

Frontolimbic Network Topology Associated With Risk and Presence of Depression in Adolescents: A Study Using a Composite Risk Score in Brazil

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ABSTRACT

BACKGROUND: There have been significant challenges in understanding functional brain connectivity associated with adolescent depression, including the need for a more comprehensive approach to defining risk, the lack of representation of participants from low- and middle-income countries, and the need for network-based approaches to model connectivity. The current study aimed to address these challenges by examining resting-state functional connectivity of frontolimbic circuitry associated with the risk and presence of depression in adolescents in Brazil.

METHODS: Adolescents in Brazil ages 14 to 16 years were classified into low-risk, high-risk, and depressed groups using a clinical assessment and composite risk score that integrates 11 sociodemographic risk variables. After excluding participants with excessive head movement, resting-state functional magnetic resonance imaging data of 126 adolescents were analyzed. We compared group differences in frontolimbic network connectivity using region of interest-to-region of interest, graph theory, and seed-based connectivity analyses. Associations between self-reported depressive symptoms and brain connectivity were also explored.

RESULTS: Adolescents with depression showed greater dorsal anterior cingulate cortex (ACC) connectivity with the orbitofrontal cortex compared with the 2 risk groups and greater dorsal ACC global efficiency than the low-risk group. Adolescents with depression also showed reduced local efficiency and a lower clustering coefficient of the subgenual ACC compared with the 2 risk groups. The high-risk group also showed a lower subgenual ACC clustering coefficient relative to the low-risk group.

CONCLUSIONS: These findings highlight altered connectivity and topology of the ACC within frontolimbic circuitry as potential neural correlates and risk factors of developing depression in adolescents in Brazil. This study broadens our understanding of the neural connectivity associated with adolescent depression in a global context.

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Depression is the leading cause of disability among adolescents across the globe (1). Characterizing neurobiological risk factors and correlates of depression in adolescents could lead to improvements in preventing and treating adolescent depression. Prior research has identified several patterns of resting-state functional connectivity (rsFC) associated with the risk or presence of depression (2–9). However, a number of barriers to a comprehensive understanding of rsFC in adolescent depression remain, which if addressed could clarify our understanding of the neural correlates of risk and presence of depression in adolescents.

First, previous studies examining rsFC in relation to adolescent depression have used either a case-control approach (depressed vs. control) or a risk approach (high risk vs. low risk). Research is needed that combines these approaches to compare low-risk (LR) adolescents, high-risk (HR) adolescents, and adolescents with major depressive disorder (MDD) to distinguish between potential neural risk factors and neural

correlates of depression. Second, studies with a risk approach have generally relied on parental history of depression as the risk factor (9–11). However, adolescents without parental history of depression can be highly heterogeneous (12), and some of them may have a high risk for depression based on other factors (e.g., social isolation). Moreover, parental history of depression can be accurately reported only by interviewing parents. Examining risk factors that can be directly reported by the adolescent could have future novel applications for identifying and preventing depression risk in a range of settings. A more comprehensive and accessible risk assessment is needed. Third, the majority of rsFC studies on adolescent depression have used a seed-based approach, restricting our knowledge to the connectivity of particular brain regions. An alternative and more comprehensive approach is a network-based approach (13) that examines strength of connectivity or organizational patterns (e.g., number of connections, efficiency of connections) across multiple regions within a network of interest. Only a few

studies (14,15) have applied network-based approaches targeting the whole brain or the reward-related network. More studies with a network-based approach targeting the frontolimbic network, a network important for adolescent depression and affective development, are needed. Finally, only 38% of rsFC studies on adolescent depression were conducted in low- and middle-income countries (LMIC), and the majority of studies in LMIC (i.e., 13 out of 15) were from China (16). Considering that 89% of all youth in the world live in LMIC (16), studies in LMIC are urgently needed to address adolescent depression research disparities across the globe.

To overcome these barriers, the current study compared rsFC of 39 LR adolescents, 45 HR adolescents, and 42 adolescents with MDD recruited in Brazil, which is classified as a middle-income country according to the World Bank (17). To address the limitations of prior research that used parental history of depression to determine depression risk, adolescents in this study were classified using a clinical assessment and an empirically validated multivariable prognostic model (18) that integrated 11 sociodemographic variables (e.g., childhood maltreatment, social isolation), which has been shown to predict depression risk across a variety of countries, including Brazil, Nepal, the United Kingdom, and Nigeria (18–20). Moreover, to better understand aberrant functional neural architecture in high-risk and depressed adolescents, in addition to seed-based connectivity analysis, this study employed a network-based approach targeting frontolimbic circuitry implicated in both adolescent affective brain development (21,22) and adolescent depression (23–25).

The connectivity within the frontolimbic circuit changes significantly during adolescence (26,27), and changing interactions between the amygdala, striatum, and prefrontal cortex (PFC) are theorized to underlie the development of affective functions (21,22), such as emotion regulation (28), self-conscious emotion (29), and cognitive control to emotional cues (30). Moreover, frontolimbic connectivity was found to be affected by adverse early experiences (31), such as maternal deprivation (32), institutional care (33,34), and trauma exposure (35). This suggests that abnormal frontolimbic connectivity and development may be significantly associated with risk for and development of adolescent depression (23,25). Indeed, the majority of adolescent depression rsFC studies have focused on the amygdala (3,5,35–38), anterior cingulate cortex (ACC) (4,8,39–41), PFC (10,42), striatal regions (43,44), and hippocampus (40,45,46) and found their altered connectivity with other brain regions in high-risk and depressed adolescents (e.g., decreased amygdala–medial PFC [mPFC]/ACC connectivity, increased ACC–ventromedial PFC connectivity). Interestingly, a study (24) using predictive modeling found that rsFC within the nodes of frontolimbic circuitry, but not whole-brain connectivity, predicted both current and future depressive symptoms measured after 18 months, highlighting its high relevance to adolescent depression.

The current study aimed to examine the strength and topology of frontolimbic network connectivity associated with the risk and presence of depression in Brazilian adolescents. Given that the above-mentioned study (24) examining rsFC of frontolimbic nodes in adolescents observed that positive dorsal ACC (dACC) connectivity with other regions exhibited the greatest contribution to predicting depressive symptoms, we

hypothesized that adolescents with high risk for depression and depressed adolescents in our sample would show stronger (i.e., greater rsFC), more efficient (i.e., greater global efficiency, lower average path length), and a greater number of connections (i.e., greater degree) of the same dACC node compared with the LR adolescents. To test this hypothesis, we used region of interest (ROI)–to–ROI analysis and graph theory analysis. Owing to the nascent literature that has used network-based approaches for frontolimbic rsFC, we also explored group differences in connectivity strength and topological properties of all the regions within the frontolimbic network. We additionally conducted amygdala seed-based connectivity analysis to see whether the most well-established connectivity pattern in the depression literature [i.e., reduced amygdala–mPFC/ACC connectivity identified using a seed-based approach (5,6,8,9,38,46–49)] would be replicated in our sample of Brazilian adolescents. We hypothesized that the HR and MDD groups would show reduced amygdala–mPFC/ACC connectivity compared with the LR group. Besides examining the association of connectivity with risk group status and clinical depression, we also explored the association of frontolimbic connectivity with subjectively experienced depressive symptoms using a self-reported, continuous measure, which allowed us to examine associations with depressive symptoms spanning the subclinical through clinical range.

