The Journal of Child Psychology and Psychiatry

Journal of Child Psychology and Psychiatry 63:5 (2022), pp 579–590 doi:10.1111/jcpp.13496

Reward- and threat-related neural function associated with risk and presence of depression in adolescents: a study using a composite risk score in Brazil

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Background: Neuroimaging studies on adolescents at risk for depression have relied on a single risk factor and focused on adolescents in high-income countries. Using a composite risk score, this study aims to examine neural activity and connectivity associated with risk and presence of depression in adolescents in Brazil. **Methods:** Depression risk was defined with the Identifying Depression Early in Adolescence Risk Score (IDEA-RS), calculated using a prognostic model that included 11 socio-demographic risk factors. Adolescents recruited from schools in Porto Alegre were classified into a low-risk (i.e., low IDEA-RS and no lifetime depression), high-risk (i.e., high IDEA-RS and no lifetime depression), or clinically depressed group (i.e., high IDEA-RS and depression diagnosis). One hundred fifty adolescents underwent a functional MRI scan while completing a reward-related gambling and a threat-related face-matching task. We compared group differences in activity and connectivity of the ventral striatum (VS) and amygdala during the gambling and face-matching tasks, respectively, and group differences in whole-brain neural activity. **Results:** Although there was no group difference in reward-related VS or threat-related amygdala activity, the depressed group showed elevated VS activity to punishment relative to high-risk adolescents. The whole-brain analysis found reduced reward-related activity in the lateral prefrontal cortex of patients and high-risk adolescents compared with low-risk adolescents. Compared with low-risk adolescents, high-risk and depressed adolescents showed reduced threat-related left amygdala connectivity with thalamus, superior temporal gyrus, inferior parietal gyrus, precentral gyrus, and supplementary motor area. **Conclusions:** We identified neural correlates associated with risk and presence of depression in a well-characterized sample of adolescents. These findings enhance knowledge of the neurobiological underpinnings of risk and presence of depression in Brazil. Future longitudinal studies are needed to examine whether the observed neural patterns of high-risk adolescents predict the development of depression. **Keywords:** Depression; functional MRI (fMRI); adolescence; risk factors.

Introduction

Adolescence is a developmental stage during which steep increases in the onset of depression are observed (Andersen & Teicher, 2008). Research in adolescents (Toenders et al., 2019) suggests that altered functioning of brain networks supporting affective processing may be associated with the development of depression. To improve prevention and treatment of depression, it is crucial to identify patterns of neural function associated with risk and presence of depression in diverse samples of participants. The goal of this study is to examine how risk for depression, assessed using a composite risk score that incorporates 11 risk factors, and presence of clinical depression, assessed with a diagnostic interview, are associated with reward-related and threat-related neural function in a sample of adolescents from Brazil.

Altered activity during reward processing (Luking, Pagliaccio, Luby, & Barch, 2016), especially blunted activity of the ventral striatum (VS), is associated with risk, symptoms, and presence of depression in adolescents and young adults. The VS is implicated in positive affect and reward-based learning (Haber & Knutson, 2010) and its reduced activity to reward is thought to contribute to anhedonia (Keedwell, Andrew, Williams, Brammer, & Phillips, 2005), one of the cardinal symptoms of depression. Other research suggests that neural activity during the processing of loss is altered in depressed patients (Ubl et al., 2015), which may lead to aberrant

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Conflict of interest statement: See Acknowledgements for full disclosures.

valuation for negative outcomes. Studies have also found that heightened amygdala activity when viewing threatening stimuli is associated with risk and presence of depression (Redlich et al., 2018; Swartz, Williamson, & Hariri, 2015). The amygdala is a region responsible for threat detection, fear learning, and defensive behavior (Janak & Tye, 2015) and its heightened activity during emotional processing is thought to contribute to depression symptoms of negative affect, such as negative mood (Wang, Labar, & Mccarthy, 2006).

In addition to neural activity, altered VS and amygdala functional connectivity with other brain regions, especially the medial prefrontal cortex (MPFC), has been associated with risk or presence of depression. The MPFC is implicated in reward processing (Oldham et al., 2018), valuation (Bartra, Mcguire, & Kable, 2013), and emotion regulation (Etkin, Egner, & Kalisch, 2011). Greater functional connectivity between the VS and MPFC has been associated with lifetime depression episodes among adolescents (Morgan et al., 2016), high levels of anhedonia (Olson, Kaiser, Pizzagalli, Rauch, & Rosso, 2018), and stress exposure and depressive symptoms (Hanson, Knodt, Brigidi, & Hariri, 2018). Meanwhile, reduced or negative connectivity between the amygdala and MPFC has been observed in youth with trauma exposure (Wolf & Herringa, 2016), whereas greater connectivity has been shown to protect adolescents from developing depression (Fischer, Camacho, Ho, Whitfield-Gabrieli, & Gotlib, 2018). Therefore, increased VS-MPFC and reduced amygdala-MPFC connectivity have been related to adolescent depression.

While prior research has identified patterns of neural activity and connectivity associated with risk and presence of depression, major gaps in our knowledge remain. First, more comprehensive and convenient assessments of depression risk are needed. Most prior studies that have examined samples at high risk for depression focused on a single factor for assigning risk status (e.g., family history of depression; Luking et al., 2016). However, a group of individuals without a single risk factor of interest can be highly heterogeneous (Feczko et al., 2019), so that, for instance, someone classified as low-risk based on the lack of family history of depression can have a high probability of developing the disorder based on other risk factors (e.g., childhood maltreatment). Moreover, family history may be difficult to assess by interviewing adolescents, because adolescents may not be aware of a family history of depression. Developing risk measurements that can be assessed directly through interviewing adolescents could lead to improvements in assessing depression risk from a wide range of adolescents. To address this need, our group has developed and validated an empirically derived composite risk score (Rocha et al., 2021) consisting of 11 sociodemographic variables. This study examines the neural correlates of risk for depression based on this composite risk score.

