

Intrinsic Functional Brain Connectivity Predicts Onset of Major Depression Disorder in Adolescence: A Pilot Study

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Abstract

Children with familial risk for major depressive disorder (MDD) have elevated risk for developing depression as adolescents. Here, we investigated longitudinally whether resting-state functional connectivity (RSFC) could predict the onset of MDD. In this pilot study, we followed a group of never-depressed children with familial risk for MDD and a group of age-matched controls without familial risk who had undergone an MRI study at 8–14 years of age. Participants were reassessed 3–4 years later with diagnostic interviews. We first investigated group differences in RSFC from regions in the emotion regulation, cognitive control, and default mode networks in the children who later developed MDD (converted), the children who did not develop MDD (nonconverted), and the control group. We then built a prediction model based on baseline RSFC that was independent of the group differences to classify the individuals who later developed MDD. Compared with the nonconverted group, the converted group exhibited hypoconnectivity between subgenual anterior cingulate cortex (sgACC) and inferior parietal lobule (IPL) and between left and right dorsolateral prefrontal cortices. The nonconverted group exhibited higher sgACC-IPL connectivity than did both the converted and control groups, suggesting a possible resilience factor to MDD. Classification between converted and nonconverted individuals based on baseline RSFC yielded high predictive accuracy with high sensitivity and specificity that was superior to classification based on baseline clinical rating scales. Intrinsic brain connectivity measured in healthy children with familial risk for depression has the potential to predict MDD onset, and it can be a useful neuromarker in early identification of children for preventive treatment.

Keywords: children; depression risk; machine learning; resilience; resting-state fMRI; subgenual ACC

Introduction

MAJOR DEPRESSIVE DISORDER (MDD) is one of the most common psychiatric disorders, with an estimated lifetime prevalence of 16% (Kessler et al., 2003). It is associated with high comorbidity, social and occupational dysfunction (Godard et al., 2012), and high financial burden (Greenberg et al., 2015). A peak period of onset is adolescence and early adulthood (Merikangas and Avenevoli, 2002). An estimated 11% of adolescents are affected with MDD, which leads to significant distress, dysfunction, and mortality in these youth (Avenevoli et al., 2015). MDD is characterized by a negative feedback cycle in which individuals experience

negative affect, perceive events negatively, and withdraw from social and pleasurable activities, leading to further exacerbation of negative mood, biased cognitions, and social withdrawal (Beck and Haigh, 2014).

People with MDD exhibit functional brain differences, as measured by neuroimaging, in default mode network (DMN), cognitive control, and emotion regulation networks. The DMN, anchored by the midline regions of medial prefrontal cortex (MPFC) and posterior cingulate cortex (PCC), is a set of brain regions that has been linked to self-referential processing and rumination in depression (Hamilton et al., 2015). The emotion regulation network, which involves the amygdala, the anterior cingulate cortex (ACC), and the MPFC,

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has shown functional brain differences in MDD (Hamilton et al., 2015; Sheline et al., 2009; Stuhmann et al., 2011; Vilgis et al., 2018). The cognitive control network, which includes dorsolateral prefrontal cortex (DLPFC) and parietal regions, has shown abnormal activation and connectivity patterns in MDD (Fales et al., 2008; Ye et al., 2012). Within the emotion regulation network, subgenual ACC (sgACC) has been considered a core region in the pathophysiology of MDD (Drevets et al., 2008; Mayberg, 1997; Ongür et al., 1998; Siegle et al., 2012) and has been a successful target for deep brain stimulation treatment for MDD (Mayberg et al., 2005).

To identify possible neural risk factors for depression, several studies have examined brain function in children who are not themselves depressed but who have a parent with a history of MDD, which increases the risk of MDD in the offspring threefold to fivefold (Lieb et al., 2002; Williamson et al., 2004). Functional and anatomical brain differences between never-depressed children with familial risk for depression and children without familial risk have been reported in emotion processing regions (Chai et al., 2015; Foland-Ross et al., 2015; Monk et al., 2008), suggesting that these neural traits predispose children toward depression. Resting-state fMRI (rs-fMRI) has revealed altered patterns of functional connectivity in both the DMN and in emotion regulation and cognitive control networks in never-depressed at-risk children. At-risk children have exhibited hyperconnectivity between sgACC and DMN, and hypoconnectivity between sgACC and DLPFC and within the control network regions (Chai et al., 2016). Similar differences have been observed in adult (Greicius et al., 2003; Liston et al., 2014; Ye et al., 2012) and pediatric (Cullen et al., 2009; Gaffrey et al., 2010) patients with MDD. Finding these functional network differences among at-risk offspring who are not affected with MDD, before the period of risk for MDD onset, raises the hypothesis that the differences represent vulnerability factors for depression.

To examine this question, we conducted a follow-up study of the children imaged in our previous study (Chai et al., 2016, 2015). The children were 8–14 years old at baseline and 12–18 years old at follow-up. This age range at the follow-up is a heightened time for onset of MDD in at-risk youth, as rates of MDD from early to late adolescence increase as much as sixfold (Hankin et al., 1998). We investigated whether baseline resting-state connectivity in regions that had been previously associated with depression would predict the onset of MDD in these high-risk adolescents. We examined baseline resting-state functional connectivity (RSFC) data from seed regions in sgACC, DMN, amygdala, and DLPFC in children at familial risk for depression, and we tested whether they would predict which individuals would later develop MDD.

