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Prefrontal cortex and amygdala anatomy in youth with persistent levels of harsh parenting practices and subclinical anxiety symptoms over time during childhood

Sabrina Suffren^{1,2,3,4,5,6} , Valérie La Buissonnière-Ariza^{1,2,3} , Alan Tucholka^{1,2}, Marouane Nassim¹, Jean R. Séguin^{1,7,8}, Michel Boivin^{7,9}, Manpreet Kaur Singh¹⁰, Lara C. Foland-Ross¹⁰, Franco Lepore^{1,2,3}, Ian H. Gotlib¹¹, Richard E. Tremblay^{1,3,7,12,13} and Françoise S. Maheu¹

¹Research Center, Sainte-Justine Hospital, University of Montreal, Canada; ²Research Center in Neuropsychology and Cognition, University of Montreal, Canada; ³Department of Psychology, University of Montreal, Canada; ⁴Department of Psychology, University of Quebec in Trois-Rivières, Canada; ⁵Research Center, Hôpital en santé mentale Albert-Prévost, CIUSSS du Nord-de-l'Île-de-Montreal, Canada; ⁶Centre de Recherche Universitaire sur les Jeunes et les Familles (CRUJeF), Québec, Canada; ⁷Research Group on Children's Psychosocial Maladjustment, University of Montreal, Canada; ⁸Department of Psychiatry and Addictology, University of Montreal, Canada; ⁹Department of Psychology, Laval University, Quebec City, Canada; ¹⁰Department of Psychiatry and Behavioral Sciences, School of Medicine, Stanford, CA, USA; ¹¹Department of Psychology, Stanford University, Stanford, CA, USA; ¹²Department of Pediatrics, University of Montreal, Canada and ¹³School of Public Health, Physiotherapy and Sport Sciences, University College Dublin, Ireland

Abstract

Childhood adversity and anxiety have been associated with increased risk for internalizing disorders later in life and with a range of brain structural abnormalities. However, few studies have examined the link between harsh parenting practices and brain anatomy, outside of severe maltreatment or psychopathology. Moreover, to our knowledge, there has been no research on parenting and subclinical anxiety symptoms which remain persistent over time during childhood (i.e., between 2.5 and 9 years old). Here, we examined data in 94 youth, divided into four cells based on their levels of coercive parenting (high / low) and of anxiety (high / low) between 2.5 and 9 years old. Anatomical images were analyzed using voxel-based morphometry (VBM) and FreeSurfer. Smaller gray matter volumes in the prefrontal cortex regions and in the amygdala were observed in youth with high versus low levels of harsh parenting over time. In addition, we observed significant interaction effects between parenting practices and subclinical anxiety symptoms in rostral anterior cingulate cortical thickness and in amygdala volume. These youth should be followed further in time to identify which youth will or will not go on to develop an anxiety disorder, and to understand factors associated with the development of sustained anxiety psychopathology.

Keywords: anxiety, FreeSurfer, internalized disorders, parental practices, VBM

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Childhood adversity and anxiety symptoms are associated with a greater risk of developing internalizing disorders, especially anxiety disorders (Hirshfeld-Becker, Micco, Simoes, & Henin, 2008; Teicher & Samson, 2013). Harsh parenting (i.e., hostile, cold, rejection, critical and coercive child-rearing behaviors), though a milder form of adversity, is closely related to high levels of anxiety and worry in childhood (Brown & Whiteside, 2008; McLeod, Wood, & Weisz, 2007). Given the significant prevalence of harsh parenting practices in the absence of severe maltreatment and of subclinical anxiety symptoms among youth (Wood, McLeod, Sigman, Hwang, & Chu, 2003), understanding neural correlates of these two risk factors concurrently may have significant public

health relevance. The present study aimed to examine how enduring harsh parenting in the absence of severe maltreatment and subclinical anxiety symptoms relate, both independently and in concert, to brain structure in youth.

