and slice alignment during acquisition. The parameters for each time-point were updated based on motion correction parameters calculated from the previous two time-points. Two dummy scans were included at the start of the sequence.

Head Motion and Artifact Detection

We identified problematic time points during the scan using Artifact Detection Tools (ART, http://www.nitrc.org/projects/artifact_detect). Specifically, an image was defined as an outlier (artifact) image if the average intensity deviated more than 3 SD from the mean intensity in the session or composite head movement exceeded 1 mm from the previous image, based on prior

studies with the same acquisition parameters (2, 3). The composite head movement was computed by first converting 6 rotation/translation motion parameters into another set of 6 parameters characterizing the trajectories of 6 points located on the center of each of the faces of a bounding box around the brain. The maximum scan-to-scan movement of any of these points is then computed as the single composite movement measure. Outlier images were modeled as nuisance covariates, one regressor per outlier image, in the first level general linear models.

Anatomical CompCor

The anatomical image for each participant was segmented into white matter (WM), gray matter, and cerebrospinal fluid (CSF) masks using SPM8. To minimize partial voluming with gray matter, the WM and CSF masks were eroded by one voxel, which resulted in substantially smaller masks than the original segmentations (4). The eroded WM and CSF masks were then used as noise regions of interest (ROI). Based on previous results (4), five principal components of the signals from WM and CSF noise ROIs were removed with regression.

Classification Model of At-Risk Children and Controls

For the classification model based on connectivity from anatomically defined regions in the AAL atlas, connectivity between left DLPFC and right supramarginal gyrus, between left DLPFC and left inferior temporal cortex, between DMN and left rectus (medial OFC and sgACC), between DMN and left IFG, between DMN and left/right inferior temporal cortex contributed most to the classification.

Table S1. Between-group connectivity differences after including CBCL total scores as a covariate from default mode network (DMN), right dorsolateral prefrontal cortex (DLPFC), left DLPFC, and right amygdala.

	k (mm^3)	BA	x, y, z	*t*	*p*-value
DMN Connectivity					
At-risk > Control					
Subgenual ACC/ OFC	1794	25/11	-6, 26, -24	3.86	.01
R inferior parietal lobule	1416	40	44, -30, 28	4.04	.01
R mid cingulum	4136	24/31	10, -22, 36	4.41	< .001
Controls > At-risk					
None					
R DLPFC Connectivity					
At-risk > Control					
None					
Control > At-risk					
R DLPFC	9936	46/9	42, 30, 20	5.56	< .001
R inferior parietal lobule	1344	40	36, -42, 38	4.18	.01
L DLPFC Connectivity					
At-risk > Control					
Post-central gyrus	3256	5	20, -44, 72	4.01	.007
Control > At-risk					
Subgenual ACC	1564	25/11	-12, 12, -26	4.71	.003
L lingual gyrus	2664	18	-14, -82, -14	4.89	.004
R superior frontal gyrus	3592	8/6	14, 34, 60	4.51	.002
R inferior temporal gyrus	7672	21/20	62, -46, -12	5.59	< .001
R superior frontal gyrus	2424	8	42, 22, 54	4.06	.008
R Amygdala Connectivity					
At-risk > Control					
Inferior frontal gyrus	2144	47/44	58, 18, -2	3.72	.004
Supramarginal gyrus	1272	40	68, -42,28	4.85	.009
Control > At-risk					
None					

t, peak t value from the cluster (degrees of freedom = 40); k, cluster size in mm^3.

ACC, anterior cingulate cortex; BA, Brodmann area; OFC, orbital prefrontal cortex; *p*-value, FDR-corrected cluster-level *p* value.

Supplemental References

1. Chai XJ, Ofen N, Gabrieli JDE, Whitfield-Gabrieli S (2014): Development of deactivation of the default-mode network during episodic memory formation. *Neuroimage*. 84: 932–938.

2. Redcay E, Moran JM, Mavros PL, Tager-Flusberg H, Gabrieli JDE, Whitfield-Gabrieli S (2013): Intrinsic functional network organization in high-functioning adolescents with autism spectrum disorder. *Front Hum Neurosci*. 7: 573.

3. Uchida M, Biederman J, Gabrieli JDE, Micco J, Angeles C de L, Brown A, *et al.* (2015): Emotion regulation ability varies in relation to intrinsic functional brain architecture. *Soc Cogn Affect Neurosci*. doi: 10.1093/scan/nsv059.

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