We performed two types of analyses. First, we examined group-level intrinsic connectivity differences. To understand risk factors for depression, we compared seed-to-voxel connectivity between the subset of children who later developed MDD (the converted group) and the subset of children who did not develop depression (the nonconverted group). To understand resilience to depression, we compared the nonconverted group with the control group in terms of sgACC connectivity, given the anatomical position of the sgACC that connects to the limbic and cortical structures (Johansen-

Berg et al., 2008), and the link between sgACC connectivity and depression symptom in at-risk children (Chai et al., 2016). Second, we computed connectivity between the seed regions and regions from two different whole-brain atlases, defined independently from the regions that exhibited group differences, and trained machine learning models to classify which individuals would later develop depression. We hypothesized that (1) there would be differences in resting-state connectivity from these seed regions between the converted and nonconverted groups, and (2) models based on resting-state connectivity of these seed regions to other brain regions defined in the atlases could predict the onset of depression with higher accuracy than a model based on baseline clinical scores (the Child Behavior Checklist, CBCL) alone, even though depressive symptoms carry some prediction power for the onset of depression (Horwath et al., 1992).

Materials and Methods

Procedures

Children at risk for MDD based on lifetime history of parental depression, who had not themselves had mood episodes, had undergone rs-fMRI scans at baseline. At a 3- to 4-year follow-up, participants and their parents were invited back for diagnostic assessments to determine whether they had developed an episode of MDD at any point during the interval since the scan. The study was approved by the Institutional Review Boards at the Massachusetts General Hospital and at the Massachusetts Institute of Technology. Parents provided written informed consent for their and their child's participation, and youths provided written assent. Adolescents aged 18 years provided written consent for their own participation.

Participants

Baseline. Thirty-eight high-risk participants between 8 and 14 years old who were offspring of parents with a lifetime history of MDD (at-risk group) and 30 age-matched controls with no familial history of MDD were recruited in the baseline study (Chai et al., 2016, 2015). Exclusion criteria at baseline had included the presence of acute psychosis or suicidality in a parent or a child; the presence of bipolar disorder at any point in the lifespan in the parent; autism or intellectual disability in the child; a lifetime history of a traumatic brain injury or neurological disorder in the child; or any variables that would interfere with fMRI (e.g., braces, claustrophobia). At baseline, children had no current or prior history of major depressive disorder. The final sample included 46 participants (30 at-risk children and 16 control children). 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). Two participants from the at-risk group and two participants from the control group did not complete the resting-state scan.

Follow-up. We re-assessed 33 (25 at-risk and 8 controls) (72%) of the 46 participants who had useable baseline rs-fMRI data at a 3- to 4-year follow-up. Participants who

had an incomplete resting scan or had too much head movement during the scan were not included in the present analysis. At the follow-up assessment, participants were between 12 and 18 years old (mean age = 15.3 years, $SD = 1.7$ years). Follow-up assessments were on average 205 weeks after the initial study (range 166–258 weeks, $SD = 19.8$ weeks). An overlapping set of participants was included in a separate report (Shapiro et al., 2019), which examined whether structural and functional brain measures that differentiated children with familial risk for MDD from children without familial risk were related to symptom severity and MDD onset at follow-up.

Diagnostic assessment

Baseline. Each child and both parents in each family were assessed for current and lifetime mood disorders (MDD, bipolar disorder, and dysthymia), using structured clinical interviews in which the mother was the informant (Chai et al., 2016). Interviews about parents used the depression, mania, dysthymia, and psychosis modules from the Structured Interview for DSM-IV (First et al., 1995) and those about the child used the depression, mania, dysthymia, and psychosis modules from the Schedule of Affective Disorders and Schizophrenia for School-Aged Children–Epidemiological Version for DSM-IV (K-SADS-E) (Orvaschel, 1994). Parents completed the CBCL (Achenbach and Rescorla, 2001), which assessed symptom scores in the children. The CBCL includes a total problems score, as well as scores reflecting internalizing (affective and anxiety) and externalizing (attentional problems and disruptive behavior) symptoms. We also administered self-report depression symptom scores, the Child Depression Inventory (CDI) (Kovacs, 1985), to all children. More details on CBCL and CDI are included in Supplementary Data. We conducted two-sample *t*-tests in CBCL total problem scores, CBCL internalizing, externalizing, and anxiety scores, and CDI scores between the converted and nonconverted group, and between the control group and nonconverted group.

Follow-up. At follow-up, the child and one parent completed the K-SADS-E to report on the child's current history of psychopathology since the baseline assessment, to determine MDD conversion. The same interviewer administered the K-SADS-E first to the parent and then to the youth, and then created summary ratings. Currently, no consensus exists about how best to integrate discrepant information from multiple informants, despite the fact that parents and children often disagree in their reports of the child's symptoms (Braaten et al., 2001; Cantwell et al., 1997; Martel et al., 2017). To maintain fidelity to the K-SADS-E, we used the interviewer's summary ratings based on his/her "best-estimate" clinical judgment from interviewing both parent and child. The K-SADS-E diagnostic interviews have good inter-rater and retest reliability (Orvaschel et al., 1995). An advanced postdoctoral psychology fellow (B.G.S.) conducted all prospective interviews. He had extensive experience interviewing adolescents and parents with semi-structured diagnostic interviews, and was trained on reliability on the K-SADS-E with a perfect diagnostic reliability ($K = 1.00$, $p < 0.001$) and high item-level correlation ($ICC =$

0.88 , $p < 0.001$). In addition, all diagnostic decisions were reviewed with a senior child and adolescent psychologist (D.R.H.B.) who has extensive expertise reliably administering, training, and supervising interviewers on the structured clinical interview for DSM-IV and K-SADS-E.