Several past studies in youth with a history of severe childhood adversity (e.g., physical, emotional, sexual abuse; physical, emotional neglect; institutionalization; domestic violence; trauma, early-life stress, all without posttraumatic stress disorder [PTSD]), have demonstrated lower prefrontal cortex (including orbitofrontal and anterior cingulate cortex) volume and thickness compared to youth unexposed to severe childhood adversity (Baker et al., 2012; De Brito et al., 2013; Hanson et al., 2010; Hodel et al., 2015; Kelly et al., 2013; McLaughlin et al., 2014). Lower prefrontal cortex volume and anterior cingulate cortex volume and thickness have also been associated with higher trauma levels (Edmiston et al., 2011; Korgaonkar et al., 2013). Amygdala volume was smaller in youth with a history of childhood adversity, compared to youth without such a history (Edmiston et al., 2011; Hanson et al., 2015; Korgaonkar et al., 2013). To our

Author for Correspondence: Dr. Sabrina Suffren, PhD Research Centre, Ste-Justine University Hospital, 3175 Côte Ste-Catherine, Montréal, Québec, H3T 1C5, Canada; E-mail: sabrina.suffren@gmail.com

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knowledge, no study has looked at the anatomy of amygdala and prefrontal cortex in youth who have experienced coercive parenting practices in the absence of severe maltreatment. Nevertheless, extant studies point to possible reductions in prefrontal cortical volume and cortical thinning, as well as amygdala volume reduction, that may be present in youth who have experienced high levels of persistent coercive parenting practices during childhood.

In youth with, compared to without, anxiety disorders, prefrontal, orbitofrontal, or anterior cingulate cortical volumes did not differ (De Bellis *et al.*, 2002; Liao *et al.*, 2013, 2014; Milham *et al.*, 2005; Mueller *et al.*, 2013). However, orbitofrontal (Jones *et al.*, 2015) and rostral anterior cingulate (Suffren, Chauret, Nassim, Lepore, & Maheu, 2019) cortex thinning have been observed in youth with anxiety disorders. Further, in youth without any anxiety disorders, but with at least one parent with an anxiety disorder, we have previously reported rostral anterior cingulate cortex thinning compared to youth with no parent with an anxiety disorder (Suffren *et al.*, 2019). Others have reported increased ventromedial prefrontal cortex thickness (including prefrontal cortex and rostral anterior cingulate cortex) with increased anxiety levels (Ducharme *et al.*, 2013). In addition, amygdala volume is more often reported as smaller (Milham *et al.*, 2005; Mueller *et al.*, 2013; Suffren *et al.*, 2019); but in some studies observed to be greater (De Bellis *et al.*, 2000; Jones *et al.*, 2015) or no different (Liao *et al.*, 2013, 2014), in pediatric anxiety disorders, compared to youth without a psychiatric disorder. In youth without anxiety disorder, anxiety symptoms (Juranek *et al.*, 2006; Qin *et al.*, 2014) and exposure to maternal depressive symptomatology (Lupien *et al.*, 2011) seem to be linked to increased amygdala volume. Thus, we expect that subclinical anxiety symptoms in youth will be linked to greater prefrontal cortex thickness and greater amygdala volume.

It is important to keep in mind that we cannot infer causality, either in reported literature reviews or in this study. Observed cerebral differences may be consequences of experienced parenting practices and anxiety. However, it is also possible that brain differences are risk markers for both a tendency in children to be more difficult, in parents to become more severe, and in parents and children to be more anxious. In studies previously reported, we did not know if the youth have experienced anxiety and coercive parenting practices, respectively. It is unclear whether anatomical differences reported in the extant literature are directly associated with experienced adversity or anxiety (Bremner *et al.*, 2003; Kitayama, Quinn, & Bremner, 2006; Weniger, Lange, Sachsse, & Irle, 2008). The lack of comparison groups of participants with a history of adversity but who do not have anxious symptoms, or who conversely have anxious symptoms without a history of adversity, limits the ability to determine whether observed cerebral differences are linked more specifically to adversity or anxiety (Hart & Rubia, 2012; McCrory, De Brito, & Viding, 2011). An interaction between parental practices and subclinical anxiety symptoms is particularly interesting considering that these two factors are both important risk factors to develop anxiety disorders later in life.