METHODS AND MATERIALS

Participants

Participants were recruited for the IDEA-RiSCo (Identifying Depression Early in Adolescence Risk Stratified Cohort). Full details regarding the procedures of recruitment, screening, exclusion, clinical assessment, and questionnaires assessing sociodemographic variables are provided in the published protocol for the study (50). Results of analyses with task-based functional magnetic resonance imaging (MRI) data using this cohort have been previously reported (51).

For sampling adolescents who met the criteria of LR, HR, and MDD groups, 7720 adolescents 14 to 16 years of age were screened from June 2018 to November 2019 in Porto Alegre, Brazil. To stratify risk groups, we used a multivariable prognostic model, the IDEA Risk Score (IDEA-RS) (18). This model was developed by our group using data from the Pelotas 1993 Cohort Study (52) and was recently validated in multiple countries (18–20). This model integrates 11 sociodemographic variables (i.e., skin color, biological sex, school failure, drug use, fight involvement, ran away from home, social isolation, childhood maltreatment, poor relationship with mother, father, and between parents) and generates the probability of presenting with a unipolar depressive episode in 3 years.

The LR group met the criteria of having a risk score equal to or below the 20th percentile of the Pelotas 1993 cohort, and the HR and MDD groups met the criteria of having a risk score equal to or above the 90th percentile of the Pelotas 1993 cohort. We required the MDD group to have high-risk sociodemographic profiles (an IDEA-RS equal to or above the 90th percentile) to attribute any neural differences between the HR and MDD groups only to the presence of depression.

Presence of a current MDD episode (in the MDD group) or absence of a current or past MDD episode (in the LR and HR

groups) was determined with the Brazilian Portuguese version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (53), conducted by a child psychiatrist. Self-reported instruments were administered, including the Brazilian Portuguese version of the adolescent-reported Mood and Feelings Questionnaire (MFQ-C) (54), measuring depressive symptoms. IQ was assessed using the Brazilian Portuguese version of the Wechsler Abbreviated Scale of Intelligence (55).

To make our sample more homogeneous, we included only participants without long-term or current use of psychotropic medications. Percentages of participants with lifetime comorbid diagnoses are reported in the [Supplement](#).

After screening and clinical assessment, 150 participants who met inclusion criteria and did not meet exclusion criteria [see inclusion and exclusion criteria in the published protocol (50)] underwent MRI scanning from August 2018 to December 2019. Written informed assent and consent were obtained from adolescents and their caregivers, respectively, after the procedures had been fully explained. After exclusion of 24 participants with excessive head movement (i.e., greater than 20% volumes were censored), the sample size was 126 (LR group: $n = 39$; HR group: $n = 45$; MDD group: $n = 42$). This study was approved by the Brazilian National Ethics in Research Commission.

Data Acquisition, Preprocessing, and Denoising

All images were acquired on a 3T Ingenia (Philips Healthcare) MRI scanner. Structural MRI images were acquired before acquiring blood oxygen level–dependent functional MRI images for resting-state connectivity. Full details regarding the data acquisition parameters, preprocessing, and denoising are reported in the [Supplement](#). The data were analyzed using CONN toolbox 18b. We confirmed that data from all participants had good signal coverage (i.e., signal coverage over 98% of voxels within each of our ROIs) (see [Supplement](#) for a specific method to inspect signal loss).

ROI-to-ROI Analysis

We estimated rsFC between all pairs of 47 ROIs ([Figure 1](#); see [Table S1](#) for the coordinates of the ROIs), which consisted of

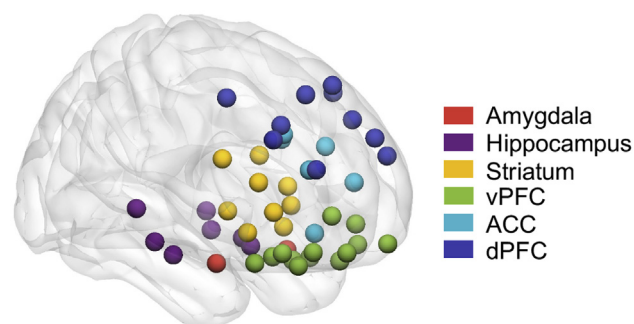


Figure 1. The 47 nodes of frontolimbic circuitry used for region of interest–region of interest and graph theory analysis. We adopted 40 nodes from a previous study (26) that defined these nodes as an adolescent depression circuit. We added 7 nodes corresponding to hippocampus, ACC, anterior cingulate cortex; dPFC, dorsal prefrontal cortex; vPFC, ventral PFC.

the frontolimbic circuitry or adolescent-depression network, as defined in a previous study (24), which selected the bilateral amygdala, subregions of the striatum, the ACC, and the PFC from a functional brain atlas with 268 nodes (56). We added 7 ROIs corresponding to the hippocampus from the same functional brain atlas given that the hippocampus is also a key frontolimbic region associated with early life stress (31) and depression in adolescents (40,45,46). Pearson's correlation coefficients were normalized through Fisher's z-transformation.

An analysis of covariance (ANCOVA) was conducted to examine group differences (LR vs. HR vs. MDD) in dACC (center of mass [mm]: 7, 21, 32) connectivity with all other nodes, controlling for age, sex, and head movement (i.e., mean framewise displacement). False discovery rate (FDR) correction was applied to correct for the number of target nodes (i.e., 46). Next, we explored group differences in connectivity in any pair of 47 frontolimbic nodes using ANCOVA. We combined the connection-level threshold (uncorrected $p < .001$) and network-based statistics FDR-corrected p (p_{FDR}) (by intensity) $< .05$ (two-sided). Any pattern of connectivity that showed a significant group difference was submitted to a pairwise comparison t test (Tukey corrected) to specify the pattern of group difference. With the same statistical threshold, we conducted multiple regression analyses with the independent variable of log-transformed MFQ-C (self-reported depressive symptoms) and covariates of age, sex, and head movement.

Graph Theory Analysis

To identify group differences in the topological properties of the frontolimbic circuit, which consisted of 47 nodes ([Figure 1](#)), we used CONN's automated protocol to construct individuals' graph theory measures. This protocol thresholded each participant's 47×47 correlation matrix to generate an adjacency matrix. We adopted cost thresholding for constructing the adjacency matrix. To illustrate, if the cost value (i.e., K) is 0.15, only the pairs with the highest 15% of the correlation coefficient values have a value of 1, and all other pairs have a value of 0. Based on 100 simulations that generated 4 unique optimal cost values (i.e., 0.1198, 0.12997, 0.14015, 0.14986) (see [Figure S1](#) for details), we defined our graph theory measures by averaging graph theory measures obtained using each of the 4 optimal values. We report results from both one-sided cost thresholding that considers only positive correlations when defining the highest $K\%$ connections and two-sided cost thresholding that considers both positive and negative correlations when defining the highest $K\%$ connections.