MRI procedure and image preprocessing

Data were acquired on a 3T TrioTim Siemens scanner by using a 32-channel head coil. T1-weighted whole-brain anatomical images and resting fMRI images were acquired. Rs-fMRI data were preprocessed by using standard procedure. The analysis was performed at $2 \times 2 \times 2$ mm resolution. Functional connectivity analysis was carried out by using a seed-driven approach with in-house, custom software "CONN" (Chai et al., 2012; Whitfield-Gabrieli and Nieto-Castanon, 2012). We addressed head motion related artifacts by using a censoring method, which mitigates both motion artifact and distance-dependence artifacts in connectivity (Ciric et al., 2017). Head movement related noise was modeled by including additional regressors for outliers in the model. The converted, nonconverted, and control groups did not differ significantly in head movement parameters and the number of outlier scans in the resting scan. Details on the scanning procedure, image preprocessing, and noise estimation are described in Supplementary Data.

Resting-state connectivity analysis

We computed whole-brain seed-to-voxel resting-state connectivity from six regions of interests (seeds) that are core regions in the DMN, emotion regulation, and cognitive control networks (Drevets et al., 2008; Hamilton et al., 2015; Stuhmann et al., 2011): DMN, sgACC, left and right DLPFC, and left and right amygdala (Fig. 1). The DMN (MPFC and PCC), left and right DLPFC, and sgACC seeds were defined as 6-mm spheres around peak coordinates from literature (Fair et al., 2009; Kelly et al., 2009). DMN connectivity was calculated from the averages of the time series from MPFC and PCC seeds (Fox et al., 2005; Whitfield-Gabrieli et al., 2009), given their similar connectivity patterns. The amygdala seeds were defined from the WFU Pick Atlas (Maldjian et al., 2003). Time series of all the voxels within each seed were averaged, and first-level correlation maps were produced by extracting the residual BOLD time course from each seed and computing Pearson's correlation coefficients between that time course and the time course of all other voxels. Correlation coefficients were converted to normally distributed *z*-scores by using the Fisher transformation to allow for second-level General Linear Model analyses. To determine connectivity differences between the converted group and nonconverted group, first-level connectivity maps for each participant in the converted group and nonconverted group were entered into a between-group *t*-test for each seed. Two layers of multiple comparison correction were used, one for correcting the number of clusters and one for correcting the number of seeds used. We first used a cluster-forming threshold for voxel-level statistics ($p < 0.001$), and we corrected for multiple comparison at the cluster level by using false discovery rate correction (Genovese et al., 2002), as implemented in SPM. The cluster-level corrected *p*-values were further

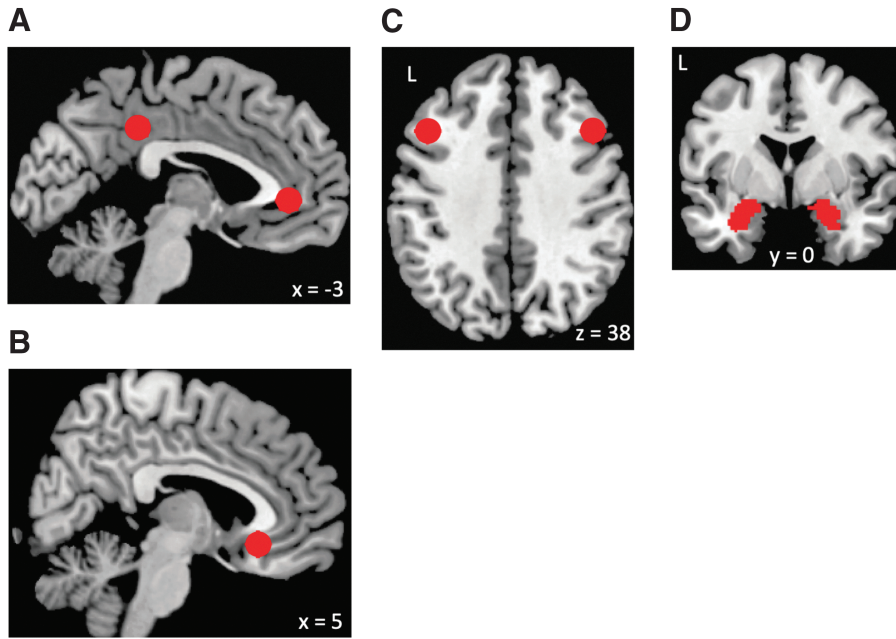


FIG. 1. Seeds (regions of interest) used in the study. (A) DMN (posterior cingulate cortex and medial prefrontal cortex), (B) sgACC, (C) left and right DLPFC, (D) left and right amygdala. Images are presented in neurological convention in all figures (left side of the brain is on the left side of the image). DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; L, left hemisphere; R, right hemisphere; sgACC, subgenual anterior cingulate cortex.

corrected for the number of seeds used (six), using Bonferroni correction. Regions that showed significant connectivity differences (survived Bonferroni correction for the number of seeds tested) between groups were further examined for their connectivity values (significantly above or below zero) by using one-sample *t*-tests in each group.

