Title

A magnetic resonance imaging-based morphometric and structural covariance network study of Brazilian adolescents stratified by depression risk

Journal

Brazilian Journal of Psychiatry, 45(4)

ISSN

1516-4446

Authors

Rohrsetzer, Fernanda

Balardin, Joana Bisol

Picon, Felipe

et al.

Publication Date

2023

DOI

10.47626/1516-4446-2023-3037

Peer reviewed

Brazilian Journal of Psychiatry
bjp
Revista Brasileira de Psiquiatria

Braz J Psychiatry. 2023 Jul-Aug;45(4):318-326
doi:10.47626/1516-4446-2023-3037
Brazilian Psychiatric Association

ORIGINAL ARTICLE

A magnetic resonance imaging-based morphometric and structural covariance network study of Brazilian adolescents stratified by depression risk

Fernanda **Rohrsetzer**,[1,2] Joana Bisol **Balardin**,[1,2] Felipe **Picon**,[1,2] João Ricardo **Sato**,[3] Lucas **Battel**,[1,2] Anna **Viduani**,[1,2] Pedro Henrique **Manfro**,[1,2] Leehyun **Yoon**,[4] Brandon A. **Kohrt**,[5] Helen L. **Fisher**,[6,7] Valeria **Mondelli**,[8,9] Johnna R. **Swartz**,[4*] Christian **Kieling**[1,2*]

[1]*Departamento de Psiquiatria e Medicina Legal, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil.* [2]*Serviço de Psiquiatria da Infância e Adolescência, Hospital de Clínicas de Porto Alegre, UFRGS, Porto Alegre, RS, Brazil.* [3]*Centro de Matemática, Computação e Cognição, Universidade Federal do ABC, São Paulo, SP, Brazil.* [4]*Department of Human Ecology, University of California, Davis, CA, USA.* [5]*Division of Global Mental Health, Department of Psychiatry, School of Medicine and Health Sciences, The George Washington University, Washington, DC, USA.* [6]*Social, Genetic & Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom.* [7]*Economic and Social Research Council, Centre for Society and Mental Health, King's College London, London, United Kingdom.* [8]*Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom.* [9]*National Institute for Health Research Mental Health, Biomedical Research Centre, South London and Maudsley National Health Service Foundation Trust, King's College London, London, United Kingdom.*
** These authors contributed equally and are joint senior authors.*

Objectives: To explore differences in regional cortical morphometric structure between adolescents at risk for depression or with current depression.
Methods: We analyzed cross-sectional structural neuroimaging data from a sample of 150 Brazilian adolescents classified as low-risk (LR) (n=50) or high-risk (HR) for depression (n=50) or with current depression (n=50) through a vertex-based approach with measurements of cortical volume (CV), surface area (SA), and cortical thickness (CT). Differences between groups in subcortical volume and in the organization of networks of structural covariance were also explored.
Results: No significant differences in brain structure between groups were observed in whole-brain vertex-wise CV, SA, or CT. Also, no significant differences in subcortical volume were observed between risk groups. In relation to the structural covariance network, there was an indication of an increase in the hippocampus betweenness centrality index in the HR group network compared to the LR and current depression group networks. However, this result was only statistically significant when applying false discovery rate correction for nodes within the affective network.
Conclusion: In an adolescent sample recruited using an empirically based composite risk score, no major differences in brain structure were detected according to the risk and presence of depression.

Keywords: adolescent; depression; risk factors; methods, neuroimaging/structural

Introduction

Major depressive disorder (MDD) is a leading cause of disease-related burden worldwide.[1] Considering that adolescence and early adulthood constitute periods of peak incidence of MDD, identifying brain characteristics associated with elevated risk and early occurrence of the disorder during this developmental period provides an important opportunity to understand the mechanisms associated with MDD onset.[2]

Over the past few decades, neuroimaging studies have explored structural brain alterations associated with MDD in adolescents, yielding highly heterogeneous findings.[3,4] Morphometry investigations have mainly focused on specific brain regions of interest (ROIs), which may have contributed to inconsistencies in the literature. For example, some studies have reported differences in subcortical volumes.[3,4] Studies investigating neuroanatomical differences in samples with adolescents at elevated risk for MDD report greater, smaller, or similar volumes of the amygdala, hippocampus, and putamen in high-risk (HR) groups compared to low-risk (LR) groups.[5,6] Likewise, differences in cortical thickness (CT) have also been described in samples of adolescents at high risk for MDD.[7]

Correspondence: Christian Kieling, Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, Departamento de Psiquiatria e Medicina Legal, Serviço de Psiquiatria da Infância e Adolescência, Rua Ramiro Barcelos, 2350, 400N, CEP 90035-903, Porto Alegre, RS, Brazil.
E-mail: ckieling@ufrgs.br
Submitted Jan 08 2023, accepted Mar 29 2023.