Second, while 90% of the world's children and adolescents live in low- and middle-income countries (LMIC; Erskine et al., 2015), most neuroimaging studies on adolescent depression have been conducted in high-income countries (HIC). A systematic review indicated that only 7% of task-based functional magnetic resonance imaging (fMRI) studies on adolescent depression were conducted in LMIC (Battel et al., 2021). To improve the prevention and treatment of adolescent depression in LMIC, we need to investigate risk factors for depression within samples from LMIC. To address this gap, we recruited adolescents in Brazil, a country where more than 30 million adolescents live.

Third, previous studies have compared either low-risk adolescents (LR) versus high-risk adolescents (HR) or non-depressed adolescents versus depressed adolescents (MDD). Research that compares all three groups of adolescents (i.e., LR, HR, and MDD), will help to distinguish between potential neural risk factors for depression (i.e., observed in both HR and MDD groups) and neural correlates of depression (i.e., only observed in the MDD but not HR group).

Based on the previous findings in HIC, we hypothesized that the HR and MDD groups would show blunted reward-related VS activity, increased reward-related VS-MPFC connectivity, heightened threat-related amygdala activity, and reduced threat-related amygdala-MPFC connectivity compared with the LR group. We additionally explored whole-brain group differences in neural function and the association between self-reported depressive symptoms and neural function.

Methods

Participants

We screened 7,720 adolescents aged 14 to 16 years from 101 public schools in Porto Alegre, Brazil, who completed socio-demographic questionnaires and the adolescent version of the Patient Health Questionnaire (PHQ-A) from June 2018 to November 2019. The risk groups were stratified using a multivariable prognostic model developed and validated by our group, the IDEA-RS (Rocha et al., 2021). This model integrated 11 socio-demographic variables: biological sex, skin color, drug use, school failure, social isolation, fight involvement, poor relationship with father, mother, and between parents, childhood maltreatment, ran away from home (Table S1). Participants meeting the following a priori defined criteria were invited to complete a laboratory visit to confirm their diagnostic status: IDEA-RS $\leq$ 20th percentile and PHQ-A $\leq$ 6 for the LR group; IDEA-RS $\geq$ 90th percentile and PHQ-A $\leq$ 6 for the HR group; and IDEA-RS $\geq$ 90th percentile and PHQ-A $\geq$ 10 for the MDD group (see Appendix S1 in Supporting Information for details).

A total of 260 participants who met the additional screening criteria during phone interview (Appendix S2) visited Hospital de Clínicas de Porto Alegre (HCPA). Written informed consent/assent was obtained from adolescents and their caregivers after the procedures had been fully explained. Clinical assessment was conducted by board-certified child and adolescent

psychiatrists unaware of the participant's risk group status. Presence of a current depressive episode diagnosis for the MDD group and absence of lifetime history of a depressive episode for the LR and HR groups were determined by interviewing both adolescents and their primary caregivers using the Brazilian Portuguese translation of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL; Caye et al., 2017). Clinical assessments and diagnostic formulation were reviewed by an experienced child and adolescent psychiatrist. Participants with select psychiatric diagnoses and IQ less than 70 were excluded (Appendix S3). We collected self-reported instruments including depressive symptoms measured by the Brazilian Portuguese version of the adolescent-reported Mood and Feelings Questionnaire (MFQ-C; Rosa, Metcalf, Rocha, & Kieling, 2018). Of the 260 participants, 150 participants (50% female) completed MRI scanning from August 2018 to December 2019. Of these 150 participants, 50 were both high-risk (IDEA-RS ≥ 90th percentile) and clinically depressed (MDD group), 50 were high-risk but had no prior or current diagnosis of depressive disorders (HR group), and 50 were low-risk (IDEA-RS ≤ 20th percentile) and had no prior or current diagnosis of depressive disorders (LR group). After exclusion for fMRI data quality control (e.g., excessive head movement, insufficient ROI signal coverage, low behavioral accuracy; see Appendix S4 for details), the sample sizes were 134 and 124 for the gambling and face-matching tasks, respectively. The flow chart for the exclusion procedure is presented in Figure S1. A more detailed study protocol and group characteristics are reported in another article (Kieling et al., 2021). This study was approved by the Brazilian National Ethics in Research Commission (CAAE 50473015.9.0000.5327).

Tasks

During the gambling task (Barch et al., 2013), participants had to guess if a number behind a question mark was higher or lower than 5 and then received feedback that they were correct (reward) or incorrect (punishment). The task included four runs, each with two reward and two punishment blocks. During the face-matching task (Hariri et al., 2006), participants viewed a trio of faces or shapes and had to select which of two stimuli on the bottom row matched the target stimuli on the top row. The task was to match the identity of the actors. This task included alternately presented face and shapes blocks. Face blocks included blocks with 5 facial expressions including angry and fearful faces. Details are presented in Appendix S5.

Subject-level fMRI analysis

Procedures for fMRI data acquisition, preprocessing, and General Linear Models (GLMs) estimation with SPM12 are presented in Appendix S6. We generated contrast maps of reward versus punishment (gambling task), angry versus shapes, and fearful versus shapes (face-matching task) to examine reward-related and threat-related neural activity, respectively. We additionally generated contrast maps of reward versus fixation and punishment versus fixation to examine VS activity separately for reward and punishment. For connectivity analysis, GLMs were created using a generalized psychophysiological interaction (gPPI) toolbox (Mclaren, Ries, Xu, & Johnson, 2012). Seed regions were the left/right VS and amygdala for the gambling and face-matching tasks, respectively.