To investigate resilience to depression, we performed an additional analysis to compare the nonconverted and control groups on sgACC connectivity, given the pivotal role of sgACC in emotion regulation and treatment in depressed patients (Drevets et al., 1997; Mayberg et al., 2005; Siegle et al., 2012). First-level sgACC connectivity maps were entered into a between-group *t*-test to determine sgACC connectivity differences between the control and nonconverted groups. The same procedure for multiple comparison correction was applied. Due to the low sample size ($n=8$) of the control group who were later assessed at follow-up, we conducted this test twice, once with the entire control group from Chai et al. (2016) ($n=16$) and once with the subset of controls who were assessed at the follow-up visit (0 conversion

to depression). We performed an additional exploratory analysis comparing RSFC of the amygdala and DLPFC seeds between the nonconverted and control groups (Supplementary Data). To account for the effect of sex, we performed additional group analyses with sex included as a covariate. We also examined age-related changes in connectivity for the seeds that showed significant group differences, given the range of the participants' age (8–14 at the time of the scan) (Supplementary Data).

Prediction models for onset of depression

We trained three linear classification models with support vector machine, implemented in machine-learning software Weka (Hall et al., 2009), to categorize individual participants into those who later developed depression and those who did not, based on their rs-fMRI data (first two models) or clinical scores (third model) at the baseline visit. To create robust prediction models that can be generalized to new cases, we performed leave-one-out cross-validation so that each

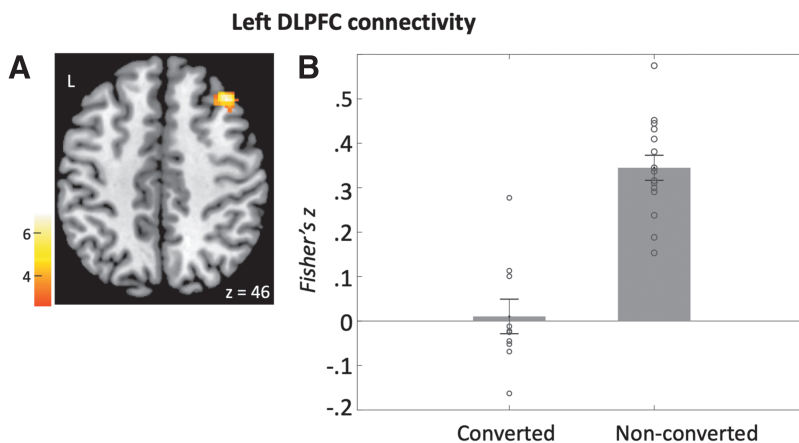


FIG. 2. Left DLPFC connectivity. (A) Left DLPFC seed exhibited higher connectivity with the right DLPFC in the nonconverted group compared with the converted group. (B) Bars represent mean connectivity (Fisher's *z*) between the left and right DLPFC in each group.

TABLE 1. PARTICIPANT DEMOGRAPHIC AND CLINICAL SCORES AT BASELINE

	Group mean (SD)			Between-group test		
	Converted	Nonconverted	Controls	p^a	p^b	p^c
Age	11.5 ± 1.41	10.9 ± 1.51	11.3 ± 1.84	0.34	0.57	0.72
Gender	7 F, 3 M	4 F, 11 M	8 F, 8 M	0.05	0.27	0.42
IQ (KBIT)	115.3 ± 13.2	119.3 ± 13.5	115.8 ± 12.8	0.47	0.47	0.92
CBCL total	52.5 ± 9.8	47.5 ± 12.8	41.0 ± 11.8	0.31	0.20	0.03
CBCL internalizing	52.7 ± 10.9	50.6 ± 13.2	44.3 ± 8.50	0.68	0.18	0.06
CBCL externalizing	52.4 ± 7.8	45.3 ± 9.8	45.1 ± 10.5	0.07	0.95	0.09
CDI	46.6 ± 5.9	44.0 ± 7.6	43.0 ± 8.1	0.40	0.97	0.44

Mean ± SD where appropriate. All group tests were *t*-tests except for Gender (Fisher's exact test).

^a*p*-Value, between-group test *p*-value (converted vs. nonconverted groups).

^b*p*-Value, between-group test *p*-value (control group vs. nonconverted group).

^c*p*-Value, between-group test *p*-value (control group vs. converted group).