How to cite this article: Rohrsetzer F, Balardin JB, Picon F, Sato JR, Battel L, Viduani A, et al. A magnetic resonance imaging-based morphometric and structural covariance network study of Brazilian adolescents stratified by depression risk. Braz J Psychiatry. 2023; 45:318-326. http://doi.org/10.47626/1516-4446-2023-3037

Methodological differences in the processing pipelines used to derive structural magnetic resonance imaging (MRI) measures or in ascertainment criteria among studies can also contribute to the limited consistency in results. For example, there has been emphasis on the examination of region-based compared to more fine-grained vertex-wise estimates of CT.[8] Although both approaches are effective for estimating cortical morphology indices, they provide information at different scales.[9] Vertex-wise analysis is used to calculate local morphological parameters for each point (vertex) of the cortical surface, whereas parcel-wise analysis is used to assess large-scale cortical organization at the area level based on cortical parcellation.[10]

Evidence from neuroimaging research also supports the view that MDD-related structural brain differences do not occur in isolated brain regions but are characterized in terms of altered networks of brain structures.[11] For example, four well-established networks that are thought to contribute to the development of MDD include a limbic affective network that appears to be associated with emotion processing and regulation, a frontal-striatal reward network that has been related to anhedonia, the default mode network that seems to be associated with depressive rumination, and a dorsal cognitive control network that is thought to underlie cognitive deficits related to emotion regulation.[12,13]

The characterization of this systems-level connectivity can be considered at multiple levels.[14] One such level is structural covariance, which can be used to define anatomical relationships among several brain regions based on interregional statistical associations of different morphometric gray matter features, such as CT or gray matter density.[15] Graphical analysis of brain structural covariance networks (SCNs) (networks constructed based on statistical correlations of morphological indices between brain regions) can provide comprehensive information at the network level and therefore clues to the identification of biomarkers of altered development that contribute to the emergence of mood disorders and have been explored in a few studies comparing adults with MDD with healthy controls.[10,16] Beyond providing a better understanding of the neural substrates associated with depression, such analyses in adolescents at risk for the disorder could also be useful in the identification of potential brain markers associated with vulnerability for MDD. Various organizational properties of networks derived from structural covariance have been characterized using graph theory. Although the neurobiological interpretation of these associations remains elusive, it has been hypothesized to reflect both genetic and plastic influences, including maturational timing.[17]

Altered patterns in the emotional regulation network in individuals with MDD have been reported by Wu et al.[18] through an increase in the strength of the gray matter volume correlation between the angular gyrus and the amygdala, as well as a decrease in the strength of the gray matter volume correlation between the right angular gyrus and the posterior cingulate cortex. Other studies have also reported changes in structural networks such as: (i) the medial temporal lobe network primarily involving the hippocampus and parahippocampal gyrus was significantly correlated with the severity of individual symptoms in MDD, with more severe symptoms associated with negative volume correlations within the medial temporal lobe network[19]; (ii) decreased node strength of the right horn hippocampus in patients with MDD, indicating decreased connectivity between the hippocampus and the rest of the brain in patients with MDD[20]; (iii) lower structural network integrity in the default mode, ventromedial prefrontal cortical and salience networks in individuals with MDD[15]; and (iv) disrupted CT network organization in MDD, especially connections within and between frontal, temporal, and limbic areas.[21] However, no studies have explored brain SCNs in adolescents at risk for MDD.

In addition, heterogeneity of the control and depression groups may contribute to inconsistencies in the published findings. Recent studies showed that healthy individuals and those with depression are very similar with respect to univariate neurobiological and genetic measures, with both groups being nearly indistinguishable at a single-participant level.[22,23] Along these lines, it might be argued that heterogeneity in the group without depression could also hinder the identification of brain-based contrasts between cases and controls.

Heterogeneity in published findings can also be explained by the definition of depression risk through a single factor.[24] The investigation of neurobiological correlates of risk factors for the onset of depression has mostly focused on single factors for assigning risk status (e.g., family history of depression).[25] However, the focus on single risk factors results in the reliance on only one source of information for stratifying individuals in terms of HR and LR. For instance, adolescents without family history of the disorder (often classified as LR in many studies) may have a high probability of developing MDD based on other risk factors (e.g., maltreatment during childhood).[2]

Our group developed a composite risk score to estimate the individual probability of developing major depression among Brazilian adolescents. The Identifying Depression Early in Adolescence Risk Score (IDEA-RS) comprises only sociodemographic variables that can be easily obtained directly from the adolescent.[26] In addition to its initial development in a Brazilian sample, the tool has been externally assessed in different countries from five continents (Africa, Asia, Europe, North America, and Oceania), showing above-chance discriminative ability in all contexts.[26-29] Using the IDEA-RS, we recently enrolled 150 adolescents in the Identifying Depression Early in Adolescence Risk Stratified Cohort (IDEA-RiSCo),[30] a well-characterized sample of Brazilian adolescents at LR, at HR, and with current MDD.

In this study, we present cross-sectional structural neuroimaging analyses using data from the baseline assessment of the IDEA-RiSCo sample. We aim to explore regional cortical morphometric differences associated with the risk and presence of depression through a spatially unbiased vertex-based approach that provides measurements of CV, surface area (SA), and CT across several thousand points along the cortical sheet. We also

examined between-group differences in subcortical volumes. Finally, we explored the differences in the organization of SCNs between groups.

Methods

Participants

We analyzed neuroimaging data on 150 adolescents aged 14-16 years ascertained from a population of 7,720 adolescents screened in 101 public state schools located in the city of Porto Alegre, Brazil. The sample of 150 adolescents (50% female) was stratified using an empirically defined algorithm, the IDEA-RS, and divided into three groups: LR, HR, and current depression (MDD).[24] Individuals in both LR and HR had no current or past depressive disorders. Whereas LR adolescents were operationalized as those scoring equal to or below the 20th percentile of the IDEA-RS, HR adolescents were those scoring equal to or above the 90th percentile of the risk score. The MDD group comprised adolescents in a current unipolar depressive episode and with an IDEA-RS equal to or above the 90th percentile. This design allowed two-by-two comparisons in which the LR and HR groups were similar in showing no lifetime history of any depressive disorder, but markedly different regarding the IDEA-RS; conversely, the HR and MDD groups were similar regarding IDEA-RS, but while HR participants showed no evidence of depression at any time, those in the MDD group had to be in a current depressive episode at the time of the assessment. Further details on the rationale and design of the IDEA-RiSCo study are described elsewhere.[28] It is also important to mention that cross-sectional functional neuroimaging data from the IDEA-RiSCo cohort have already been published.[25,31,32]