Group-level fMRI analysis

With the search volumes of VS and amygdala (see Appendix S7 for ROI definition), we conducted one-sample *t*-tests for the contrasts of reward versus punishment, angry faces versus shapes, and fearful faces versus shapes to confirm that reward-related VS activation and threat-related amygdala activation found in numerous studies were replicated in our sample. The beta estimates of clusters within ROIs significant at one-sided $p < .05$ family-wise error (FWE) small-volume corrected (i.e., functional ROIs) were extracted from SPM12 and submitted to ANCOVA in SPSS26 to examine differences in activation across the three groups (LR, HR, and MDD) while controlling for sex and age. Statistical significance was set at two-sided Bonferroni-corrected *p*-value (i.e., $p = .005$) to adjust for 10 comparisons (see Appendix S8). When significant group differences were observed, we conducted pair-wise comparison tests with Bonferroni correction.

For whole-brain analyses, we submitted the contrast maps to second-level analyses to conduct ANCOVA. We used a one-way ANOVA option in SPM12 and included covariates of age and sex. We used Analysis of Functional NeuroImages (AFNI) software and 3dClustSim to determine the desired cluster size for surviving multiple comparison correction at $\alpha < .05$ with an uncorrected *p*-value < .001. Required cluster sizes are presented in Table S2. For connectivity analyses, we estimated required cluster sizes limited to a search of an MPFC ROI (see Appendix S7) as well as for the whole brain. Beta estimates of significant clusters were submitted to pair-wise comparison tests.

We conducted multiple regression analyses to examine the association between continuous depression symptoms measured with the MFQ-C (see Appendix S9 for log-transformation procedure) and brain activity, controlling for age and sex. The procedures for the multiple comparison correction were the same as ANCOVA. Supplementary analyses to examine the interaction effect of risk status and sex and the effect of the continuous variable of IDEA-RS are reported in Appendix S10.

Results

Demographic, clinical, and behavioral data

Results from demographic, clinical, and behavioral data are presented in Table 1. Although there was a group difference in age, we controlled for age in all analyses.

Gambling task

There was significant VS activity during reward versus punishment across all the participants (statistics in Table S3). We found no group difference in VS activity during reward versus punishment (left: $F(2, 129) = 3.01$, $p = .053$, right: $F(2, 129) = 0.27$, $p = .76$). However, there was a group difference in left VS activity during punishment versus fixation ($F(2, 129) = 5.84$, $p = .004$; Figure 1A). This effect was driven by greater activity in the MDD relative to the HR group ($t(129) = 3.4$, $p = .003$).

Whole-brain ANCOVA revealed group differences in activity during reward versus punishment in the posterior ventrolateral prefrontal cortex (VLPFC) and a region including the dorsolateral prefrontal cortex (DLPFC) and white matter (WM; Figure 1B; statistics in Table 2). The HR and MDD groups showed reduced VLPFC activity compared with the LR group, but the HR and MDD group did not significantly differ from each other. The DLPFC/WM activity showed a gradually decreasing pattern of activity in the order of LR, HR, and MDD (Table 2). There was

Table 1 Description of demographic, screening, clinical, head motion, and behavioral measurement

Gambling Task

	Low Risk Group ($N = 43$)		High Risk Group ($N = 46$)		MDD patient Group ($N = 45$)		Analysis	
	N	%	*N*	%	*N*	%	χ^2	*p*
Gender							0.57	.75
Boys	24	55.81	22	47.83	23	51.11		
Girls	19	44.19	24	52.17	22	48.89		
Skin color[a]							8.30	.40
Yellow	0	0	0	0	2	4.44		
White	24	55.81	23	50.00	22	48.89		
Native Brazilian	4	9.30	1	2.17	2	4.44		
Brown	9	20.93	11	23.91	9	20.00		
Black	6	13.95	11	23.91	10	22.22		

	Mean	*SD*	Mean	*SD*	Mean	*SD*	*F*	*p*
Age	15.43	1.18	15.85	1.05	15.88	1.05	5.20	.007[b]
WASI IQ[c]	90.49	10.38	87.87	8.86	88.47	10.10	0.87	.42
Risk Score[d] (%)	1.29	0.32	8.42	4.72	9.12	5.62	44.96	<.001[e]
PHQ-A[f]	2.91	1.57	4.09	1.52	18.6	4.43	418.10	<.001[g]
MFQ-C[h]	6.67	4.74	13.46	8.28	40.27	11.30	190.70	<.001[i]
Censored number of volumes	4.91	7.21	6.07	7.66	5.69	7.09	0.29	.75
Overall Reaction Time (RT) (ms)	446.30	108.51	471.84	127.47	440.61	109.88	0.82	.46

Face Matching Task

	Low-Risk Group ($N = 41$)		High-Risk Group ($N = 41$)		MDD patient Group ($N = 42$)		Analysis	
	N	%	*N*	%	*N*	%	χ^2	*p*
Gender							0.21	.90
Boys	22	53.66	20	48.78	21	50.00		
Girls	19	46.34	21	51.22	21	50.00		
Skin color							5.39	.72
Yellow	0	0	0	0	1	2.38		
White	25	60.98	20	48.78	19	45.24		
Native Brazilian	3	7.32	2	4.88	2	4.76		
Brown	7	17.07	9	21.95	9	21.43		
Black	6	14.63	10	24.39	11	26.19		

	Mean	*SD*	Mean	*SD*	Mean	*SD*	*F*	*p*
Age	15.32	0.81	15.82	0.81	15.78	0.78	4.89	.009[j]
WASI IQ	90.76	10.43	88.37	9.11	89.00	10.04	0.65	.53
Risk Score (%)	1.30	0.32	8.14	4.36	9.39	5.85	43.61	<.001[k]
PHQ-A	2.61	1.48	3.83	1.56	19	4.48	417.14	<.001[l]
MFQ-C	6.37	4.66	12.71	8.08	41.76	10.49	224.76	<.001[m]
Censored number of volumes	2.95	4.92	3.05	4.35	4.29	5.54	0.93	.40
Overall accuracy (%)	94	4	94	5	92	5	2.70	.07
Overall RT (ms)	887.71	88.84	884.22	133.24	882.89	116.32	0.12	.89
Accuracy (Angry) (%)	96	6	97	5	97	6	0.36	.70
Accuracy (Fearful) (%)	95	7	98	4	96	5	2.56	.08
Accuracy (Shapes) (%)	92	6	91	7	89	9	2.69	.07

(continued)

no group difference in VS connectivity during reward versus punishment. The association with self-reported depression symptoms did not reveal significant results.