We first conducted an ANCOVA that examines the group difference of 6 graph theoretical measures of the dACC node: global efficiency, local efficiency, clustering coefficient, betweenness centrality, average path length, and degree (see [Supplement](#) for definitions). Age, sex, and head movement were entered as covariates. Next, we explored the group difference of graph theory measures of all other frontolimbic nodes. To correct for the number of nodes, we adopted a statistical threshold of two-sided $p_{FDR} < .05$. To compare group differences in the integrated and segregated nature of the frontolimbic network as a whole, we conducted ANCOVA

on the network-level global efficiency, local efficiency, and clustering coefficient (see [Supplement](#) for the calculation and choice of measures). Any measures that showed a significant group difference were submitted to a pairwise comparison *t* test (Tukey corrected) to specify the pattern of group difference. We conducted multiple regression analyses with the independent variable of log-transformed MFQ-C and covariates of age, sex, and head movement with the same statistical threshold to examine associations with continuous depression symptoms. To facilitate interpretation of the results, we identified the anatomical label of the nodes with significant results based on the Automated Anatomical Labeling atlas 3 (57).

Seed-Based Connectivity Analysis

Individuals' rsFC maps with the seed regions of the left and right amygdala from the Automated Anatomical Labeling atlas 3 were estimated. We first conducted an ANCOVA with the search volume of an mPFC/ACC mask. The mPFC/ACC mask was created by combining medial orbitofrontal regions, rectus, superior medial prefrontal regions, and ACC of the Automated Anatomical Labeling atlas 3. We conducted a small-volume correction for the search region with familywise error rate correction provided in SPM12. The α value was divided by 2 to correct for 2 tests for left and right amygdala seeds. Then, whole-brain results were examined with a whole-brain $p_{FDR} < .025$ threshold (two-sided). To explore the association between continuous self-reported depressive symptoms and amygdala connectivity with mPFC/ACC and whole brain, we ran multiple

regression analyses with the independent variable of log-transformed MFQ-C and covariates of age, sex, and head movement. The same statistical threshold was used as ANCOVA.

Outlier Treatment

After identifying any significant result, we identified outliers, defined as 3 standard deviations from the mean of the risk group that each participant belonged to (for ANCOVA) or the mean of all participants (for the regression analysis). We planned to report only the results that remained significant after excluding the outliers (see [Table S2](#) for the number of excluded participants).

RESULTS

Demographic and Clinical Data

Demographic and clinical data are presented in [Table 1](#).

ROI-to-ROI Connectivity Within Frontolimbic Circuitry

We found that dACC connectivity with the posterior orbitofrontal cortex (OFC) (center of mass: 27, 20, -21) showed a significant group difference ($F_{2,119} = 8.98, p_{FDR} = .01$), with the effect driven by greater connectivity of the MDD group compared with the LR group ($t_{119} = 3.86, p < .001$) and HR group ($t_{119} = 3.39, p = .003$) ([Figure 2](#)). Effects of the exploratory analysis with other nodes were not significant.

Table 1. Demographic, Clinical, and Head Motion Data

Categorical Variables	LR Group (n = 39)	HR Group (n = 45)	MDD Group (n = 42)	Analysis	
	n (%)	n (%)	n (%)	χ^2	p
Sex				$\chi^2_{2} = 0.11$.95
Females	19 (48.72%)	23 (51.11%)	22 (52.38%)		
Males	20 (51.28%)	22 (48.89%)	20 (47.62%)		
Skin Color/Race ^a				$\chi^2_{8} = 5.41$.71
Black	7 (17.95%)	10 (22.22%)	8 (19.05%)		
Brown	7 (17.95%)	12 (26.67%)	7 (16.67%)		
Native Brazilian	1 (2.56%)	2 (4.44%)	3 (7.14%)		
White	24 (61.54%)	21 (46.67%)	23 (54.76%)		
Yellow	0 (0%)	0 (0%)	1 (2.38%)		
Continuous Variables	Mean (SD)	Mean (SD)	Mean (SD)	$F_{2,123}$	p
Age	15.44 (0.74)	15.82 (0.82)	15.81 (0.79)	3.03	.052
WASI IQ	90.64 (10.64)	88.09 (9.07)	88.81 (10.14)	0.72	.49
IDEA-RS ^b , %	1.30 (0.33)	8.28 (4.54)	9.59 (5.81)	42.62	< .001 ^c
MFQ-C ^d	6.44 (4.71)	12.73 (8.07)	41.90 (11.17)	206.75	< .001 ^e
Censored Number of Volumes	12.44 (13.01)	13.93 (10.23)	14.31 (10.41)	0.31	.73
Mean Framework Displacement	0.19 (0.05)	0.20 (0.07)	0.19 (0.05)	0.32	.73

HR, high-risk; IDEA-RS, Identifying Depression Early in Adolescence Risk Score; LR, low-risk; MDD, major depressive disorder; MFQ-C, Mood and Feelings Questionnaire-Child; WASI, Wechsler Abbreviated Scale of Intelligence.

^aCategories were based on the Brazilian national census classification of race.

^bIDEA-RS was developed with data from the Pelotas 1993 Cohort Study. Using 11 sociodemographic variables measured at age 15, the model predicted risk of a current unipolar depressive episode at age 18 years [see (18,19) for more details].

^cThe effect was driven by the difference in LR < HR ($t_{123} = 7.37, p < .001$) and LR < MDD ($t_{123} = 8.61, p < .001$).

^dBrazilian Portuguese version of the adolescent-reported MFQ-C.

^eThe effect was driven by the difference in LR < HR ($t_{123} = 3.40, p = .003$), LR < MDD ($t_{123} = 18.83, p < .001$), and HR < MDD ($t_{123} = 16.05, p < .001$).

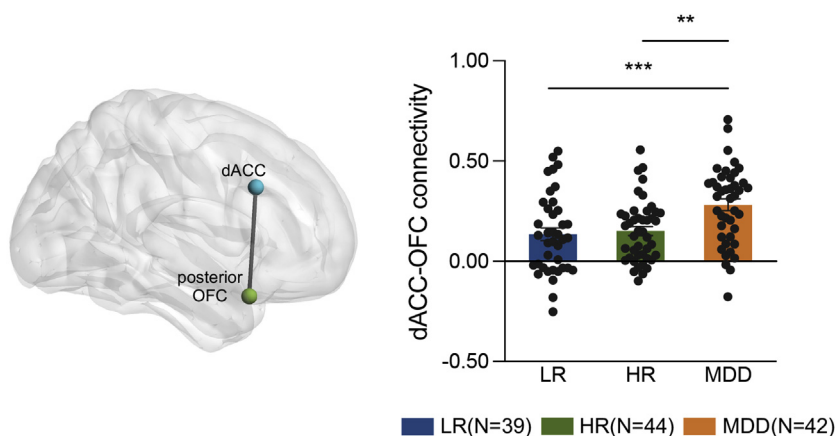


Figure 2. The significant group difference in connectivity between dorsal anterior cingulate cortex (dACC) and posterior orbitofrontal cortex (OFC). The left panel describes the location of dACC (blue) and posterior OFC (green), of which connectivity strength showed a significant group difference. The right panel describes the specific pattern of group differences in dACC-OFC connectivity. Error bar indicates standard error. $**p \leq .01$; $***p \leq .001$. HR, high-risk; LR, low-risk; MDD, major depressive disorder.