Importantly, there has been no research on the link between brain anatomy and parental practices and subclinical anxiety symptoms which persist over the course of childhood, specifically between the ages of 2.5 and 9 years. A design in which youth are prospectively followed every year for 7 years allows for identification of youth with distinctive and persistent harsh parenting and anxiety experience over time. Moreover, few studies have examined the association between harsh parenting practices in the

absence of severe maltreatment and brain structure anatomy (Merz, Maskus, Melvin, He, & Noble, 2019). Understanding these associations could: (a) provide insights on neurodevelopmental correlates of parental practices and subclinical anxiety symptoms; (b) raise awareness about the importance of reducing the use of coercive parenting practices in the absence of severe maltreatment; (c) implement effective family-based interventions for anxiety symptoms in the context of harsh parenting at a young age; (d) develop interventions that are informed by neural alterations as well as symptoms. If youth with one or more risk factors to develop anxiety disorders have anatomical brain differences similar to those seen in youth who already have anxiety disorders, interventions that reduce anxiety symptoms that also decrease the impact of the risk factors might reduce brain differences. The goal of this study was to investigate the association between harsh parenting, in the absence of severe maltreatment, and subclinical anxiety symptoms, measured yearly from 2.5 to 9 years old. We aimed to study how harsh parenting, in the absence of severe maltreatment, how subclinical anxiety symptoms, and how the interaction between these two factors, are associated with the prefrontal cortical and amygdala anatomy in 12–16 years-old youth who had no history of psychopathology or medication exposure at the time of magnetic resonance imaging (MRI).

Material and Method

Participants

Sample

Participants were recruited in two related cohorts from two prospective longitudinal studies: in 2001, I was 5 years old (Jetté, Desrosiers, & Tremblay, 1998) and The Quebec Longitudinal Study of Children's Development (Jetté & Des Groseilliers, 2000). The total sample of 2,174 youths born in Quebec, Canada, between 1996 and 1998 (children from the far north, Cree or Inuit regions, and aboriginal reservations excluded) were followed since birth. Youth were evaluated yearly between 2.5 and 9 years old (at 2.5, 3.5, 4, 5, 6, 7, 8, 9 years old). For the purpose of the current study, we narrowed down the cohort to 1,761 possible participants after selecting those for whom data on their anxiety symptoms profile and their parents' harsh parenting practices were collected at least three times from the time they were 2.5 years old until 9 years old. At least one of those measures had to be taken from one of the last two times they were evaluated, at age 8 or 9 years old.

Measures evaluated over time

Items evaluating youth subclinical anxiety symptoms were selected from the Child Behavior Checklist' anxious/depressed and emotionally reactive subscales (Achenbach, 1991). Three items were selected: the child "is nervous, high strung or tense," "appears fearful or anxious," "appears worried." Mothers indicated on a two-point scale ranging from 0 (*never*) to 2 (*often*) if their child exhibited these symptoms.

Harsh parenting practices were assessed by the "Hostile/Ineffective" scale, used in a Canadian national longitudinal study of children and youth (Boyle *et al.*, 2004; StatisticsCanada, 1995) as the "Parental Cognitions and Conduct Toward the Infant" scale (Boivin *et al.*, 2005). Items evaluating harsh parenting practices included: "how often do you get angry when you punish your child?"; "in the last 12 months, how often did you spank your child when he/she was difficult?"; "in the last