Face-matching task

We confirmed significant amygdala activity during angry faces versus shapes and fearful faces versus shapes across all the participants (statistics in Table S3). There were no group differences in amygdala activity during angry (left: $F(2, 119) = .01$, $p = .99$, right: $F(2, 119) = .17$, $p = .85$) or fearful faces versus shapes (left: $F(2, 119) = .22$, $p = .80$, right: $F(2, 119) = .08$, $p = .92$). The whole-brain analysis did not reveal any group differences in neural activity.

Whole-brain ANCOVA revealed group differences in left amygdala connectivity with the thalamus,

Table 1 (continued)

	Mean	*SD*	Mean	*SD*	Mean	*SD*	*F*	*p*
RT (Angry) (ms)	907.32	139.37	914.39	148.96	907.74	105.32	0.04	.96
RT (Fearful) (ms)	909.11	158.51	895.07	154.64	877.36	131.75	0.48	.62
RT (Shapes) (ms)	857.97	98.96	878.09	148.06	860.56	108.14	0.34	.71

Statistics for behavioral measurement (i.e., reaction time, accuracy) were computed controlling for age and sex.
[a]Self-reported and based on the Brazilian national census classification of race. To calculate the risk score, two categories (i.e., white vs. non-white) were used.
[b]The effect was driven by the difference in LR<HR ($t = 2.47$, $df = 131$, $p = .04$) and LR<MDD ($t = 3$, $df = 131$, $p = .008$)
[c]IQ measured by Wechsler Abbreviated Scale of Intelligence.
[d]Generated by using the prognostic model that was originally developed with data from the Pelotas 1993 Cohort Study, using data at age 15 to predict a current unipolar depressive episode at age 18 years. Score reflects the probability of being depressed at exactly age 18 (point-prevalence); lifetime probability of having developed depression by the age of 18 is expected to be higher.
[e]The effect was driven by the difference in LR<HR ($t = 7.78$, $df = 131$, $p < .001$) and LR<MDD ($t = 8.67$, $df = 131$, $p < .001$).
[f]The adolescent version of the Patient Health Questionnaire
[g]The effect was driven by the difference in LR<MDD ($t = 25.72$, $df = 131$, $p < .001$) and HR<MDD ($t = 24.18$, $df = 131$, $p < .001$)
[h]Brazilian Portuguese version of the adolescent-reported Mood and Feelings Questionnaire.
[i]The effect was driven by the difference in LR<HR ($t = 3.73$, $df = 131$, $p = .001$), LR<MDD ($t = 18.46$, $df = 131$, $p < .001$) and HR<MDD ($t = 14.89$, $df = 131$, $p < .001$).
[j]The effect was driven by the difference in LR<HR ($t = 2.82$, $df = 121$, $p = .017$) and LR<MDD ($t = 2.58$, $df = 121$, $p = .033$).
[k]The effect was driven by the difference in LR<HR ($t = 7.31$, $df = 121$, $p < .001$) and LR<MDD ($t = 8.7$, $df = 121$, $p < .001$).
[l]The effect was driven by the difference in LR<MDD ($t = 25.87$, $df = 121$, $p < .001$) and HR<MDD ($t = 23.95$, $df = 121$, $p < .001$).
[m]The effect was driven by the difference in LR<HR ($t = 3.53$, $df = 121$, $p = .002$), LR<MDD ($t = 19.85$, $df = 121$, $p < .001$), and HR<MDD ($t = 16.29$, $df = 121$, $p < .001$).

superior temporal gyrus (STG), inferior parietal gyrus (IPG), a region including precentral gyrus (PreCG) and WM, and supplementary motor area (SMA) for fearful faces versus shapes (Figure 2A; Table 2). The HR and MDD groups showed reduced amygdala connectivity in all these regions compared with the LR group (Table 2). There were group differences in right amygdala connectivity with IPG and a region including supramarginal gyrus (SMG) and WM for fearful faces versus shapes (Figure 2B; Table 2). The pair-wise comparison tests revealed that the HR group showed more reduced connectivity than the LR and MDD groups (Table 2).

Multiple regression analyses with the search volume of MPFC found a negative association between self-reported depressive symptoms and bilateral amygdala connectivity with MPFC (left amygdala: $t(120) = 3.74$, $k = 92$, [0, 48, 40], right amygdala: $t(120) = 5.14$, $k = 89$, [0, 62, 20]; Figure 3) during fearful faces versus shapes, indicating that higher depression symptoms were associated with reduced amygdala-MPFC connectivity. The negative association was additionally found in connectivity between left amygdala and vermis ($t(120) = 4.21$, $k = 120$, [2, −46, −22]) during fearful faces versus shapes. Results of the effect of the interaction between risk status and sex and the effect of the continuous IDEA-RS are reported in Appendix S11, Figures S2 and S3.

Discussion

This study investigated neural function associated with risk and presence of depression in Brazilian adolescents by screening over 7,000 adolescents and using an empirically derived risk score and clinical interviews to stratify adolescents into richly phenotyped groups. There were no group differences in reward-related VS activity, threat-related amygdala activity, and their connectivity with MPFC. However, we found that the MDD group showed greater VS activity to punishment compared with the HR group. Moreover, the HR and MDD groups showed reduced reward-related LPFC activity and threat-related left amygdala connectivity with the thalamus, IPL, STG, SMA, and PreCG, compared with the LR group. The HR group also showed reduced right amygdala connectivity with IPL and SMG relative to the other groups.