Graph Theory Measures Within Frontolimbic Circuitry

In the analysis with one-sided cost thresholding, the ANCOVA targeting dACC revealed a significant group difference in global efficiency driven by greater global efficiency of the MDD group compared with the LR group (Figure 3). In the analysis with two-sided cost thresholding, the analysis exploring all other frontolimbic nodes found significant group differences in local efficiency and clustering coefficient of left subgenual ACC (sgACC). For sgACC local efficiency, the group difference was driven by reduced local efficiency in the MDD group compared with the 2 risk groups. For the sgACC clustering coefficient, the group difference was driven by a decreasing pattern in the order of LR, HR, and MDD groups (Figure 4). The statistical values and center of mass of each node are presented in Table 2. Note that the results of the local efficiency and clustering coefficient of the sgACC could not include 18 participants because they did not have a neighboring subgraph, and 3 participants were excluded as outliers from the LE analysis

(Table S2). There was no difference between included and excluded participants in clinical status and risk score (Tables S3 and S4).

Multiple regression analysis with MFQ-C showed that greater self-reported depressive symptoms are associated with greater dACC global efficiency ($t_{120} = 2.23, p = .03$) and degree ($t_{121} = 2.24, p = .03$) when using one-sided cost thresholding and reduced sgACC local efficiency ($t_{100} = -4.01, p_{FDR} = .005$) and clustering coefficient ($t_{103} = -3.89, p_{FDR} = .008$) when using two-sided cost thresholding (Figure 5). Network-level global efficiency, local efficiency, and clustering coefficient did not show significant group differences or associations with self-reported depressive symptoms.

Amygdala Seed-Based Connectivity

Amygdala connectivity with the regions within mPFC/ACC or the whole brain did not show group differences or associations with MFQ-C.

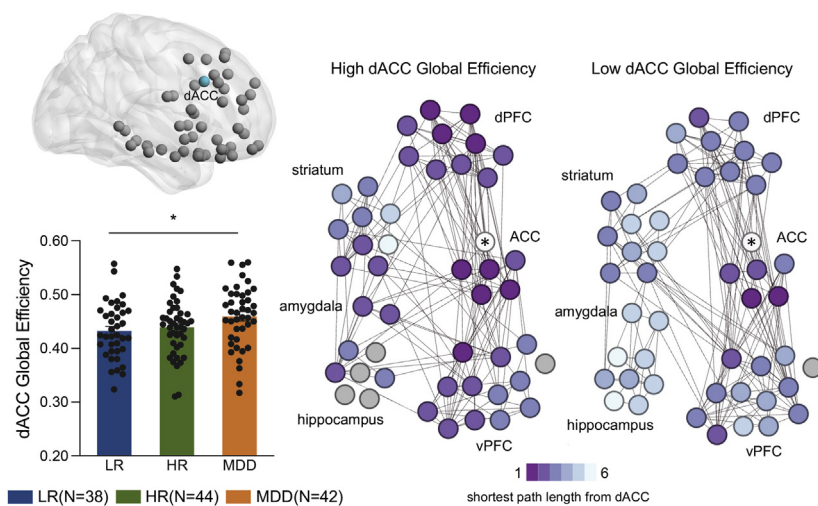


Figure 3. The significant group difference in dorsal anterior cingulate cortex (dACC) global efficiency. The left top panel describes the location of dACC (blue), of which global efficiency showed a significant group difference, and other nodes (gray) in the frontolimbic circuit. The left bottom panel describes the specific pattern of group differences in dACC global efficiency. Error bar indicates standard error. The right panel illustrates the high and low global efficiency of dACC. The data of participants with the highest and lowest dACC global efficiency were used. The graphs were generated using one of the optimal cost values (i.e., 0.14986). Circles and lines indicate nodes and edges, respectively. The circle with an asterisk indicates the dACC node. The brightness of nodes represents the shortest path length from dACC (a darker circle means shorter path length, and a lighter circle means longer path length). A participant with high dACC global efficiency has a greater number of dark circles, while a participant with low dACC global efficiency has a greater number of light circles. $*p \leq .05$. dPFC, dorsal prefrontal cortex; HR, high-risk; LR, low-risk; MDD, major depressive disorder; vPFC, ventral PFC.

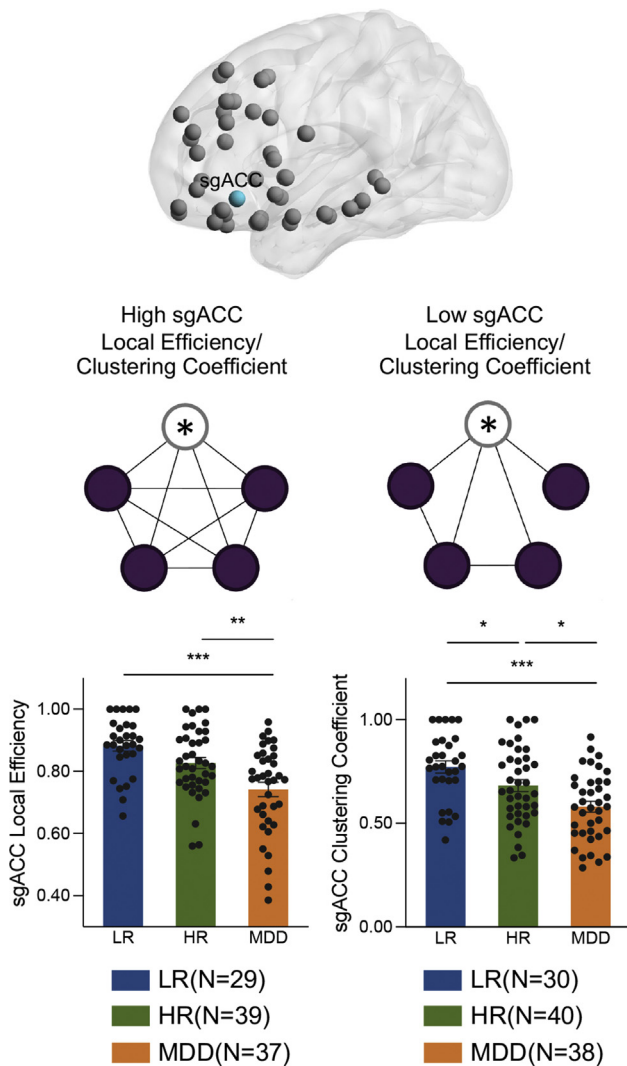


Figure 4. The significant group difference in subgenual anterior cingulate cortex (sgACC) local efficiency and clustering coefficient. The top panel describes the location of sgACC (blue), of which local efficiency and clustering coefficient showed significant group differences, and other nodes (gray) in the frontolimbic circuitry. The middle panel illustrates the high and low local efficiency and clustering coefficient of sgACC. We used data of participants with the highest and lowest local efficiency and clustering coefficient among the participants who had 4 direct connections originating from sgACC. The graphs were generated using one of the optimal cost values (i.e., 0.14986). Circles and lines indicate nodes and edges, respectively. The circle with an asterisk indicates the sgACC node. The subgraph of a participant with the highest local efficiency and clustering coefficient shows that all the nodes in the subgraph are connected to each other, while the subgraph of a participant with the lowest local efficiency and clustering coefficient shows that only 2 connections are present between the nodes other than sgACC. The left bottom panel describes the specific pattern of group differences in sgACC local efficiency and clustering coefficient. The black dot indicates individuals' data, and the error bar indicates standard error. * $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$. HR, high-risk; LR, low-risk; MDD, major depressive disorder.