CBCL, Child Behavior Checklist; CDI, total score on the Child Depression Inventory; F, female; M, male; SD, standard deviation.

individual was classified on the basis of data from the other individuals. Specifically, data from all participants except one were used as the training set to build a classification model, and the remaining participant was classified with the model and used as the validation case. This procedure was iterated for each participant and used to estimate specificity/sensitivity from the out-of-sample predictions. In the first model, connectivity values between each of the six seed regions and 116 anatomically defined areas from the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) were estimated and used in the prediction model. The matrix of connectivity values for all participants were used in feature selection. Feature selection was carried out before training the classification model. We used information gain (IG) (Mitchell, 1997; Yang and Pedersen, 1997), a filter approach for feature selection. IG ranks the features by the IG (entropy) for each feature that measures how important and relevant it is to the group label. Based on Austin and Steyerberg (2015), we used 13 features in the model, which is roughly half of the number of participants ($n=25$). The top 13 features that carried the most information (calculated by the feature's contribution on decreasing overall entropy) based on the IG method were then used in the classification procedure to classify between converted and nonconverted at-risk participants. In the second model, connectivity values between the six seed regions and all areas in the Human Connectome Project (HCP) atlas, an atlas based on multimodal MRI data (Glasser et al., 2016), were estimated and used in the prediction model. The same feature selection procedure was applied in this model. We constructed a third model based on baseline CBCL scores (Total, Internalizing, Externalizing, Anxiety/Depressed symptoms, and Affective Problem Scale) to examine how well these baseline scores predict the onset of MDD.

Results

Depression conversion

Ten out of the 25 at-risk children developed MDD by the time of follow-up. None of the control participants assessed at follow-up developed MDD. The converted and nonconverted group did not differ significantly in age [$t(23)=0.96$,

$p=0.34$], IQ [$t(23)=0.73$, $p=0.47$], or baseline clinical questionnaire measures [CBCL total: $t(23)=1.03$, $p=0.31$; CBCL internalizing: $t(23)=0.42$, $p=0.68$; CBCL externalizing: $t(23)=1.9$, $p=0.07$; CDI: $t(21)=0.86$, $p=0.40$] (Table 1). Gender distribution was only marginally different in the converted group compared with the converted group (Fisher's exact test, $p=0.05$, Table 1). The nonconverted group and the control group also did not differ significantly in age [$t(29)=0.57$, $p=0.57$], IQ [$t(29)=0.73$, $p=0.47$], or baseline clinical questionnaire measures [CBCL total: $t(24)=1.3$, $p=0.20$; CBCL internalizing: $t(24)=1.4$, $p=0.18$; CBCL externalizing: $t(24)=0.06$, $p=0.95$; CDI: $t(21)=0.03$, $p=0.97$] (Table 1). The converted group had elevated baseline CBCL total scores [$t(19)=2.4$, $p=0.03$] compared with the control group, but it did not differ significantly from the control group in age [$t(24)=0.42$, $p=0.68$], IQ [$t(24)=0.098$, $p=0.92$], and other baseline clinical measures [CBCL internalizing: $t(19)=1.99$, $p=0.06$; CBCL externalizing: $t(19)=1.79$, $p=0.09$; CDI: $t(16)=0.80$, $p=0.44$] (Table 1).

Connectivity differences between converted and nonconverted groups

Decreased DLPFC connectivity in children who later developed depression. Compared with the nonconverted group, the converted group exhibited decreased baseline connectivity between the left DLPFC seed and a region in the right DLPFC (BA46) (left DLPFC seed; Fig. 2 and Table 2A). The nonconverted group had significant positive connectivity between left DLPFC seed and right DLPFC [$t(14)=12.2$, $p<0.001$], whereas the converted group did not have significant connectivity between left and right DLPFC regions [$t(9)=0.26$, $p=0.8$].

Decreased sgACC-parietal connectivity in children who later developed depression. Compared with the nonconverted group, the converted group exhibited decreased connectivity between the sgACC seed and right inferior parietal lobule (IPL)/precentral gyrus (Fig. 3 and Table 2B). The nonconverted group had significant positive connectivity [$t(14)=5.9$, $p<0.001$], whereas the converted group had negative connectivity [$t(9)=-2.8$, $p=0.02$]. All the group differences described earlier for DLPFC connectivity and