The MDD group showed higher VS activity in punishment blocks than the HR group. This is consistent with reports of enhanced VS activity encoding loss-related prediction error (Ubl et al., 2015) in adults with depression or a history of depression. The observation that the group difference was only present in the MDD group versus HR group suggests that the elevated punishment-related VS activity may be related to the emergence of depression (i.e., transition from HR to MDD) rather than the risk for developing depression. If confirmed in future research, these results suggest that potential treatments for adolescents with MDD could target the aberrant valuation for loss. However, these results should be interpreted with caution until replicated in future research, as we did not observe a difference in VS activity to punishment between the LR and MDD groups.

Interestingly, the HR and MDD groups showed attenuated reward-related activity of two regions of the LPFC (i.e., VLPFC, DLPFC), compared with the

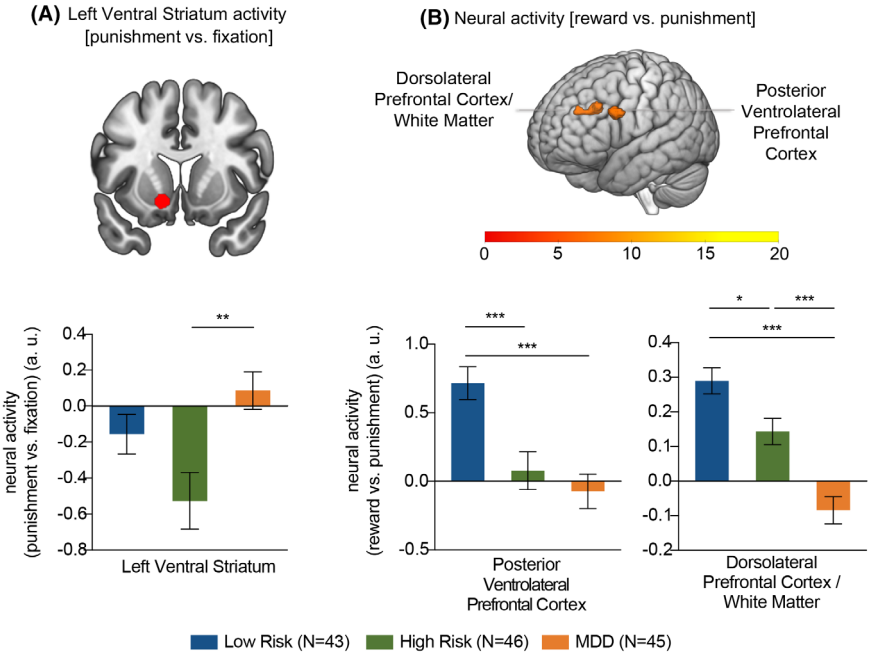

Figure 1 Group differences in neural activity during the gambling task. (A) Region-of-Interest analyses revealed a significant group difference in left ventral striatum activity during punishment vs. fixation, driven by greater activity in the MDD relative to HR group. In the graph, the y-axis shows extracted left ventral striatum activity during punishment vs. fixation. (B) Whole-brain analyses of neural activity during reward vs. punishment revealed significant group differences in the posterior ventrolateral prefrontal cortex and dorsolateral prefrontal cortex/white matter. The color bar indicates *F* value from the ANCOVA analysis. To present the specific patterns of group differences, mean extracted neural activity for the two clusters are plotted for each group. Error bars indicate standard error. In the graph, the y-axis shows extracted neural activity during reward vs. punishment. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$; a. u. = arbitraty unit

LR group. The observation that these patterns were observed in both the HR and MDD groups suggests that these may be neural markers of depression risk. LPFC has been shown to have functions of integrating rewarding information (Dixon & Christoff, 2014), value-based goal pursuit (Davidow, Insel, & Somerville, 2018), and reward-motivated performance enhancement (Jimura, Locke, & Braver, 2010). The reduced LPFC activity of the HR and MDD groups could be related to affective dysfunction implicated in depression, including reduced incentive-based performance improvement (Hardin, Schroth, Pine, & Ernst, 2007). Notably, we observed different patterns of group differences in VLPFC and DLPFC activity: while the HR and MDD groups showed the same pattern of VLPFC activity, the MDD group showed more reduced activity of DLPFC than the HR group. This suggests that, unlike the VLPFC, the DLPFC may undergo additional functional disruption after high-risk adolescents develop depression.

Intriguingly, the HR and MDD groups showed reduced left amygdala connectivity with multiple brain regions (i.e., thalamus, STG, IPG, PreCG, and SMA), compared with the LR group. This is consistent with studies that found reduced activation or amygdala connectivity with these regions in individuals with depression (Mel'nikov et al., 2018) and risk for depression (Wackerhagen et al., 2017). The thalamus is known to relay sensory information to the amygdala in a fearful context (Penzo et al., 2015), thereby facilitating the amygdala to orchestrate the fear signaling system. The STG and IPG comprise the mirror network responsible for inferring affective states of others (Zaki, Hennigan, Weber, & Ochsner, 2010). These two regions are also suggested to be involved in emotion and attention regulation (Ochsner, Silvers, & Buhle, 2012) that could be related to ignoring task-irrelevant emotional content during the face-matching task. The PreCG and SMA, comprising the motor cortex, have been found to have intrinsic connections with the amygdala (Toschi, Duggento, & Passamonti, 2017) and their connectivity was suggested to subserve the execution of adaptive behavior appropriate for a given emotional context (Rizzo et al., 2018). Taken together, our findings indicate that the risk and presence of depression are related to joint disruption of amygdala connectivity with multiple brain regions that may lead to decreased capacity to optimally integrate social signals from fearful faces, regulate emotion or attention, or adapt behavior to a given context. The observation that reduced left amygdala connectivity with other regions was evident in both the HR and MDD groups suggests that these alterations may be evident before the development of MDD and may serve as a biological marker of depression risk.