DISCUSSION

The current study investigated how frontolimbic network connectivity is associated with the risk and presence of

depression in Brazilian adolescents stratified using 11 sociodemographic variables and clinical assessment. We found that the MDD group showed greater dACC-OFC connectivity compared with the 2 risk groups and greater dACC global efficiency compared with the LR group. The MDD group showed reduced sgACC local efficiency and a lower clustering coefficient than the 2 risk groups, and the HR group showed a lower sgACC clustering coefficient than the LR group. Adolescents with greater self-reported depressive symptoms showed greater dACC global efficiency, greater dACC degree, reduced sgACC local efficiency, and a lower sgACC clustering coefficient. This study indicates that the risk and presence of adolescent depression in Brazil is associated with altered ACC connectivity patterns within frontolimbic circuitry.

We found several connectivity patterns of frontolimbic circuitry associated with the presence of depression, which supports the theory suggesting the critical role of interactions of the regions within the frontolimbic circuit in adolescent affective development (21,22) and depression (23–25). Interestingly, consistent with our hypothesis based on the recent discovery showing that dACC connectivity to other frontolimbic regions has a critical role in predicting depressive symptoms (24), we found that adolescents with MDD showed greater dACC-OFC connectivity compared with adolescents in the other 2 groups and that they showed greater dACC global efficiency compared with adolescents in the LR group. This result indicates that greater and more efficient dACC connectivity may be a neural correlate or outcome of the development of depression in adolescents.

In addition to the recent study by Jin *et al.* (24), multiple studies have reported abnormal dACC connectivity in depressed adolescents. Two studies (14,58) showed heightened degree and efficiency of ACC in depressed adolescents in terms of connectivity with whole-brain regions, although the ACC was not divided into its subregions in these studies. Studies with a seed-based approach have also demonstrated that depressed adolescents showed heightened dACC rsFC with frontal (7) and striatal (43) regions and that depressive symptoms were associated with greater dACC rsFC with perigenual ACC (8). Based on the functions of dACC in salience detection (59) and action selection based on reward contingency (60), we speculate that heightened resting-state global efficiency of dACC in depressed adolescents may be associated with extensive transfer of salience signals detected from negative and self-relevant information or selecting avoidance behavior by weighting expected cost and de-weighting expected benefit of normally rewarding events (e.g., social activities). As the prominent role of OFC is value updating (61), high dACC-OFC connectivity of depressed adolescents could be related to increased propensity to update the value of an object or behavior when it is associated with an outcome with high saliency, such as an unexpected or threatening experience. It should be noted that, in contrast to the dACC-OFC connectivity effect, there was no difference in dACC global efficiency between high-risk and depressed adolescents, which suggests that the high dACC global efficiency could not be attributed solely to the diagnosis of depression, but rather the combination of high-risk profiles and the clinical diagnosis.

Table 2. Statistical Values for Analysis of Covariance of Graph Theory Measures

Graph Theory Measures	Node (CoM)	F Statistics	Pairwise Comparison Statistics
Global Efficiency	Right dACC (7, 21, 32)	$F_{2,118} = 3.34, p = .039$	LR < MDD: $t_{118} = 2.419, p = .045$ HR < MDD: $t_{118} = 1.951, p = .129$ LR < HR: $t_{118} = 0.575, p = .834$
Local Efficiency	Left sgACC (-5, 29, -10)	$F_{2,99} = 11.6, p_{FDR} = .001$	LR > MDD: $t_{99} = 4.71, p < .001$ HR > MDD: $t_{99} = 3.07, p = .008$ LR > HR: $t_{99} = 1.93, p = .135$
Clustering Coefficient	Left sgACC (-5, 29, -10)	$F_{2,102} = 11.47, p_{FDR} = .002$	LR > MDD: $t_{102} = 4.77, p < .001$ HR > MDD: $t_{102} = 2.61, p = .028$ LR > HR: $t_{102} = 2.41, p = .047$

CoM, center of mass; dACC, dorsal anterior cingulate cortex; FDR, false discovery rate; HR, high-risk; LR, low-risk; MDD, major depressive disorder; sgACC, subgenual ACC.

Adolescents with MDD also showed reduced sgACC local efficiency and clustering coefficient compared with adolescents in the LR and HR groups. The sgACC has been a major target of depression treatment through deep brain stimulation (62), as it is consistently implicated in depression, potentially owing to its critical role in affective processing, such as reappraising visceral signals (63), sustaining physiological arousal during anticipation of reward (64), and self-reported

distress after a negative experience such as social exclusion (65). Studies have documented that adolescents with MDD showed reduced sgACC functional connectivity with distributed frontal cortical regions (39,66), and adolescents with greater depressive symptoms and more severe anhedonia showed reduced sgACC functional connectivity with mPFC (41) and nucleus accumbens (43), respectively. Our results extend the finding of major disruption of sgACC connectivity in

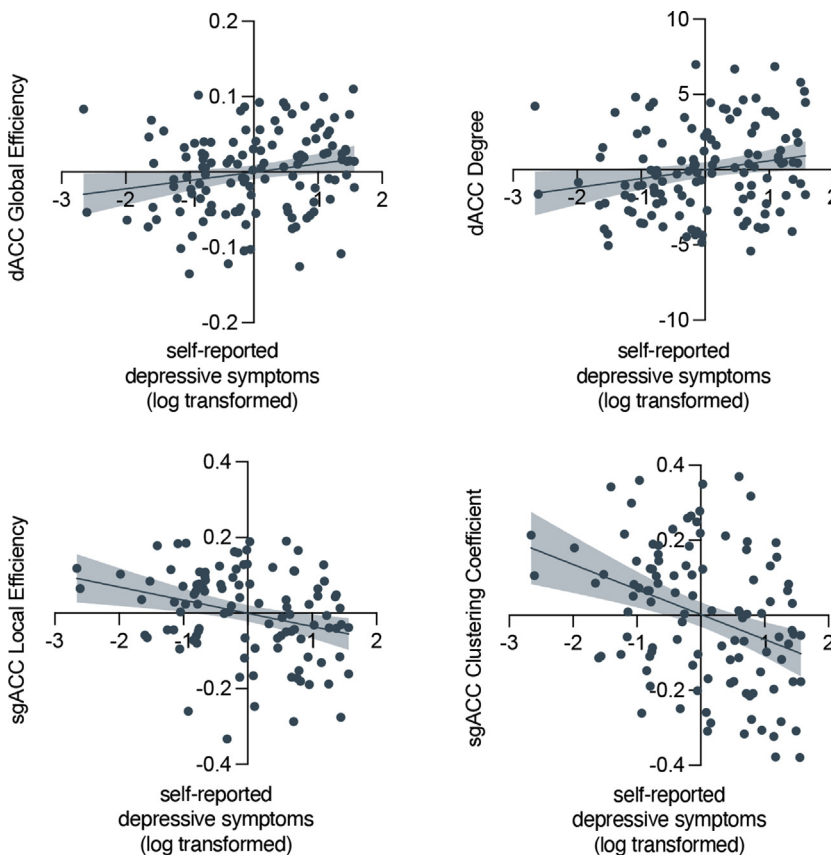


Figure 5. The association between self-reported depressive symptoms and dorsal anterior cingulate cortex (dACC) and subgenual ACC (sgACC) graph theory measures. The top panels are the partial regression plots that describe the positive association between self-reported depressive symptoms and dACC global efficiency and degree, controlling for age, sex, and head movement (i.e., mean framewise displacement). The bottom panels are the partial regression plots that describe the negative association between self-reported depressive symptoms and sgACC local efficiency and clustering coefficient, controlling for age, sex, and head movement (i.e., mean framewise displacement). The shaded area represents the 95% confidence interval.