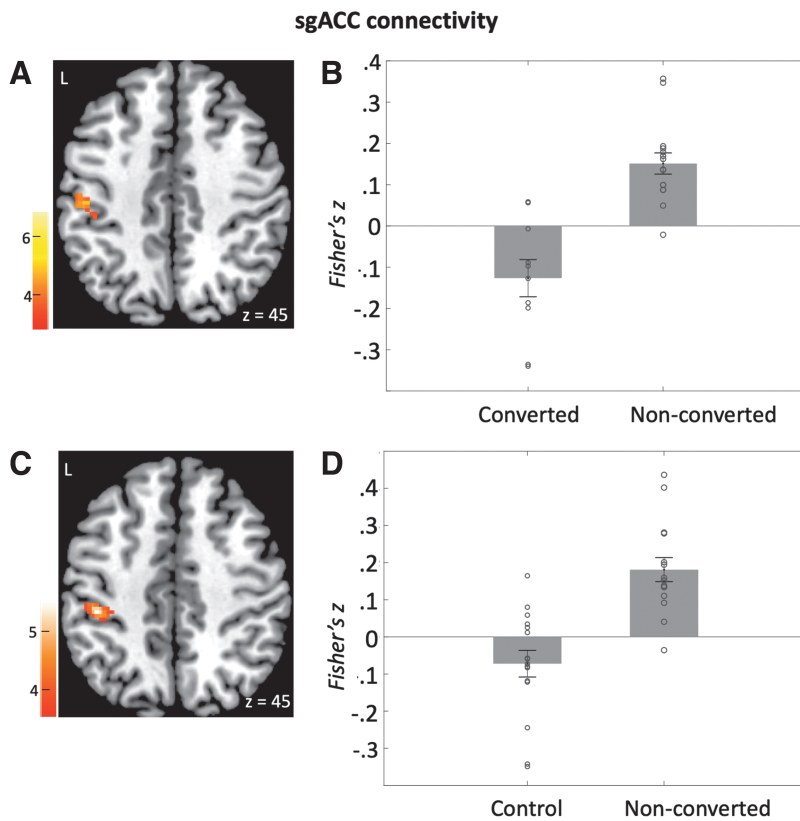


FIG. 3. sgACC connectivity. (A) sgACC seed exhibited higher connectivity with the left inferior parietal lobule/postcentral gyrus in the nonconverted group compared with the converted group. (B) Bars represent mean sgACC-parietal connectivity (Fisher’s z) in the converted and nonconverted groups in cluster shown in (A). (C) sgACC exhibited higher connectivity with the left inferior parietal lobule/postcentral gyrus in the nonconverted group compared with the control group. (D) Bars represent mean sgACC-parietal connectivity (Fisher’s z) in the nonconverted group and control group in the cluster shown in (C). Error bars represent standard errors of the means.

sgACC-parietal connectivity remained when sex was included as a covariate (Supplementary Table S1).

Connectivity differences between nonconverted and control groups

Compared with the entire control group (including those who did not return for the follow-up), the nonconverted

group exhibited greater baseline connectivity between the sgACC seed and right IPL/precentral gyrus (Fig. 3 and Table 2B). The nonconverted group had significant positive connectivity [$t(14)=5.6, p<0.001$], whereas the control group did not show connectivity significantly different from zero [$t(15)=-2.0, p=0.06$]. This difference remains if only those who were assessed at follow-up (0 conversion

TABLE 2. BETWEEN-GROUP CONNECTIVITY DIFFERENCES FROM (A) LEFT DLPFC, AND (B) SUBGENUAL ANTERIOR CINGULATE CORTEX SEEDS

	BA	Volume	x, y, z	t	df	p
(A) Left DLPFC connectivity						
Nonconverted>converted						
R DLPFC	9/8	968	38, 28, 46	6.51	23	0.007
Converted>nonconverted						
None						
	BA	Volume	x, y, z	t	df	p
(B) sgACC connectivity						
Nonconverted>converted						
L IPL/postcentral gyrus	40/2	896	-40, -30, 52	5.22	23	0.005
Converted>nonconverted						
None						
Nonconverted>control						
L IPL/postcentral gyrus	40/2	1128	-42, -30, 46	5.54	29	0.004

Peak coordinates ($x y z$) based on MNI brain.

t , peak t -value from the cluster; p , FDR-corrected cluster-level p -value.

BA, Brodmann area; DLPFC, dorsolateral prefrontal cortex; FDR, false discovery rate; IPL, inferior parietal lobule; MNI, Montreal Neurologic Institute; sgACC, subgenual anterior cingulate cortex; volume, cluster size in microliter.

to MDD) were included in the analysis or when sex was included as a covariate (Supplementary Data).

Classification of at-risk children and controls

The classification model based on connectivity data between the seeds and areas from the AAL atlas yielded 92% accuracy, 90% sensitivity, and 93% specificity (Fig. 4). Nine out of the 10 individuals who later developed depression were correctly classified. Fourteen out of the 15 nonconverted subjects were correctly classified. Features used in the prediction model and normalized attribute weights are listed in Table 3. Attribute weights represent the hyperplane separating the two classes. The absolute magnitudes of the weights represent the importance of each feature in classifying the data points: Features with higher weights are more relevant than lower weights in discriminating the two classes.

The parietal cluster that showed different sgACC connectivity between the converted and nonconverted groups (from Table 2) overlapped with the AAL parietal region that contributed to the classification model (Table 3): 77% of the left postcentral gyrus/IPL cluster derived from the group analysis lies within the AAL left postcentral gyrus region; 21% of the group analysis cluster lies within the AAL left inferior parietal region.

The model based on connectivity values between the seeds and areas in the HCP atlas yielded similar discrimination performance (96% accuracy, 100% sensitivity, and 93% specificity). Features used in the prediction are listed in Table 4. In contrast, the model based on baseline CBCL scores (Total, Internalizing, Externalizing, Anxiety/Depressed symptoms, and Affective Problem Scale) yielded only 64% accuracy with 40% sensitivity and 80% specificity. Only 4 out of the 10 converted subjects were correctly classified. Twelve out of the 15 nonconverted subjects were correctly classified.

Discussion

In this study, we investigated the potential of using rs-fMRI for early identification of high-risk children who are likely to develop MDD over the subsequent 3–4 years.