Risk stratification

The IDEA-RS integrates data from 11 sociodemographic variables (skin color; biological sex; school failure; drug use; involvement in fights; running away from home; social isolation; childhood abuse; and poor relationship with mother, father, and between parents), generating an individual-level probability of having a unipolar depressive episode in 3 years. IDEA-RS was initially developed in a sample of 15-year-old adolescents to estimate the individual-level probability of a diagnosis of MDD at age 18 years in the 1993 Pelotas Birth Cohort Study, exhibiting a C-statistic of 0.78. The model was externally evaluated in other countries, showing discriminative capacity above chance.[26-29]

Clinical assessment

Board-certified child and adolescent psychiatrists, unaware of the participant's risk group status, individually interviewed the adolescents and their primary caregivers.[30] Absence of a lifetime history of depressive disorders (including dysthymia) for the LR and HR groups and presence of a current depressive episode for the MDD group were determined using the Brazilian Portuguese translation of the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL). Moreover, the severity of depressive symptoms was measured with the Mood and Feelings Questionnaire (MFQ) and Children's Depression Rating Scale-Revised (CDRS-R). Socioeconomic status was measured by The Brazilian Economic Classification Criteria proposed by the Brazilian Market Research Association (Associação Brasileira de Empresas de Pesquisa [ABEP]).[33] Adolescents were excluded from the study if they met diagnostic criteria for autism spectrum disorder, bipolar disorder, eating disorders, post-traumatic stress disorder, schizophrenia, or substance use disorders, if they were not right-handed, or if they had an intelligence quotient (IQ) < 70. Summary clinical, laboratory, and imaging inclusion flow diagrams can be found in online-only supplementary Figure S1 and in Kieling et al.[30]

Magnetic resonance imaging data acquisition

Neuroimaging data were acquired from a 3T Ingenia scanner (Koninklijke Philips N.V., Amsterdam, The Netherlands), software version 5.3.1, and 16-channel head coil at Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil. Structural images were collected using MPRAGE T1-weighted volumetric acquisition in the sagittal plane with repetition time (TR) = 8.55 ms, echo time (TE) = 3.94 ms, inversion time (TI) = 900 ms, rotation angle = 8°, field of view = 240 $\times$ 240 mm, 170 slices 0.94 mm thick, acquisition matrix 256 $\times$ 256, resulting in a voxel resolution of 0.94 $\times$ 0.94 $\times$ 0.94 mm^3. The original image format (Digital Imaging and Communications in Medicine [DICOM] [http://www.rsna.org/Technology/DICOM/]) was converted to the NifTI-1 format (Neuroimaging Informatics Technology [http://www.nifti.nimh.nih.gov/nifti-1]) using dcm2niigui software (http://cabitl.com/mricro/mricon/dcm2nii.html).

Before MRI acquisition, participants were instructed to remove any metallic objects from the body (e.g., earrings, piercings, rings, watches); they were also informed about the duration of the exam and the importance of keeping their head still. In addition, some strategies were applied during the scan to create a good experience and obtain adequate data based on the participant's needs, such as having one of the guardians present in the scanner room, having a conversation with them through the intercom between sequences, and using head cushions to maintain comfort and reduce scanner movement. After performing the structural sequence, the images were immediately inspected visually by primary author and a trained radiologist, which allowed for reacquisition, if necessary.

Image processing

Each T1-weighted image was processed using FreeSurfer v.7.2.0 software (http://surfer.nmr.mgh.harvard.edu/) to derive models of the cortical surface. These well-validated and fully automated procedures have been

extensively described elsewhere.[34,35] In brief, a single filled white matter volume was generated for each hemisphere after intensity normalization, ''skull stripping,'' and image segmentation using a connected components algorithm.[36] A surface tessellation was then generated for each white matter volume by fitting a deformable template. This resulted in a triangular cortical mesh for gray/white matter surfaces consisting of 150,000 vertices (i.e., points of triangles) per hemisphere. Measures of CT were defined as the closest distance from the gray and white matter boundary to the gray matter and cerebrospinal fluid boundary at each vertex on the tessellated surface.[33] SA measurements were calculated as the average of the area of triangles indicated for a vertex (i.e., sharing that vertex). Regional CV estimates were obtained by multiplying CT measures by their areal expansion or compression at each vertex.[35] Each parameter was smoothed using a 10-mm surface-based smoothing kernel.

FreeSurfer software was also used to target subcortical structures.[35] Parcellation into ROIs was based on the Fischl atlas.[37] To assess differences in risk groups, the volume of eight bilateral subcortical structures (nucleus accumbens, caudate nucleus, putamen, pallidum, thalamus, amygdala, and hippocampus) were selected based on previous studies that addressed the association of these brain structures and depression in adolescence.[38] All segmentations were visually inspected for accuracy following standardized protocols of the ENIGMA quality control procedures (http://enigma.ini.usc.edu/protocols/imaging-protocols).

Statistical analysis

Statistical analyses were performed in R 3.6.1 (R Core Team, 2018) and implemented in RStudio v1.383,[39] except for whole-brain vertex-wise analyses, which were conducted using the FreeSurfer command line (see below).