adolescent depression by demonstrating the reduced inter-connectedness of its neighboring regions. Importantly, we also observed a reduced sgACC clustering coefficient but not local efficiency in the HR group compared with the LR group. This result indicates that while both a reduced number of direct connections and inefficient connections among the neighboring regions of the sgACC are neural correlates or outcomes of depression, only a reduced number of direct connections serves as a potential risk factor for developing depression.

It is important to note that the observed abnormal efficiency of dACC and sgACC in depressed adolescents supports the recent proposal (67,68) suggesting that ACC connectivity is key for healthy behavioral development in multiple domains (e.g., relationships, achievement) owing to its hublike function of integrating multimodal inputs (e.g., social, cognitive, and visceral) to guide adaptive self-regulation. Interestingly, the analysis with self-reported depressive symptoms mirrored the findings from the group analysis, with an addition of greater number of edges originating from dACC (i.e., degree), suggesting that abnormal ACC topological properties are related not only to clinical diagnosis of depression but also to subjective experience of depressive symptoms across the sub-clinical to clinical range.

Contrary to our expectation, there was no group difference in amygdala-mPFC/ACC connectivity, which has consistently been implicated in depression in adolescents and adults in high-income countries (48,49). It should be noted that we did find in another article using this sample that higher depressive symptoms were associated with decreased amygdala-mPFC connectivity during a face-matching task (51), suggesting that this association may become more apparent when connectivity is elicited by a stimulus, such as a threatening face.

This study has several limitations. First, this study is cross-sectional. A longitudinal study that examines the intraindividual change in frontolimbic network topology before and after developing depression is needed to understand the timing of changes in topology in relation to developing depression. Second, although the IDEA-RS provides a more comprehensive approach to measuring depression risk, it did not include parental history of depression, as this cannot be assessed accurately through adolescent self-report. A future study is needed to systematically compare the IDEA-RS and parental history of depression to determine the advantages and disadvantages of the 2 approaches for understanding neural correlates of depression risk. Note that a study testing the predictive validity of the IDEA-RS within a different Brazilian sample found that the risk score improved prediction of depression risk above and beyond family history (18), suggesting that it may capture risk not captured by family history. Third, we did not examine whether the three topological properties altered in adolescents with MDD were associated with different symptom dimensions (e.g., decision-making ability, rumination, anhedonia). A future study that examines specific depression symptom dimensions would have implications for personalized treatment. Fourth, we did not collect a field map and did not apply distortion correction to the images, so results and/or lack of results for regions susceptible to distortion, such as the OFC, should be interpreted with caution.

In conclusion, with an underrepresented and extensively phenotyped Brazilian adolescent sample, we found that aberrant connectivity of the ACC in frontolimbic circuitry may be involved in risk for and the presence of depression in adolescence. The present study provides the first evidence to our knowledge that high-risk adolescents and adolescents with clinical depression show altered topology of the frontolimbic network implicated in adolescent affective brain development and depression. These results advance our knowledge on the atypical neural architecture of adolescents with depression and depression risk, specifically in Brazil, and will ultimately contribute to the prevention and treatment of adolescent depression across the globe.

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LY had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. LY, VM, CK, and JRS were responsible for study concept and design. All authors were responsible for acquisition, analysis, and interpretation of data. LY drafted the original manuscript. All authors critically revised the manuscript for important intellectual content. LY performed statistical analysis. LAR, VM, CK, and JRS obtained funding.

The sociodemographic and self-reported measures were used and reported in another article (50) that detailed the protocol for the larger IDEA-RiSCo study. A subset of resting-state functional MRI data (i.e., 29 adolescents in the MDD group) was used and reported in another article (69), which was a preliminary study that examined the feasibility of MRI research in adolescents in Brazil. Task-based functional MRI data and sociodemographic and self-reported measures from this cohort of participants have been reported in another article (51).