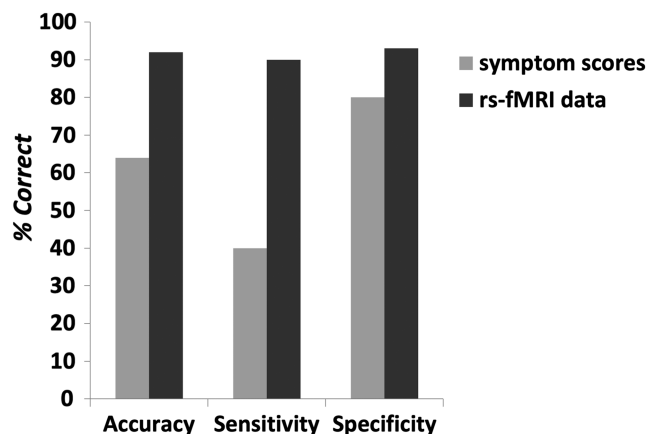


FIG. 4. Performance of the prediction models based on baseline rs-fMRI data from the AAL atlas (dark gray bars) or baseline symptom scores (light gray bars). AAL, Automated Anatomical Labeling; rs-fMRI, resting-state fMRI.

TABLE 3. LIST OF FEATURES (CONNECTIVITY VALUES BETWEEN SEEDS AND BRAIN AREAS FROM THE AUTOMATED ANATOMICAL LABELING ATLAS) USED IN THE SUPPORT VECTOR MACHINE PREDICTION MODEL ORDERED BY NORMALIZED ATTRIBUTE WEIGHTS FROM THE MODEL

Seed	AAL area	SVM attribute weight
DMN	L IFG (pars opercularis)	0.9906
R DLPFC	R Mid cingulum	0.8846
L Amygdala	R Hippocampus	−0.8647
R DLPFC	L Parahippocampal gyrus	0.8394
DMN	L Middle cingulate area	0.7858
sgACC	L Postcentral gyrus	0.783
L Amygdala	R Cerebellum lobule IV, V	−0.7769
DMN	L IPL	0.7289
sgACC	L Superior frontal gyrus	−0.6393
R DLPFC	L Superior parietal lobule	0.5375
DMN	R Hippocampus	−0.3475
R Amygdala	R Superior parietal lobule	0.1328
DMN	R Middle cingulate area	−0.106

AAL, Automated Anatomical Labeling; DMN, default mode network; SVM, support vector machine.

First, in regards to neurobiological risk, there were marked differences in intrinsic functional connectivity in the emotion regulation and cognitive control networks between previously never-depressed children with familial risk for MDD who either converted or did not convert to MDD. The children who later developed MDD, compared with the children who did not develop MDD, showed lower baseline bilateral DLPFC connectivity and lower baseline sgACC-IPL connectivity. Second, in regards to resilience, compared with the control group who had no familial risk for MDD, the nonconverted group exhibited higher baseline sgACC-IPL connectivity. Lastly, machine-learning models based on baseline resting-state connectivity in brain regions defined from two different atlases (independent from the clusters that exhibited

TABLE 4. LIST OF FEATURES (CONNECTIVITY VALUES BETWEEN SEEDS AND BRAIN AREAS FROM THE HUMAN CONNECTOME PROJECT ATLAS) USED IN THE SUPPORT VECTOR MACHINE PREDICTION MODEL, ORDERED BY NORMALIZED ATTRIBUTE WEIGHTS FROM THE MODEL

Seed	HCP atlas area	SVM attribute weight
sgACC	L Area 23d	1.285
DMN	R Area 5m ventral	1.0665
DMN	R Area PFcm	0.9983
L Amygdala	R PreSubiculum	−0.8381
LDLPFC	L Area 1	−0.8373
sgACC	L Area 2	0.7733
R Amygdala	L Area STGa	−0.7497
DMN	L Area 23c	0.6657
DMN	L Area 7PC	0.5974
R Amygdala	R Medial IntraParietal area	0.5053
DMN	L Area IFJa	0.4971
DMN	R Area 2	0.4719
DMN	L Area 8C	0.2409

HCP, Human Connectome Project.

group differences) accurately predicted the onset of MDD, with high sensitivity and specificity that was superior to a model based on baseline behavioral scores.

Risk for MDD onset

Reduced baseline connectivity between sgACC and a region in the frontoparietal control network (IPL) was observed in at-risk children who later developed MDD compared with those who did not develop MDD. We previously reported reduced baseline connectivity between sgACC and another frontoparietal network region (left DLPFC) in this same sample of at-risk children compared with control children (Chai et al., 2016). Altered sgACC connectivity has been linked with symptom severity scores in children and adolescents with MDD (Connolly et al., 2013; Gaffrey et al., 2010). Given these findings and the unique anatomical position of sgACC that connects to both limbic subcortical regions and cortical regions (Johansen-Berg et al., 2008), it is possible that the reduced coupling of sgACC and the cognitive control network in at-risk children contributes to dysfunction of emotion regulation, and it appears to place children at risk for onset of MDD.

Compared with at-risk children who did not develop MDD, connectivity within the cognitive control network—between left and right DLPFC—was reduced in the children who developed MDD 3–4 years later. A similar pattern of connectivity difference was found in these never-depressed children with familial risk for depression when they were contrasted to children without familial risk for depression: At baseline, these at-risk children showed lower connectivity within the frontal-parietal control network (Chai et al., 2016). Similar patterns of reduced connectivity in cognitive control regions have been observed in adults with MDD (Alexopoulos et al., 2012; Veer et al., 2010; Ye et al., 2012), and this reduced connectivity may contribute to difficulty in cognitive control and emotion regulation in patients (Gotlib and Hamilton, 2008). The present results suggest that weakened connectivity in cognitive control regions is present in the brain years before the onset of depression and greater weakness is a possible risk factor for the development of depression in offspring of depressed parents.