Whole-brain vertex-wise differences in CT, CV, and SA

The main analyses were conducted using the command line group analysis flow in FreeSurfer, which uses a general linear model (GLM) at each point of the inflated cortical surface. Parameter estimates for each measure (CV, CT, SA) and the main effect of risk group were calculated using a linear regression model at each vertex and subject, with age, sex, and the respective total brain measure as covariates (total CV for CV, average thickness for CT, and total SA for SA). Cluster-based correction for multiple comparisons was performed using the permutation procedure implemented by mri_glmfit-sim with 10,000 permutations, a vertex-wise cluster forming threshold of 0.001, and a cluster-wise p threshold of 0.05. Between-group differences in global brain measures were assessed using a Kruskal-Wallis test (for average CT) and a one-way analysis of variance (ANOVA) (for total CV and total SA). Statistical significance was defined as the bilateral Dunn-Bonferroni corrected p-value ($p < 0.05$). Data by risk group were first tested for normality of distribution and homogeneity of variance using the Shapiro-Wilk and Levene tests, respectively.

Subcortical volume

We examined possible differences between groups (LR vs. HR vs. MDD) in subcortical volume corrected by sex, age, and total intracranial volume (ICV) (for analyses, we used the average of left and right volumes) through analysis of covariance (ANCOVA).

Structural covariance

We performed an SCN analysis using the python P-based scona toolkit (https://github.com/WhitakerLab/scona). A cortical network for each risk group was obtained by structural covariance, that is, Pearson's pairwise correlation coefficient of CV for all possible pairs of regions in the splitting model, estimated by FreeSurfer using the Desikan-Killiany atlas.[40] The bilateral mean values of 33 CV ROIs and 6 subcortical volume ROIs were corrected for age, sex, and individual brain size. Binary graphics were built to be connected by nodes, with a connection density of 10%.[17] For each node in the graphs, we estimated two measures of topological centrality: closeness and betweenness. Closeness represents the sum of the shortest path distance from a specific node to all other nodes in a network. Closeness centrality is viewed less as a metric of node importance and more as an ease of reach to many nodes with the fewest steps possible. High closeness centrality of a node indicates that the other nodes in the network are only a small number of steps away from that node. On the other hand, low closeness centrality means a node cannot be easily reached from other nodes without many steps.[41] Betweenness centrality represents the frequency with which a node lies on all the shortest paths between other nodes. A node with a high betweenness centrality is more likely to act as an intermediary in the transmission of information between other nodes or even clusters of nodes in the network.[20]

We focused on these two measures since previous studies have highlighted their sensitivity to neurodevelopmental changes.[42] Statistical significance of the group differences in measures of closeness and betweenness at each node was assessed using permutation tests, in which risk group labels were randomly distributed among the individuals between risk groups, and the correlation matrix for each risk group was recalculated 100,000 times. This allowed the nonparametric estimation of the null distribution for the risk group difference observed at each node. The significance level was set at 5% following false discovery rate (FDR) correction for multiple comparisons at the whole-brain network and also within four subnetworks (affective, reward, default, and control). Subnetworks were defined a priori from previous research on brain network models for depression,[13] and nodes were based on the following neuroanatomical regions from FreeSurfer's subcortical and Desikan-Killiany[40] atlases: affective (medial orbital frontal, rostral anterior cingulate, insula, hippocampus, amygdala), reward (rostral middle frontal, caudate, putamen, accumbens),

default mode network (inferior parietal cortex, posterior cingulate, precuneus), and cognitive control (pars opercularis of the inferior frontal gyrus, superior parietal cortex).

Ethics statement

This study was approved by the Brazilian National Ethics in Research Commission (Comissão Nacional de Ética em Pesquisa [CONEP]) (CAAE 50473015.9.0000.5327). Adolescents provided written assent and their primary caregivers provided written informed consent prior to entering the study. Approval for the school screening phase was obtained from the 1st Regional Education Bureau (1ª Coordenadoria Regional de Educação), in charge of public state schools in the city of Porto Alegre. All participants received feedback with findings from the diagnostic assessment and were referred for care in the Brazilian Unified Health System (SUS) if clinically indicated. Situations of imminent risk of self-harm or maltreatment were referred to emergency care or protective services following Brazilian legislation. Participants received no financial incentive for taking part in the study but were compensated for expenses related to their participation (e.g., travel).

Results

Participant characteristics

Descriptive characteristics of the IDEA-RiSCo sample are presented in Table 1. From August 2018 to December 2019, 150 participants underwent MRI scans – 50 in the LR group, 50 in the HR group, and 50 in the MDD group. In terms of age, there was a small but significant difference between groups, with the LR group being slightly younger than the HR and MDD groups. In addition, the MDD group had (unsurprisingly) higher adolescent-reported (MFQ-C) and clinician-rated (CDRS-R) symptoms compared to the LR and HR groups. Further, the HR group also had higher adolescent-reported (MFQ-C) symptoms compared to the LR group.