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REFERENCES

- Gore FM, Bloem PJ, Patton GC, Ferguson J, Joseph V, Coffey C, *et al.* (2011): Global burden of disease in young people aged 10–24 years: A systematic analysis. *Lancet* 377:2093–2102.
- Toenders YJ, van Velzen LS, Heideman IZ, Harrison BJ, Davey CG, Schmaal L (2019): Neuroimaging predictors of onset and course of depression in childhood and adolescence: A systematic review of longitudinal studies. *Dev Cogn Neurosci* 39:100700.
- Davey C, Whittle S, Harrison B, Simmons J, Byrne M, Schwartz O, *et al.* (2015): Functional brain-imaging correlates of negative affectivity and the onset of first-episode depression. *Psychol Med* 45:1001–1009.
- Connolly CG, Wu J, Ho TC, Hoeft F, Wolkowitz O, Eisendrath S, *et al.* (2013): Resting-state functional connectivity of subgenual anterior cingulate cortex in depressed adolescents. *Biol Psychiatry* 74:898–907.
- Connolly CG, Ho TC, Blom EH, LeWinn KZ, Sacchet MD, Tymofiyeva O, *et al.* (2017): Resting-state functional connectivity of the amygdala and longitudinal changes in depression severity in adolescent depression. *J Affect Disord* 207:86–94.
- Pannekoek JN, Van Der Werff S, Meens PH, van den Bulk BG, Jolles DD, Veer IM, *et al.* (2014): Aberrant resting-state functional connectivity in limbic and salience networks in treatment-naïve clinically depressed adolescents. *J Child Psychol Psychiatry* 55:1317–1327.
- Rzepa E, McCabe C (2018): Anhedonia and depression severity dissociated by dmPFC resting-state functional connectivity in adolescents. *J Psychopharmacol* 32:1067–1074.
- Rzepa E, McCabe C (2016): Decreased anticipated pleasure correlates with increased salience network resting state functional connectivity in adolescents with depressive symptomatology. *J Psychiatr Res* 82:40–47.
- Fischer AS, Camacho MC, Ho TC, Whitfield-Gabrieli S, Gotlib IH (2018): Neural markers of resilience in adolescent females at familial risk for major depressive disorder. *JAMA Psychiatry* 75:493–502.
- Chai XJ, Hirshfeld-Becker D, Biederman J, Uchida M, Doehrmann O, Leonard JA, *et al.* (2016): Altered intrinsic functional brain architecture in children at familial risk of major depression. *Biol Psychiatry* 80:849–858.
- Clasen PC, Beevers CG, Mumford JA, Schnyer DM (2014): Cognitive control network connectivity in adolescent women with and without a parental history of depression. *Dev Cogn Neurosci* 7:13–22.
- Feczko E, Miranda-Dominguez O, Marr M, Graham AM, Nigg JT, Fair DA (2019): The heterogeneity problem: Approaches to identify psychiatric subtypes. *Trends Cogn Sci* 23:584–601.
- Ho TC, Dennis EL, Thompson PM, Gotlib IH (2018): Network-based approaches to examining stress in the adolescent brain. *Neurobiol Stress* 8:147–157.
- Wu B, Li X, Zhou J, Zhang M, Long Q (2020): Altered whole-brain functional networks in drug-naïve, first-episode adolescents with major depression disorder. *J Magn Reson Imaging* 52:1790–1798.
- Ely BA, Liu Q, DeWitt SJ, Mehra LM, Alonso CM, Gabbay V (2021): Data-driven parcellation and graph theory analyses to study adolescent mood and anxiety symptoms. *Transl Psychiatry* 11:1–14.
- Battel L, Cunegatto F, Viduani A, Fisher HL, Kohrt BA, Mondelli V, *et al.* (2021): Mind the brain gap: The worldwide distribution of neuroimaging research on adolescent depression. *Neuroimage* 231:117865.
- WorldBank: World bank country and lending groups. Available at: <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519>. Accessed June 3, 2021.
- Rocha TB, Fisher HL, Caye A, Anselmi L, Arseneault L, Barros FC, *et al.* (2021): Identifying adolescents at risk for depression: A prediction score performance in cohorts based in 3 different continents. *J Am Acad Child Adolesc Psychiatry* 60:262–273.
- Brathwaite R, Rocha TB, Kieling C, Goutam K, Koirala S, Mondelli V, *et al.* (2021): Predicting the risk of depression among adolescents in Nepal using a model developed in Brazil: The IDEA project. *Eur Child Adolesc Psychiatry* 30:213–223.
- Brathwaite R, Rocha TB, Kieling C, Kohrt BA, Mondelli V, Adewuyi AO, *et al.* (2020): Predicting the risk of future depression among school-attending adolescents in Nigeria using a model developed in Brazil. *Psychiatry Res* 294:113511.
- Casey B (2015): Beyond simple models of self-control to circuit-based accounts of adolescent behavior. *Annu Rev Psychol* 66:295–319.
- Casey B, Heller AS, Gee DG, Cohen AO (2019): Development of the emotional brain. *Neurosci Lett* 693:29–34.
- Jones SA, Morales AM, Lavine JB, Nagel BJ (2017): Convergent neurobiological predictors of emergent psychopathology during adolescence. *Birth Defects Res* 109:1613–1622.
- Jin J, Van Snellenberg JX, Perlman G, DeLorenzo C, Klein DN, Kotov R, *et al.* (2020): Intrinsic neural circuitry of depression in adolescent females. *J Child Psychol Psychiatry* 61:480–491.
- Hulvershorn LA, Cullen K, Anand A (2011): Toward dysfunctional connectivity: A review of neuroimaging findings in pediatric major depressive disorder. *Brain Imaging Behav* 5:307–328.
- Van Duijvenvoorde AC, Westhoff B, de Vos F, Wierenga LM, Crone EA (2019): A three-wave longitudinal study of subcortical-cortical resting-state connectivity in adolescence: Testing age- and puberty-related changes. *Hum Brain Mapp* 40:3769–3783.
- Gabard-Durnam LJ, Flannery J, Goff B, Gee DG, Humphreys KL, Telzer E, *et al.* (2014): The development of human amygdala functional connectivity at rest from 4 to 23 years: A cross-sectional study. *Neuroimage* 95:193–207.
- Silvers JA, Insel C, Powers A, Franz P, Helion C, Martin RE, *et al.* (2017): vPFC-vmPFC-amygdala interactions underlie age-related differences in cognitive regulation of emotion. *Cereb Cortex* 27:3502–3514.
- Somerville LH, Jones RM, Ruberry EJ, Dyke JP, Glover G, Casey BJ (2013): The medial prefrontal cortex and the emergence of self-conscious emotion in adolescence. *Psychol Sci* 24:1554–1562.
- Heller AS, Cohen AO, Dreyfuss MF, Casey B (2016): Changes in cortico-subcortical and subcortico-subcortical connectivity impact cognitive control to emotional cues across development. *Soc Cogn Affect Neurosci* 11:1910–1918.
- Cohodes EM, Kitt ER, Baskin-Sommers A, Gee DG (2021): Influences of early-life stress on frontolimbic circuitry: Harnessing a dimensional approach to elucidate the effects of heterogeneity in stress exposure. *Dev Psychobiol* 63:153–172.
- Gee DG, Gabard-Durnam LJ, Flannery J, Goff B, Humphreys KL, Telzer EH, *et al.* (2013): Early developmental emergence of human amygdala-prefrontal connectivity after maternal deprivation. *Proc Natl Acad Sci U S A* 110:15638–15643.
- Farei DS, Gabard-Durnam L, Goff B, Flannery J, Gee DG, Lumian DS, *et al.* (2017): Altered ventral striatal-medial prefrontal cortex resting-state connectivity mediates adolescent social problems after early institutional care. *Dev Psychopathol* 29:1865–1876.