Right amygdala connectivity also showed group differences in regions of the mirror network (i.e., IPG and SMG), however, with a different pattern: the HR group showed reduced connectivity compared with

Table 2 Brain regions with significant group differences

Anatomical description	*F*-value (peak)	Cluster Size (Voxels)	*x*	*y*	*z*	Pair-wise comparison statistics
F-test: Neural activity (Reward vs. Punishment)						
Left inferior frontal gyrus, opercular part	14.898	129	−38	8	28	LR > HR: $t = 4.15$; $p < .001$ LR > MDD: $t = 5.02$; $p < .001$ HR > MDD: $t = 0.98$; $p = .976$
White matter/left superior frontal gyrus, dorsolateral	19.805	164	−22	20	32	LR > HR: $t = 2.86$; $p = .015$ LR > MDD: $t = 6.84$; $p < .001$ HR > MDD: $t = 4.26$; $p < .001$
F-test: Left amygdala connectivity (Fearful vs. Shapes)						
Right thalamus, ventral lateral	15.919	165	14	−6	6	LR > HR: $t = 3.4$; $p = .003$ LR > MDD: $t = 5.8$; $p < .001$ HR > MDD: $t = 2.42$; $p = .051$
Right superior temporal gyrus	10.971	114	46	−32	16	LR > HR: $t = 5.22$; $p < .001$ LR > MDD: $t = 3.27$; $p = .004$ HR > MDD: $t = -2.07$; $p = .124$
Left inferior parietal gyrus	14.127	243	−54	−34	50	LR > HR: $t = 5.13$; $p < .001$ LR > MDD: $t = 4.69$; $p < .001$ HR > MDD: $t = -.52$; $p > .99$
White matter / right precentral gyrus	18.022	449	32	−14	38	LR > HR: $t = 6.72$; $p < .001$ LR > MDD: $t = 5.53$; $p < .001$ HR > MDD: $t = -1.24$; $p = .657$
Left supplementary motor area	11.508	157	2	2	52	LR > HR: $t = 4.76$; $p < .001$ LR > MDD: $t = 3.84$; $p = .001$ HR > MDD: $t = -.98$; $p > .99$
F-test: Right amygdala connectivity (Fearful vs. Shapes)						
Left inferior parietal gyrus	11.000	152	−48	−34	48	LR > HR: $t = 5.05$; $p < .001$ LR > MDD: $t = 2.18$; $p = .095$ HR > MDD: $t = -3.04$; $p = .009$
White matter / right supramarginal gyrus	11.654	176	36	−38	34	LR > HR: $t = 5.23$; $p < .001$ LR > MDD: $t = 1.99$; $p = .146$ HR > MDD: $t = -3.43$; $p = .003$

The automated anatomical labeling atlas 3 (AAL3; Rolls, Huang, Lin, Feng, & Joliot, 2020) was used for defining the regions. We named a cluster with the AAL3 label that occupies the highest proportion of the cluster. The coordinates correspond to peak voxels.

the other groups. Combined results of left and right amygdala connectivity with the mirror network indicate that the aberrancy is more pronounced in HR than MDD (see Appendix S12 for discussion of laterality effects). Note that there were no observed behavioral differences in accuracy and reaction time across the three groups. This further enhances our confidence that group differences were driven by differences in neural activity rather than differences in how the task was performed across the groups.

Notably, we found that greater connectivity between bilateral amygdala and MPFC during fearful faces was associated with lower self-reported depressive symptoms. This result is consistent with the association of amygdala-MPFC connectivity with reduced depressive symptoms (Vijayakumar et al., 2017). Importantly, our findings that the connectivity was associated with self-reported depressive symptoms rather than risk or presence of MDD highlights that amygdala-MPFC connectivity is related to subjectively experienced depressive symptoms rather than clinically diagnosed MDD or risk for developing depression. Given that altered amygdala-MPFC connectivity has consistently been implicated in depression in HIC samples (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015), the observed similar pattern suggests that this neural dysfunction may be a relatively universal pattern associated with depression symptoms across contexts.

Importantly, we did not find group differences in reward-related VS and threat-related amygdala activity. These results inconsistent with studies in HIC could be attributed to factors associated with LMIC, including different social environments with varied socioeconomic challenges in Brazil such as low household income, high crime rates, and high school dropout rates (IBGE, 2018, Murray, Cerqueira, & Kahn, 2013) and geography-based genetic variation (Manica, Prugnolle, & Balloux, 2005). These differences in results could also be driven by methodological factors, including the operationalization of risk status, the screening procedure, MRI acquisition parameters, task parameters, and analytical approaches. Future cross-cultural research is needed in which effects can be directly compared across diverse participant samples using the same protocol, which will provide important data for building a theoretical model of cultural differences in the neural pathways of developing depression in adolescents.