Table 1 Characteristics of IDEA-RiSCo sample participants (n=50)

	Low risk	High risk	MDD
Age (years)	15.36 (0.81)	15.76 (0.83)	15.80 (0.75)
IDEA-RS (%)[†]	1.33 (0.32)	8.21 (4.61)	9.24 (5.60)
MFQ-C (adolescent self-report)	6.74 (4.84)	12.82 (8.36)	41.21 (11.11)
CDRS-R	19.33 (2.85)	22.64 (5.44)	50.94 (9.79
Any comorbid disorder[‡]	14.00 (28.00)	18.00 (36.00)	31.00 (62.00)
ABEP	31.88 (9.78)	25.27 (7.63)	26.78 (9.28)
WASI (IQ)	90.06 (10.16)	88.04 (8.57)	88.64 (9.76)
Body mass index	22.61 (5.46)	22.4 (4.84)	22.75 (3.87)
Global brain measures			
Total cortical volume (mm^3)	712,426 (59,606)	696,442 (61,714)	702,848 (72,172)
Total surface area (mm^2)	173,775 (15,101)	173,511 (15,153)	174,471(19,137)
ICV (mm)	1,436,339 (202,570)	1,489,117 (138,890)	1,516,607 (181,509)
Average thickness (mm), median (IQR)	2.62 (0.12)	2.58 (0.07)	2.60 (0.06)
IDEA-RS features, n (%)			
Sex, female	25 (50.00)	25 (50.00)	25 (50.00)
Skin color, non-white	22 (44.00)	26 (52.00)	26 (52.00)
Meets friends	49 (98.00)	40 (80.00)	30 (60.00)
School failure	0 (0.00)	29 (58.00)	25 (50.00)
Ran away	1 (2.00)	3 (6.00)	13 (26.00)
Any drug use	29 (58.00)	44 (88.00)	47 (94.00)
Fights	0 (0.00)	20 (40.00)	27 (54.00)
Relationship[§] with father	4.52 (0.79)	2.48 (1.22)	2.00 (1.18)
Relationship[§] with mother	4.78 (0.54)	3.92 (1.01)	3.14 (1.14)
Relationship[§] between parents	4.18 (1.08)	2.38 (1.23)	1.94 (1.04)
Childhood maltreatment			
None	50 (100.00)	1.00 (2.00)	0.00 (0.00)
Probable	0.00 (0.00)	12.00 (24.00)	4.00 (8.00)
Severe	0.00 (0.00)	37.00 (74.00)	46.00 (92.00)

Data presented as mean (SD), unless otherwise specified.
ABEP = Brazilian Economic Classification Criteria proposed by the Brazilian Market Research Association (Associação Brasileira de Empresas de Pesquisa); CDRS-R = Children's Depression Rating Scale-Revised; ICV = intracranial volume; IDEA-RiSCo = Identifying Depression Early in Adolescence Risk Stratified Cohort; IDEA-RS = Identifying Depression Early in Adolescence Risk Score; IQ = intelligence quotient; IQR = interquartile range; MDD = major depressive disorder; MFQ-C = Mood and Feelings Questionnaire-Child; WASI = Wechsler Abbreviated Scale of Intelligence.
[†] The individual-level probability of developing depression at age 18 in the LR group is 1.33%, while for the HR group, it is 8.21%.
[‡] Comorbid disorders: generalized anxiety disorder; separation anxiety disorder; specific phobias; social anxiety disorder; panic disorder; attention-deficit/hyperactivity disorder; obsessive-compulsive disorder; enuresis; oppositional defiant disorder; agoraphobia; disruptive mood dysregulation disorder; conduct disorder; encopresis.
[§] "Relationship" variables were analyzed as continuous (mean, SD), with answers ranging from 1 (bad) to 5 (great).

The HR and MDD groups exhibited lower socioeconomic scores (ABEP) compared to the LR group. School failure, drug use, and involvement in fights were less common in the LR group compared to HR and MDD. On the other hand, a history of running away from home was reported more frequently by those in the MDD group compared to LR and HR. Adolescents in the LR group rated both their relationship with the father and that between their parents more favorably than adolescents in the HR and MDD groups. In terms of their relationship with the mother, there was a gradual decrease from LR to HR to MDD – a similar pattern was observed for the proportion of adolescents who reported meeting friends regularly. While all LR participants fell into the ''no maltreatment'' category, three-quarters and nearly all of those in the HR and MDD groups, respectively, were classified as having suffered ''severe maltreatment.'' Regarding lifetime comorbid diagnoses for the IDEA-RiSCo sample, a higher prevalence was observed for any anxiety disorder and any comorbid disorder in the MDD group.

No significant variations were observed in the percentage of adolescents who classified themselves as white amongst the three groups, or in IQ scores and body mass index. Additionally, the three groups were similar in terms of total CV and total SA. However, the HR and MDD groups had a decreased average CT when compared to the LR group. We thus covaried for the respective total brain measure in subsequent analyses.

Regional vertex-wise differences in CT, CV, and SA

We found no significant between-group differences in regional vertex-wise analysis of CV, CT, or SA, after correction for multiple comparisons. Uncorrected maps showing nonsignificant effects with small spatial extents are depicted in online-only supplementary Figure S2 only for illustrative purposes.

Subcortical volume

There were no significant differences in subcortical volume (pallidum, hippocampus, amygdala, nucleus accumbens, thalamus, caudate, putamen) between groups, even when adjusted for age, sex, and ICV. Results by risk group are shown in Figure 1.

Structural covariance

Comparisons between risk groups revealed an increased betweenness centrality of the hippocampus in the network of the HR group when compared to the MDD ($p = 0.045$) and the LR groups ($p < 0.001$), even after a permutation test and FDR correction for regions within the affective network. However, this effect was not significant when applying FDR correction for all nodes included in the analysis. Closeness and betweenness centrality measures for all nodes in the SCN estimated for each risk group can be found in Table S1 (online-only supplementary material).