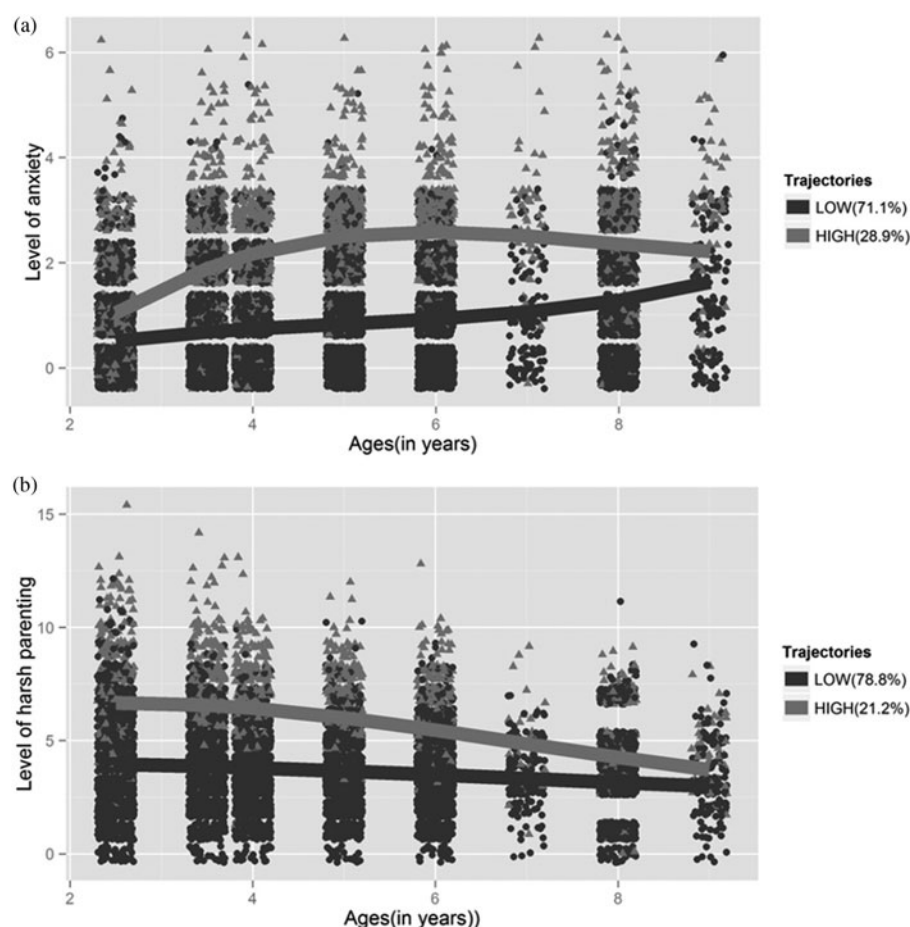


Figure 1. Developmental trajectories groups for the (a) youth anxiety symptoms and (b) maternal harsh parenting practices ($N = 1761$). Note. The curves represent the values predicted by the model, while the dots represent the values observed for each participant. All trajectories follow a cubic model. The percentages in the legend correspond to the predicted percentage of youths in each group.

12 months, when your child broke the rules or did things he/she was not supposed to do, how often did you raise your voice, scold or yell at him/her?"; "in the last 12 months, when your child broke the rules or did things he/she was not supposed to do, how often did you use physical punishment (e.g., shaking)?". Mothers indicated on a four-point scale ranging from 0 (*never*) to 4 (*always*) to what extent given statements described their parenting practices.

The coefficients of internal consistency (which indicate the interrelatedness between items supposedly measuring the same concept) for the child subclinical anxiety symptoms items were weaker at very young ages, and fair to satisfactory from 5 to 9 years old (0.5, 0.6, 0.6, 0.7, 0.7, 0.8, 0.7, 0.8 at 2.5, 3.5, 4, 5, 6, 7, 8, and 9 years old, respectively). Coefficients of internal consistency followed a reversed pattern for maternal harsh parenting practices (0.7, 0.7, 0.6, 0.6, 0.6, 0.6, 0.6, 0.6 at 2.5, 3.5, 4, 5, 6, 7, 8, and 9 years old, respectively). To further demonstrate the interrelatedness among the anxiety items, and among the harsh parenting items, a set of correlations was run between the three anxiety items, and another set was run between the four maternal harsh parenting behavior items, at every time point (2.5, 3.5, 4, 5, 6, 7, 8, and 9 years old). For each time point, youth anxiety symptoms items were correlated (r between .2 and .9, $p < .05$), and the maternal harsh parenting practices items were also correlated (r between .2 and .9, $p < .05$). Based on these items, we used an empirically based method that identifies groups of children who follow similar developmental patterns over time (Nagin, 2005) to divide youth among four cells of interest: youth with high levels of harsh parenting and anxiety symptoms, youth with high levels

of harsh parenting and low levels of anxiety symptoms, youth with low levels of harsh parenting and high levels of anxiety symptoms, and youth with low levels of harsh parenting and anxiety symptoms, all assessed over time. Details regarding design and procedure of the study are described elsewhere (La Buissonnière-Ariza et al., 2019).