Resilience to depression

The group of at-risk children who did not develop MDD 3–4 years later had greater connectivity between sgACC and left IPL compared with both control children and at-risk children who later developed MDD. This suggests that elevated sgACC-IPL connectivity may be protective and represent a neuromarker for resilience to depression in children at familial risk for MDD. Our finding is consistent with another study that found greater limbic control network connectivity in resilient high-risk adolescents compared with high-risk adolescents who developed depression and low-risk control adolescents (Fischer et al., 2018). The sgACC and frontoparietal network are typically anticorrelated in healthy adults and children (Kelly et al., 2009; Margulies et al., 2007), but the resilient group in this study showed positive connectivity between these regions. These compensatory functional connectivity patterns in the emotion regulation network in at-risk children and adolescents may

represent resilience to depression, although the origin and development of such patterns are unknown.

Prediction of MDD onset

The machine-learning models based on baseline resting-state connectivity predicted the subset of at-risk children who later converted to depression with higher accuracy and sensitivity compared with the model based on baseline clinical CBCL scores alone. The resting-state connectivity that carried the most predictive power included connections within or between three important networks for depression: the emotion regulation network, the DMN, and the cognitive control network. Abnormal patterns of connectivity in these networks have been previously reported in adult (Ye et al., 2012) and pediatric (Gaffrey et al., 2010) MDD, as well as in never-depressed children at familial risk for depression (Chai et al., 2016; Clasen et al., 2014). Here, we demonstrated that using a relatively easy and reliable brain measure (rs-fMRI), it is possible to predict the onset of MDD in adolescents with high accuracy.

Among the features that carried the most predictive power in the AAL model, sgACC-postcentral gyrus connectivity overlapped with the group difference results: Connectivity between sgACC and a cluster in the postcentral gyrus/IPL was higher in the nonconverted than the converted group. We did not find other overlaps in the brain for baseline differences between converted and nonconverted groups versus the most predictive features in the machine-learning models. This could be because the atlas regions included in the machine-learning model were much larger than the clusters that were found in the direct group comparison, which represented the clusters with maximal differences between the groups. We used well-established atlas regions in the prediction model to avoid dependency on the group difference results and showed high prediction accuracy from atlas regions, which are more generalizable to new cases. It is also possible that our small sample size was not enough to detect significant group differences in some of the features that carried predictive power in the classification model.

Both strengths and limitations of this study can be noted. Strengths include prospective examination of connectivity in regions of interest believed to be associated with MDD for their potential to predict onset of MDD in adolescents, as well as state-of-the-art neuroimaging, diagnostic assessment, and data analytic methods. However, our study should be viewed in light of several limitations. The small sample size limited our power to detect group differences in this early pilot study. Nevertheless, this study provides preliminary evidence that intrinsic functional connectivity may reflect vulnerability for and resilience to depression. All testing procedures and data analyses were carried out with careful and rigorous methods. Our findings are largely consistent with results in adult and pediatric MDD patients and children with familial risk for MDD. Future studies with larger samples are needed to confirm the results. Participants had a higher than average mean IQ, so future studies will need to examine more representative samples. In addition, participants were not asked after the study whether they fell asleep during the scan. We communicated with the participants via the scanner intercom after each scan. All participants were alert and responding after the resting-

state scan. Although we did not specifically ask whether they fell asleep during part of the resting-state scan, we believe that sleepiness was unlikely since the resting-state scan was conducted in the beginning of the session, right after MPRAGE. Lastly, we restricted our sample to offspring at risk for depression. We chose these participants because we hypothesized that they would have an elevated rate of MDD emergence during adolescence, and indeed, consistent with the larger literature (Lieb et al., 2002; Williamson et al., 2004), more than a third of the participants did develop MDD. Studies using similar methods in large samples of children who do not have familial risk for depression will be needed to determine whether these predictors operate in the population in general or only in offspring at risk.

Psychosocial approaches to preventing onset of depression in adolescence have shown promise (Hetrick et al., 2016; Merry et al., 2012), including cognitive-behavioral interventions similar to those used to treat depression (Garmy et al., 2017; Perry et al., 2017; Rohde et al., 2018, 2014). Our findings suggest that reduced connectivity within the cognitive control network and connectivity between emotion/limbic regions and control regions may indicate susceptibility for MDD onset. Future research on cognitive-behavioral interventions targeting emotion regulation and cognitive risk factors for depression is needed to evaluate the effectiveness of such interventions in reducing the risk for MDD onset. If confirmed, our findings offer the exciting prospect of being able to use fMRI studies to identify asymptomatic children who are at elevated risk to develop MDD as adolescents, so that these youths can be targeted for preventive cognitive-behavioral interventions to reduce this risk.

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Disclaimer

This article was prepared while B.G.S. was employed at the Massachusetts General Hospital/Harvard Medical School. The opinions expressed in this article are the author's own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the U.S. government.

Author Disclosure Statement

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Supplementary Material

Supplementary Data
Supplementary Table S1

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