This study has several limitations and related directions for future research. First, the cross-

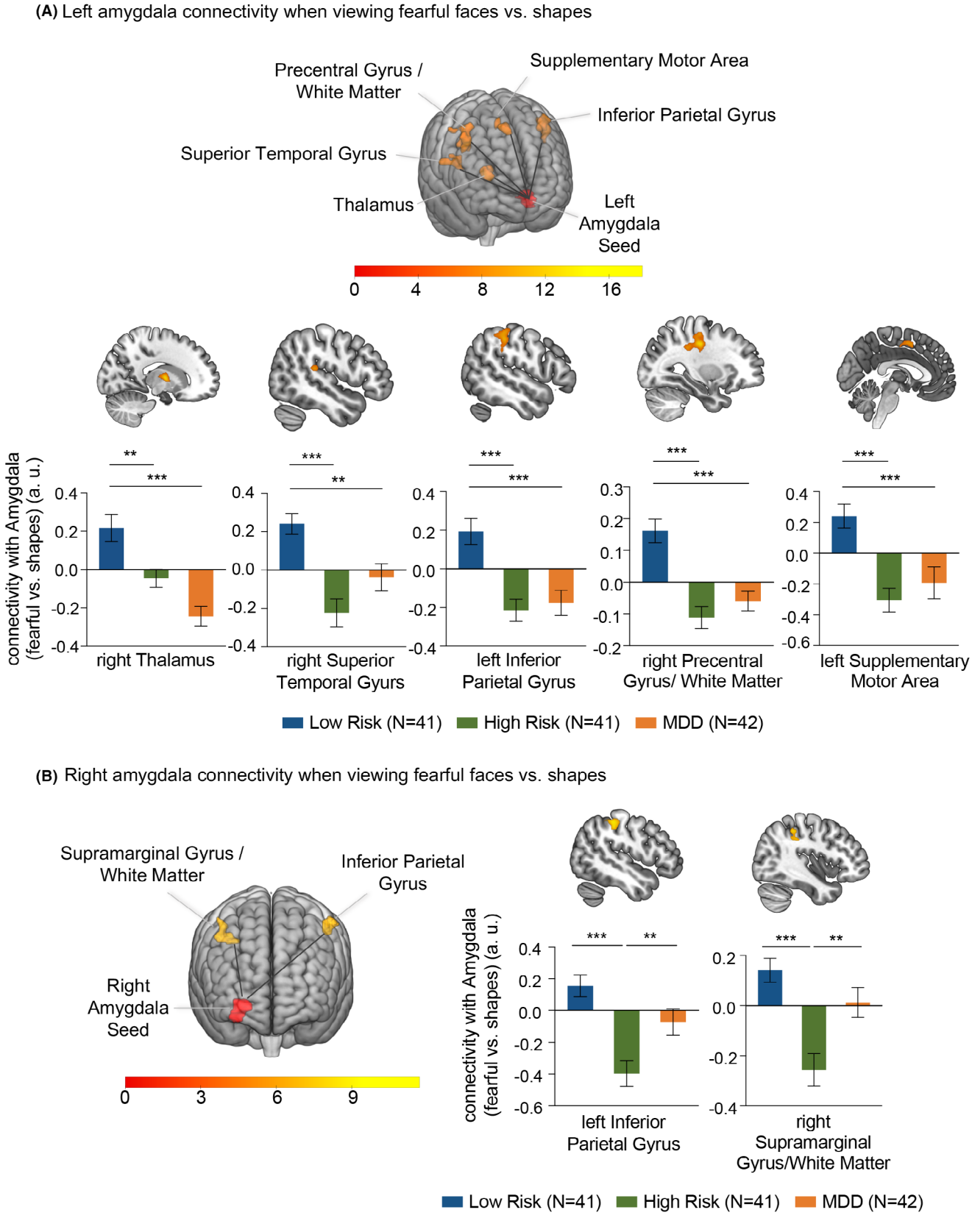

Figure 2 Group differences in amygdala connectivity when viewing fearful faces vs. shapes. (A) Whole-brain generalized psychophysiological interaction (gPPI) analysis with the left amygdala seed region during fearful faces vs. shapes revealed significant group differences in right thalamus, right superior temporal gyrus, left inferior parietal gyrus, right precentral gyrus/white matter, and left supplementary motor area. The bar graphs present the specific patterns of group differences in each region. (B) Whole-brain gPPI analysis with the right amygdala seed during fearful faces vs. shapes revealed significant group differences in left inferior parietal gyrus and right supramarginal gyrus/white matter. The specific patterns of group differences of each region are represented with bar graphs. The color bars indicate F values from the ANCOVA analyses. Error bars indicate standard error. The y-axis shows the coefficients from gPPI analyses. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$; a. u. = arbitraty unit

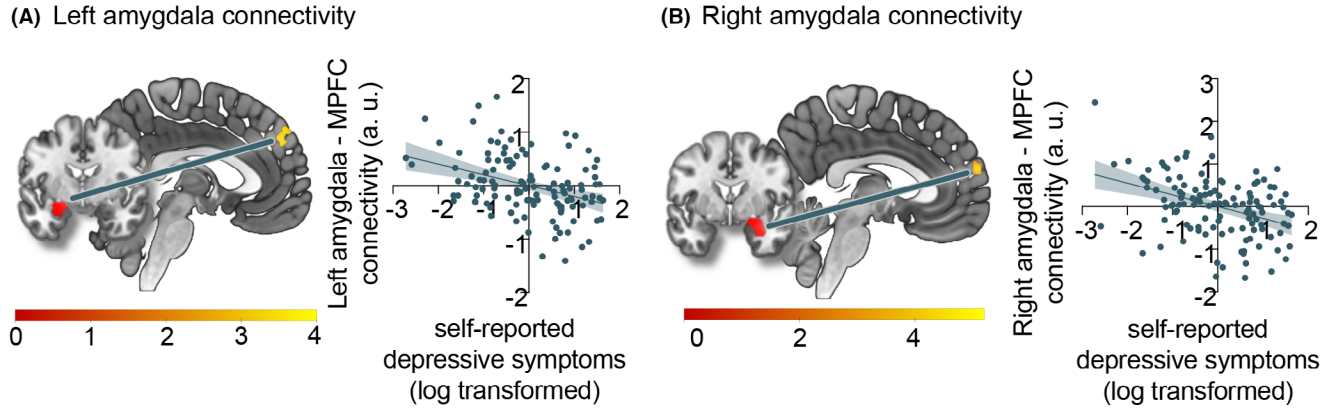

Figure 3 Association between adolescent-reported depressive symptoms and amygdala-MPFC connectivity when viewing fearful faces. Generalized psychophysiological interaction (gPPI) analysis with search volume of medial prefrontal cortex (MPFC) revealed that reduced connectivity between left amygdala and medial prefrontal cortex (panel A) and reduced connectivity between right amygdala and medial prefrontal cortex (panel B) are associated with greater adolescent-reported depressive symptoms. The scatter plots represent the association between depressive symptoms and neural connectivity, controlling for the effects of age and sex. Color bars indicate T values from the multiple regression analyses. The y-axis shows the coefficients from gPPI analyses. The shaded area indicates the 95% CI; a. u. = arbitraty unit; MPFC = Medial Prefrontal Cortex