Assignment to the four cells of this study

We used a developmental trajectory methodology to distribute the 1,761 youths across the four clusters of interest of this study (see Figure 1). This is an empirically based method that identifies groups of children who follow similar developmental patterns over time. A semi-parametric, group-based mixture model was computed using all available data points across time. The model assigns individuals to trajectory groups on the basis of a posterior probability rule (Nagin, 2005). Developmental trajectories were estimated based on youth anxiety symptoms (as evaluated by their mothers) and maternal harsh parenting practices collected when youths were 2.5, 3.5, 4, 5, 6, 7, 8, and 9 years old.

The best-fitting model, that is, the model which minimized the Bayesian information criterion (BIC) (Nagin, 2005), for both youth anxiety symptoms and maternal harsh parenting practices was a two-group (high vs. low) solution model. Formation of these two groups (high vs. low) was based on the posterior probability of group membership, that is, on the probability an individual has of belonging to a trajectory group based on observations across assessments. Figure 1a shows the developmental trajectory groups for the youth anxiety symptoms: one

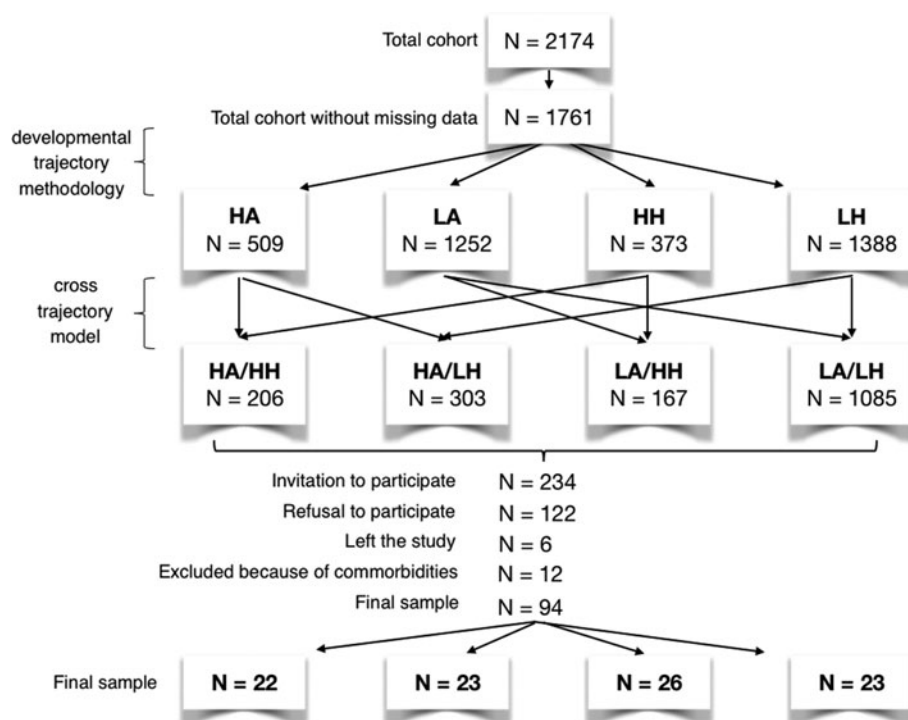


Figure 2. Selection and number of participants at each stage of the research.