Discussion

In this paper, we reported the baseline results of structural neuroimaging data from Brazilian adolescents at LR, at HR, and currently experiencing a depressive episode (MDD). Using the IDEA-RS, we compared the LR, HR, and MDD groups in terms of regional differences in CT, CV, SA, and subcortical volume. Results showed no significant differences between groups in any of these comparisons. This is in line with other studies on adolescent depression neuroimaging that have not reported clear morphometric differences associated with the risk and presence of depression in adolescence.[22,43] Our study is unique in that it used an empirically devised composite score including 11 sociodemographic variables to stratify adolescents by their risk for developing MDD.

SCN analysis showed an increase in the hippocampus betweenness centrality index in the HR group network compared to the LR and MDD group networks. This suggests an importance of the hippocampus in the affective structural network: the hippocampus, a key region of the limbic system, is involved in the formation, consolidation, and recovery of memory, as well as other complex processes such as the regulation of the hypothalamic-pituitary-adrenocortical axis. This region is also associated with the processing and regulation of emotions.[43] Therefore, it is possible to speculate that the hippocampus plays a major role in stress response within the affective network in the HR group, due to its ability to recall specific experiences and the general knowledge acquired with them.[44]

A strength of our study was the employment of an innovative method of risk stratification, which simultaneously relied on multiple variables. Further, the thorough independent clinical evaluation with child and adolescent psychiatrists who interviewed the adolescents and their caregivers individually provided a well-characterized sample of adolescents at LR, at HR, and in a current depressive episode.

There are, nonetheless, limitations of the study that should also be considered. First, the cross-sectional nature of the results presented here prevents us from drawing conclusions about the directions of any potential associations. Second, the ascertainment strategy, purposefully designed to identify empirical extremes in terms of risk for developing MDD, by its nature also limits the generalizability to other adolescent samples – a special aspect to consider here is the high load of risk factors in the MDD group. Third, the careful characterization of more homogeneous groups resulted in a limited sample size – although not smaller than most individual site studies published until now.[25] Fourth, the absence of information on the recurrence of depressive episodes throughout life and the age of the first episode may make it difficult to identify changes in brain structure, as structural measures of the brain may become more evident with multiple depressive episodes.[45]

In conclusion, we did not observe significant differences in whole-brain vertex-wise CV, SA, and CT between risk/MDD groups. This study stands out for presenting structural MRI data of a carefully ascertained

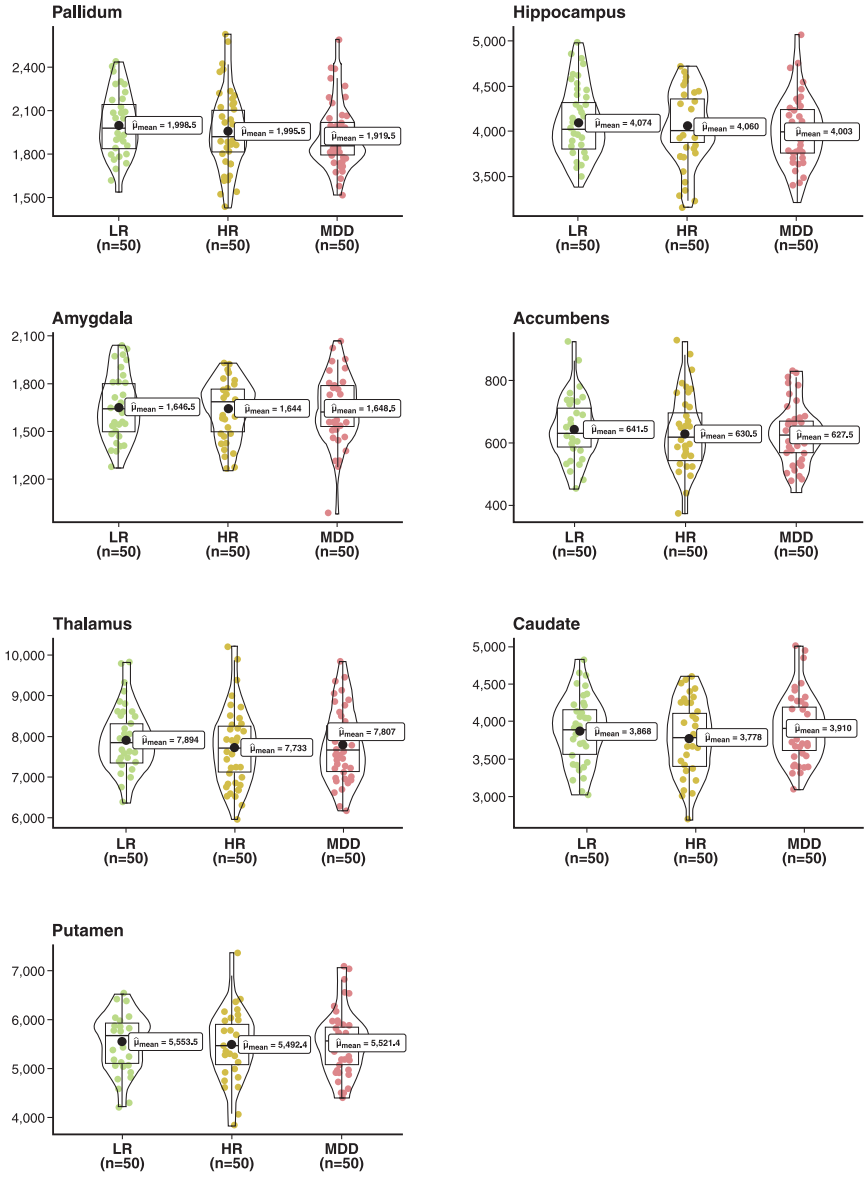

Figure 1 Subcortical volumes (in mm^3) according to risk groups. HR = high-risk; LR = low-risk; MDD = major depressive disorder.

sample of adolescents from Brazil, a middle-income country – especially considering that nine out of 10 children and adolescents in the world live in low- and middle-income areas and there is a lack of representativeness of this population in published neuroimaging studies.[25,46] Furthermore, the use of an empirically-based composite score to stratify the risk of developing depression is a promising strategy that must be further explored to support a better understanding of the neurobiological mechanisms leading to the onset of depression.