sectional design of this study limits us from determining whether patterns of neural function identified in the HR group will predict the development of depression. Although our risk score was validated to predict depression in three years in a different sample (Rocha et al., 2021), it was also shown to predict the development of other psychiatric disorders, albeit with somewhat lower accuracy. As such, some of the patterns of neural function observed could be associated with risk for other types of psychopathology. In addition, it is possible that some adolescents in the HR group will exhibit resilience and will develop no psychopathology. Moreover, for HR adolescents who do develop depression, these later-onset adolescents may be qualitatively different (in clinical presentation or neural activity) relative to the MDD group, who could be considered earlier-onset. Future longitudinal studies are needed to examine whether the observed neural patterns predict the development of depression, whether their predictive accuracy is greater for depression than other types of psychopathology, and whether there are any neural differences in earlier-onset versus later-onset MDD. Second, although the IDEA-RS has clear advantages such as the integration of multiple variables and convenient data collection from adolescents, further research is needed to examine whether IDEA-RS is a stronger predictor of depression than a family history of depression and to what extent it captures a liability distinct from the one conferred by family history of depression. Third, our MDD group criteria included ≥ 90th percentile on the IDEA-RS, which enabled us to attribute any differences in neural activity between the HR and MDD groups only to MDD diagnosis. However, we acknowledge that results may not generalize to MDD adolescents who have low-risk sociodemographic profiles. Finally, as our preliminary analysis of sex by risk status interaction revealed a significant effect in amygdala connectivity (Figure S2), future studies with a larger sample size should consider examining sex-specific neural markers of depression risk. Other limitations are discussed in Appendix S13.

Conclusion

In conclusion, this study investigated reward- and threat-related neural activity associated with risk and presence of depression in Brazilian adolescents. Our findings helped to clarify potential neural risk factors (i.e., reduced reward-related LPFC activity and threat-related amygdala connectivity) and correlates of adolescent depression (i.e., increased VS activity to punishment). This study contributes to knowledge regarding neural processes that could be targeted for the prevention and treatment of adolescent depression in Brazil.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Validation of multivariable prognostic model for predicting depression.
Appendix S2. Exclusion criteria from phone interviews.
Appendix S3. Exclusion criteria from clinical assessment.
Appendix S4. Exclusion criteria for fMRI data quality.
Appendix S5. Task paradigms.
Appendix S6. Procedure of fMRI data acquisition, preprocessing, and GLM estimation.
Appendix S7. Definition of VS, amygdala, and MPFC ROI search volume.
Appendix S8. List of 10 ROI analyses.
Appendix S9. Log-transformation of MFQ-C.

Appendix S10. Supplementary Analyses.
Appendix S11. Supplementary Results.
Appendix S12. Discussion for different results of left and right amygdala connectivity.
Appendix S13. Limitations and Future directions.
Table S1. Sociodemographic questionnaire for risk stratification.
Table S2. The required cluster size for each group map.
Table S3. Statistics for the one-sample t-tests.
Figure S1. Flow chart of exclusion of participants.
Figure S2. Interaction effect of risk status and sex.
Figure S3. The effect of continuous IDEA-RS.
Supplementary References.

Acknowledgements

The IDEA (Identifying Depression Early in Adolescence) project of which this research belongs to is funded by an MQ Brighter Futures grant (MQBF/1 IDEA). Additional support was provided by the UK Medical Research Council (MC_PC_MR/R019460/1) and the Academy of Medical Sciences (GCRFNG\100281) under the Global Challenges Research Fund. This work is also supported by research grants from Brazilian public funding agencies Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq; 477129/2012-9 and 445828/2014-5), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES; 62/2014), and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS; 17/2551-0001009-4). C.K. is a CNPq researcher and a UK Academy of Medical Sciences Newton Advanced Fellow. V.M. is supported by the Medical Research Foundation [MRF-160-0005-ELPMONDE] and by the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health and Social Care. V.M. has received in the past research funding from Johnson & Johnson as part of a research program on depression and inflammation, but the research described in this paper is unrelated to this funding. Written informed consent/assent was obtained from adolescents and their caregivers. This study was approved by the Brazilian National Ethics in Research Commission (CAAE 50473015.9.0000.5327). Unthresholded maps of Figures 1B, 2, and 3 are available at Neurovault (https://neurovault.org/collections/PKTUFVTY/). Other data and codes for the analyses are available upon request. The remaining authors have declared that they have no competing or potential conflicts of interest.

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Key points

- Studies in high-income countries have found that reward-related ventral striatum and threat-related amygdala dysfunction are associated with risk and presence of depression in adolescents and young adults.
- We recruited Brazilian adolescents and classified them as low-risk for depression, high-risk for depression, or currently depressed using a composite risk score integrating 11 sociodemographic factors and clinical assessment.
- We found that reduced reward-related lateral prefrontal cortex activity and threat-related left amygdala connectivity were associated with both risk and presence of depression. Ventral striatum activity to punishment was associated with presence but not risk of depression.
- Our findings highlight potential neural markers for risk and presence of depression in Brazilian adolescents, contributing to the prevention and treatment of youth depression across the globe.

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Accepted for publication: 22 June 2021