group included youths with moderate rates of anxiety symptoms at 2.5 years old, which increased substantially over time, and plateau around the age of 6; the other group included youths with low rates of anxiety symptoms at 2.5 years old, which also increased gradually over time. The average posterior probabilities for the assigned trajectory groups were 0.91 for the moderate-rising anxiety symptoms group, and 0.90 for the low-rising anxiety symptoms group, thereby indicating a good fit of the model (Nagin, 2005). Demonstrating the relevance of the estimated model, the continued increase in anxiety levels observed from 2.5 to 9 years old fits well with previous developmental trajectory results from two population-based longitudinal studies, this Quebec sample showing increases in the level of anxiety symptoms from 1.5 to 5 years old (Côté et al., 2009), and one in the Netherlands showing that the frequency of anxiety increases from 4 to 15 years of age (Bongers, Koot, Van der Ende, & Verhulst, 2003). Figure 1b shows the developmental trajectory groups for maternal harsh parenting practices: one group included youths submitted to moderate-high rates of harsh parenting at 2.5 years old, which moderately decreased over time; the other group included youths submitted to low rates of harsh parenting at 2.5 years old, which decreased less over time. The average posterior probabilities for the assigned trajectory groups were 0.90 for the moderate-high decreasing maternal harsh parenting practices group, and 0.90 for the low-decreasing maternal harsh parenting practices group, thereby indicating a good fit of the model (Nagin, 2005). Demonstrating the relevance of the estimated model, elevated maternal harsh parenting practices towards children of 2.5 years old were recently reported in two population-based longitudinal studies (Forget-Dubois et al., 2007; Pierce et al., 2010). Moreover, recent findings demonstrated that hostile parenting practices diminished over time, from middle childhood to mid-adolescence, in the general population (Forget-Dubois et al., 2007; Pierce et al., 2010).

Finally, further validating the distinct anxiety symptoms and harsh parenting trajectories, a repeated measures analysis of variance (ANOVA) with groups (high vs. low anxiety levels) as the between-subjects factor, and time (2.5, 3.5, 4, 5, 6, 7, 8, and 9 years old) as the within-subjects factor, shows that anxiety levels were significantly higher in the high-anxiety group compared to the low-anxiety group at every time point, independently of harsh parenting levels ($p < .05$). Similarly, an ANOVA with harsh parenting as the between-groups factor (high vs. low harsh parenting levels) revealed that harsh parenting practices were significantly greater in the high-harsh parenting group, compared to low-harsh parenting group, independently of anxiety levels ($p < .05$).

Developmental trajectories for maternal harsh parenting practices and youth anxiety symptoms were then estimated jointly (using a cross trajectory model) to get an accurate estimation of the proportion of youths in all four groups of interest (see Figure 2). Based on the anxiety levels and parenting practices, the model also gives us the probability of the participants to belong to each one of the four groups. The average posterior probabilities for the assigned trajectory groups were 0.83 for the low harsh parenting–low anxiety group, 0.79 for the high harsh parenting–low anxiety group, 0.77 for the low harsh parenting–high anxiety group, and 0.85 for the high harsh parenting–high anxiety group, thereby indicating a good fit of the model (Nagin, 2005). Youth with the highest probability of belonging to any of these respective four groups were invited to participate in the study first, until each group has reached the target number of 30 participants to perform MRI. A total of 234 families were contacted. Of these, 122 refused to participate and six left the current study. Twelve participants were excluded because they had comorbidities that could affect brain (four had attention-deficit/hyperactivity disorder (ADHD), one had severe dyslexia with central hearing disorder, four had anxiety disorders, one had major depression, and one had consumption disorder). The remaining 94 participants completed the study and MRI (see Figure 2).

Study protocol was approved by the CHU Sainte-Justine and IUGM Research Ethics Boards, Montreal, Canada. Participants and their parents gave informed assent and consent, respectively, and were compensated for their participation.

Inclusion/exclusion criteria and measures at the time of MRI

MRI was performed only once when the youth were between 12 and 16 years old, in the remaining 94 participants from the birth cohort. Inclusion criteria were defined by absence of medical illness; any past or current psychiatric disorders, as determined by a semistructured psychiatric evaluation conducted with Kiddie Schedule for Affective Disorders and Schizophrenia (Kaufman et al., 1997); treatment for psychiatric illness (pharmacological or behavioral); past or current abuse; past head injury or trauma; contraindications for MRI (e.g., braces); IQ score < 70, as assessed by Peabody Picture Vocabulary Test – Revised (Dunn & Dunn, 1981). The socioeconomic status (SES) of each participant was also measured and assessed using Hollingshead two-factor index scale (Hollingshead & Redlich, 1958; Miller & Salkind, 2002) and three components (parental education, employment, and income); pubertal stage assessed using Tanner puberty stage self-administered scale (Duke, Litt, & Gross, 1980; Morris & Udry, 1980). Current anxiety symptoms were measured through the Screen for Child Anxiety Related Emotional Disorders – Revised (Martin & Gosselin, 2012). The parenting questionnaire used to evaluate current harsh parenting practices was the same as the one used to determine harsh parenting trajectories from 2.5 to 9 years old (Boivin et al., 2005; Boyle et al., 2004; Pierce et al., 2010).