Acknowledgements

The Identifying Depression Early in Adolescence (IDEA) project was 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).

JRS receives financial support from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP; grants 2021/05332-8, 2018/04654-9, and 2018/21934-5). JRS, BAK, and CK are supported by the U.S. National Institute of Mental Health (NIMH; R21MH124072).

HLF was partly supported by the Economic and Social Research Council (ESRC) Centre for Society and Mental Health at King's College London (ES/S012567/1). VM was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London, Maudsley National Health Service (NHS) Foundation Trust, and King's College London. CK is a CNPq researcher and an Academy of Medical Sciences Newton Advanced fellow. The views expressed are those of the authors and do not necessarily reflect the views of the NHS, the NIHR, the Department of Health and Social Care, the ESRC, or King's College London.

We are extremely grateful to the schools and individuals who participated in this study, and to all members of the IDEA team for their dedication, hard work, and insights.

Disclosure

The authors report no conflicts of interest.

References

1 Herrman H, Patel V, Kieling C, Berk M, Buchweitz C, Cuijpers P, et al. Time for united action on depression: a Lancet World Psychiatric Association Commission. Lancet. 2022;399:957-1022.
2 Kieling C, Adewuya A, Fisher HL, Karmacharya R, Kohrt BA, Swartz JR, et al. Identifying depression early in adolescence. Lancet Child Adolesc Health. 2019;3:211-3.
3 Kim JH, Suh SI, Lee HJ, Lee JH, Lee MS. Cortical and subcortical gray matter alterations in first-episode drug-naïve adolescents with major depressive disorder. Neuroreport. 2019;30:1172-8.
4 Straub J, Brown R, Malejko K, Bonenberger M, Grön G, Plener PL, et al. Adolescent depression and brain development: evidence from voxel-based morphometry. J Psychiatry Neurosci. 2019;44: 237-45.
5 Nickson T, Chan SWY, Papmeyer M, Romaniuk L, Macdonald A, Stewart T, et al. Prospective longitudinal voxel-based morphometry study of major depressive disorder in young individuals at high familial risk. Psychol Med. 2016;46:2351-61.
6 Yang J, Zhang M, Ahn H, Zhang Q, Jin TB, Li I, et al. Development and evaluation of a multimodal marker of major depressive disorder. Hum Brain Mapp. 2018;39:4420-39.
7 Mills KL, Tamnes CK. Methods and considerations for longitudinal structural brain imaging analysis across development. Dev Cogn Neurosci. 2014;9:172-90.
8 Couvy-Duchesne B, Strike LT, Zhang F, Holtz Y, Zheng Z, Kemper KE, et al. A unified framework for association and prediction from vertex-wise grey-matter structure. Hum Brain Mapp. 2020;41: 4062-76.
9 Goto M, Abe O, Hagiwara A, Fujita S, Kamagata K, Hori M, et al. Advantages of using both voxel- and surface-based morphometry in cortical morphology analysis: a review of various applications. Magn Reson Med Sci. 2022;21:41-57.
10 Wei G, Si R, Li Y, Yao Y, Chen L, Zhang S, et al. "No Pain No Gain": evidence from a parcel-wise brain morphometry study on the volitional quality of elite athletes. Brain Sci. 2020;10:459.
11 Xiong G, Dong D, Cheng C, Jiang Y, Sun X, He J, et al. Potential structural trait markers of depression in the form of alterations in the structures of subcortical nuclei and structural covariance network properties. Neuroimage Clin. 2021;32:102871.
12 Chahal R, Gotlib IH, Guyer AE. Research review: brain network connectivity and the heterogeneity of depression in adolescence – a precision mental health perspective. J Child Psychol Psychiatry. 2020;61:1282-98.
13 Li BJ, Friston K, Mody M, Wang HN, Lu HB, Hu DW. A brain network model for depression: from symptom understanding to disease intervention. CNS Neurosci Ther. 2018;24:1004-19.
14 Mesulam MM. From sensation to cognition. Brain. 1998;121:1013-52.
15 He Y, Chen ZJ, Evans AC. Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. Cereb Cortex. 2007;17:2407-19.
16 Yang X, Kumar P, Nickerson LD, Du Y, Wang M, Chen Y, et al. Identifying subgroups of major depressive disorder using brain structural covariance networks and mapping of associated clinical and cognitive variables. Biol Psychiatry Glob Open Sci. 2021;1: 135-45.
17 Alexander-Bloch A, Raznahan A, Bullmore E, Giedd J. The convergence of maturational change and structural covariance in human cortical networks. J Neurosci. 2013;33:2889-99.
18 Wu H, Sun H, Wang C, Yu L, Li Y, Peng H, et al. Abnormalities in the structural covariance of emotion regulation networks in major depressive disorder. J Psychiatr Res. 2017;84:237-42.
19 Watanabe K, Kakeda S, Katsuki A, Ueda I, Ikenouchi A, Yoshimura R, et al. Whole-brain structural covariance network abnormality in first-episode and drug-naïve major depressive disorder. Psychiatry Res Neuroimaging. 2020;300:111083.
20 Jacob Y, Morris LS, Verma G, Rutter SB, Balchandani P, Murrough JW. Altered hippocampus and amygdala subregion connectome hierarchy in major depressive disorder. Transl Psychiatry. 2022;12:209.
21 Wang T, Wang K, Qu H, Zhou J, Li Q, Deng Z, et al. Disorganized cortical thickness covariance network in major depressive disorder implicated by aberrant hubs in large-scale networks. Sci Rep. 2016;6:27964.
22 Schmaal L, Hibar DP, Sämann PG, Hall GB, Baune BT, Jahanshad N, et al. Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA Major Depressive Disorder Working Group. Mol Psychiatry. 2017;22:900-9.
23 Winter NR, Leenings R, Ernsting J, Sarink K, Fisch L, Emden D, et al. Quantifying deviations of brain structure and function in major depressive disorder across neuroimaging modalities. JAMA Psychiatry. 2022;79:879-88.
24 McManimen SL, Jason LA, Williams YJ. Variability in symptoms complicates utility of case definitions. Fatigue. 2015;3:164-72.
25 Battel L, Cunegatto F, Viduani A, Fisher HL, Kohrt BA, Mondelli V, et al. Mind the brain gap: the worldwide distribution of neuroimaging research on adolescent depression. Neuroimage. 2021;231:117865.
26 Rocha TBM, Fisher HL, Caye A, Anselmi L, Arseneault L, Barros FC, et al. Identifying adolescents at risk for depression: a prediction score performance in cohorts based in 3 different continents. J Am Acad Child Adolesc Psychiatry. 2021;60:262-73.
27 Brathwaite R, Rocha TBM, Kieling C, Gautam K, Koirala S, Mondelli V, et al. Predicting the risk of depression among adolescents in Nepal using a model developed in Brazil: the IDEA Project. Eur Child Adolesc Psychiatry. 2021;30:213-23.
28 Brathwaite R, Rocha TBM, Kieling C, Kohrt BA, Mondelli V, Adewuya AO, et al. Predicting the risk of future depression among school-attending adolescents in Nigeria using a model developed in Brazil. Psychiatry Res. 2020;294:113511.
29 Caye A, E.Marchionatti L, Pereira R, Fisher HL, Kohrt BA, Mondelli V, et al. Identifying adolescents at risk for depression: assessment of a global prediction model in the Great Smoky Mountains Study. J Psychiatr Res. 2022;155:146-52.
30 Kieling C, Buchweitz C, Caye A, Manfro P, Pereira R, Viduani A, et al. The Identifying Depression Early in Adolescence Risk Stratified Cohort (IDEA-RiSCo): rationale, methods, and baseline characteristics. Front Psychiatry. 2021;12:697144.
31 Yoon L, Rohrsetzer F, Battel L, Anés M, Manfro PH, Rohde LA, et al. 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. 2022;63:579-90.
32 Yoon L, Rohrsetzer F, Battel L, Anes M, Manfro PH, Rohde LA, et al. Frontolimbic network topology associated with risk and presence of depression in adolescents: a study using a composite risk score in Brazil. Biol Psychiatry Cogn Neurosci Neuroimaging. 2023;8:426-35.
33 Associação Brasileira de Empresas de Pesquisa (ABEP). Critério de classificação econômica Brasil [Internet]. 2018 [cited 2018 Apr 17]. www.abep.org/criterio-brasil
34 Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A. 2000;97:11050-5.