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34. Silvers JA, Lumian DS, Gabard-Durnam L, Gee DG, Goff B, Fareri DS, *et al.* (2016): Previous institutionalization is followed by broader amygdala-hippocampal-PFC network connectivity during aversive learning in human development. *J Neurosci* 36:6420–6430.
35. Thomason ME, Marusak HA, Tocco MA, Vila AM, McGarragle O, Rosenberg DR (2015): Altered amygdala connectivity in urban youth exposed to trauma. *Soc Cogn Affect Neurosci* 10:1460–1468.
36. Straub J, Metzger CD, Plener PL, Koelch MG, Groen G, Abler B (2017): Successful group psychotherapy of depression in adolescents alters fronto-limbic resting-state connectivity. *J Affect Disord* 209:135–139.
37. Cullen KR, Westlund MK, Klimes-Dougan B, Mueller BA, Houry A, Eberly LE, *et al.* (2014): Abnormal amygdala resting-state functional connectivity in adolescent depression. *JAMA Psychiatry* 71:1138–1147.
38. Burghy CA, Stodola DE, Ruttle PL, Molloy EK, Armstrong JM, Oler JA, *et al.* (2012): Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence. *Nat Neurosci* 15:1736–1741.
39. Cullen KR, Gee DG, Klimes-Dougan B, Gabbay V, Hulvershorn L, Mueller BA, *et al.* (2009): A preliminary study of functional connectivity in comorbid adolescent depression. *Neurosci Lett* 460:227–231.
40. Lee J, Pavuluri MN, Kim JH, Suh S, Kim I, Lee MS (2019): Resting-state functional connectivity in medication-naïve adolescents with major depressive disorder. *Psychiatry Res Neuroimaging* 288:37–43.
41. Strikwerda-Brown C, Davey CG, Whittle S, Allen NB, Byrne ML, Schwartz OS, *et al.* (2015): Mapping the relationship between subgenual cingulate cortex functional connectivity and depressive symptoms across adolescence. *Soc Cogn Affect Neurosci* 10:961–968.
42. Subramaniam P, Rogowska J, DiMuzio J, Lopez-Larson M, McGlade E, Yurgelun-Todd D (2018): Orbitofrontal connectivity is associated with depression and anxiety in marijuana-using adolescents. *J Affect Disord* 239:234–241.
43. Gabbay V, Ely BA, Li Q, Bangaru SD, Panzer AM, Alonso CM, *et al.* (2013): Striatum-based circuitry of adolescent depression and anhedonia. *J Am Acad Child Adolesc Psychiatry* 52:628–641.e613.
44. Pan PM, Sato JR, Salum GA, Rohde LA, Gadelha A, Zugman A, *et al.* (2017): Ventral striatum functional connectivity as a predictor of adolescent depressive disorder in a longitudinal community-based sample. *Am J Psychiatry* 174:1112–1119.
45. Geng H, Wu F, Kong L, Tang Y, Zhou Q, Chang M, *et al.* (2016): Disrupted structural and functional connectivity in prefrontal-hippocampus circuitry in first-episode medication-naïve adolescent depression. *PLoS One* 11:e0148345.
46. Herringa RJ, Birn RM, Ruttle PL, Burghy CA, Stodola DE, Davidson RJ, *et al.* (2013): Childhood maltreatment is associated with altered fear circuitry and increased internalizing symptoms by late adolescence. *Proc Natl Acad Sci U S A* 110:19119–19124.
47. Kim SM, Park SY, Kim YI, Son YD, Chung US, Min KJ, *et al.* (2016): Affective network and default mode network in depressive adolescents with disruptive behaviors. *Neuropsychiatr Dis Treat* 12:49–56.
48. Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA (2015): Large-scale network dysfunction in major depressive disorder: A meta-analysis of resting-state functional connectivity. *JAMA Psychiatry* 72:603–611.
49. Marusak H, Thomason M, Peters C, Zundel C, Elrahal F, Rabinak C (2016): You say ‘prefrontal cortex’ and I say ‘anterior cingulate’: Meta-analysis of spatial overlap in amygdala-to-prefrontal connectivity and internalizing symptomatology. *Transl Psychiatry* 6:e944.
50. Kieling C, Buchweitz C, Caye A, Manfro P, Pereira R, Viduani A, *et al.* (2021): The Identifying Depression Early in Adolescence Risk Stratified Cohort (IDEA-RiSCo): Rationale, methods, and baseline characteristics. *Front Psychiatry* 12:697144.
51. Yoon L, Rohrsetzer F, Battel L, Anés M, Manfro PH, Rohde LA, *et al.* (2022): Reward- and threat-related neural function associated with risk and presence of depression in adolescents: A study using a composite risk score in Brazil. *J Child Psychol Psychiatry* 63:579–590.
52. Gonçalves H, Wehrmeister FC, Assunção MC, Tovo-Rodrigues L, Oliveira IO, Murray J, *et al.* (2018): Cohort profile update: The 1993 Pelotas (Brazil) birth cohort follow-up at 22 years. *Int J Epidemiol* 47:1389–1390e.
53. Caye A, Kieling RR, Rocha TB, Graeff-Martins AS, Geyer C, Krieger F, *et al.* (2017): Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL), DSM-5 update: Translation into Brazilian Portuguese. *Braz J Psychiatry* 39:384–386.
54. Rosa M, Metcalf E, Rocha TB, Kieling C (2018): Translation and cross-cultural adaptation into Brazilian Portuguese of the Mood and Feelings Questionnaire (MFQ)–Long Version. *Trends Psychiatry Psychother* 40:72–78.
55. Yates DB, Trentini CM, Tosi SD, Corrêa SK, Poggere LC, Valli F (2006): Apresentação da escala de inteligência Wechsler abreviada (WASI). *Aval Psicol* 5:227–233.
56. Shen X, Tokoglu F, Papademetris X, Constable RT (2013): Groupwise whole-brain parcellation from resting-state fMRI data for network node identification. *Neuroimage* 82:403–415.
57. Rolls ET, Huang CC, Lin CP, Feng J, Joliot M (2020): Automated anatomical labelling atlas 3. *Neuroimage* 206:116189.
58. Jin C, Gao C, Chen C, Ma S, Netra R, Wang Y, *et al.* (2011): A preliminary study of the dysregulation of the resting networks in first-episode medication-naïve adolescent depression. *Neurosci Lett* 503:105–109.
59. Menon V, Uddin LQ (2010): Saliency, switching, attention and control: A network model of insula function. *Brain Struct Funct* 214:655–667.
60. Hayden BY, Platt ML (2010): Neurons in anterior cingulate cortex multiplex information about reward and action. *J Neurosci* 30:3339–3346.
61. Rudebeck PH, Saunders RC, Lundgren DA, Murray EA (2017): Specialized representations of value in the orbital and ventrolateral prefrontal cortex: Desirability versus availability of outcomes. *Neuron* 95:1208–1220.e1205.
62. Berlim MT, McGirr A, Van den Eynde F, Fleck MP, Giacobbe P (2014): Effectiveness and acceptability of deep brain stimulation (DBS) of the subgenual cingulate cortex for treatment-resistant depression: A systematic review and exploratory meta-analysis. *J Affect Disord* 159:31–38.
63. Dixon ML, Thiruchselvam R, Todd R, Christoff K (2017): Emotion and the prefrontal cortex: An integrative review. *Psychol Bull* 143:1033.
64. Rudebeck PH, Putnam PT, Daniels TE, Yang T, Mitz AR, Rhodes SE, *et al.* (2014): A role for primate subgenual cingulate cortex in sustaining autonomic arousal. *Proc Natl Acad Sci* 111:5391–5396.
65. Rotge JY, Lemogne C, Hinfray S, Huguet P, Grynszpan O, Tartour E, *et al.* (2015): A meta-analysis of the anterior cingulate contribution to social pain. *Soc Cogn Affect Neurosci* 10:19–27.
66. Ho TC, Yang G, Wu J, Cassey P, Brown SD, Hoang N, *et al.* (2014): Functional connectivity of negative emotional processing in adolescent depression. *J Affect Disord* 155:65–74.
67. Lichenstein SD, Verstynen T, Forbes EE (2016): Adolescent brain development and depression: A case for the importance of connectivity of the anterior cingulate cortex. *Neurosci Biobehav Rev* 70:271–287.
68. Ho TC, Sacchet MD, Connolly CG, Margulies DS, Tymofiyeva O, Paulus MP, *et al.* (2017): Inflexible functional connectivity of the dorsal anterior cingulate cortex in adolescent major depressive disorder. *Neuropsychopharmacology* 42:2434–2445.
69. Battel L, Swartz J, Anes M, Manfro PH, Rohde LA, Viduani A, *et al.* (2020): Neuroimaging adolescents with depression in a middle-income country: Feasibility of an fMRI protocol and preliminary results. *Braz J Psychiatry* 42:6–13.