35 Fischl B. FreeSurfer. Neuroimage. 2012;62:774-81.
36 Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis: I. Segmentation and surface reconstruction. Neuroimage. 1999;9: 179-94.
37 Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron. 2002;33:341-55.
38 Wu MJ, Wu HE, Mwangi B, Sanches M, Selvaraj S, Zunta-Soares GB, et al. Prediction of pediatric unipolar depression using multiple neuromorphometric measurements: a pattern classification approach. J Psychiatr Res. 2015;62:84-91.
39 RStudio Team. RStudio: integrated development environment for R [Internet]. 2022 [cited 2022 Apr 20]. www.rstudio.com/
40 Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 2006;31:968-80.
41 Telesford QK, Simpson SL, Burdette JH, Hayasaka S, Laurienti PJ. The brain as a complex system: using network science as a tool for understanding the brain. Brain Connect. 2011;1:295-308.
42 Blank TS, Meyer BM, Wieser MK, Rabl U, Schögl P, Pezawas L. Brain morphometry and connectivity differs between adolescent- and adult-onset major depressive disorder. Depress Anxiety. 2022;39: 387-96.
43 Shapero BG, Chai XJ, Vangel M, Biederman J, Hoover CS, Whitfield-Gabrieli S, et al. Neural markers of depression risk predict the onset of depression. Psychiatry Res Neuroimaging. 2019;285: 31-9.
44 Weissman DG, Lambert HK, Rodman AM, Peverill M, Sheridan MA, McLaughlin KA. Reduced hippocampal and amygdala volume as a mechanism underlying stress sensitization to depression following childhood trauma. Depress Anxiety. 2020;37: 916-25.
45 Schmaal L, Veltman DJ, van Erp TGM, Sämann PG, Frodl T, Jahanshad N, et al. Subcortical brain alterations in major depressive disorder: findings from the ENIGMA major depressive disorder working group. Mol Psychiatry. 2016;21:806-12.
46 Kieling C, Rohde LA. Child and adolescent mental health research across the globe. J Am Acad Child Adolesc Psychiatry. 2012;51: 945-7.