Image acquisition, processing, and analysis

Structural neuroimaging was performed for 94 healthy youth from the birth cohort without anxiety disorder (12–16 years old) at the Geriatric University Institute of Montreal (IUGM, Montreal, Canada). All scans were performed on a 3 Tesla MRI scanner (Magnetom Tim Trio, Siemens) equipped with a standard head coil. Whole-brain, high-resolution, T1-weighted anatomical images were acquired using a MPRAGE sequence (repetition time [TR] = 2300 ms, echo time [TE] = 2.98 ms, flip angle = 9°, matrix size = 256 × 256 mm, voxel size = 1 × 1 × 1 mm³, MRI - field of view [FOV] = 256 mm, 176 slices). Two-dimensional DICOM files of each brain were organized into volumetric three-dimensional files using MRICron software package (<http://www.mccauslandcenter.sc.edu/mricron/mricron/>). After removing participants with motion artifacts (ghosting, blurring), a total of 88 youths were included in analyses: 21 *High harsh parenting/High anxiety symptoms youth*; 22 *High harsh parenting/Low anxiety symptoms youth*; 23 *Low harsh parenting/High anxiety symptoms youth*; and 22 *Low harsh parenting/Low anxiety symptoms youth*.

Voxel-based morphometry (VBM) processing and analysis (Ashburner, 2009; Ashburner & Friston, 2000) were performed using SPM8 (Wellcome Department of Imaging Neuroscience, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/software/spm8>) and MATLAB 7.10.0 (R2009a; MathWorks, Natick, MA, USA). All T1-weighted anatomical images were manually reoriented to place the anterior commissure (AC) at the origin of the three-dimensional Montreal Neurological Institute (MNI) space. The images were then segmented into gray matter, white matter, and cerebrospinal fluid (Ashburner & Friston, 2005). These segmentations were then inspected for their quality. A diffeomorphic nonlinear registration algorithm (diffeomorphic anatomical

registration through exponentiated lie algebra toolbox – DARTEL) (Ashburner, 2007) was used to spatially normalize the segmented images and generate a study-specific brain template. The resulting images were then spatially normalized into the MNI space; normalized, and warped to an isotropic voxel size of 1.5 mm × 1.5 mm × 1.5 mm; modulated by the Jacobian transformed tissue probability maps (to obtain volume differences rather than concentration differences in gray matter) and then smoothed with an 10-mm full-width half-maximum (FWHM) isotropic Gaussian kernel.

FreeSurfer (version 5.1; <http://surfer.nmr.mgh.harvard.edu>), a fully automated surface-based pipeline, was used to assess cortical thickness (Koolschijn & Crone, 2013; Raznahan et al., 2011; Wierenga, Langen, Oranje, & Durston, 2014). T1 images were processed into a common stereotactic space, in which cortical thickness values can be derived on a participant-by-participant basis (Fischl, 2012). Cortical segmentation procedure involves the assignment of a neuroanatomical label to each voxel in a MRI volume using voxel intensity, a probabilistic atlas estimated from a manually labeled training set, and Bayesian classification rules (Fischl et al., 2002). This technique was previously shown to be comparable in accuracy to manual tracing (Fischl et al., 2002; Morey et al., 2009). Cortical thickness was automatically quantified within FreeSurfer on a vertex-by-vertex basis by computing the average shortest distance between the white matter boundary and the pial surface (i.e., the cerebral spinal fluid boundary) at each point on the cortex (Fischl & Dale, 2000).

Based on a priori hypotheses of associations between gray matter volume and thickness, and early-life adversity and anxiety, in two regions (prefrontal cortices, including orbitofrontal cortex and rostral anterior cingulate cortex) and amygdala, we adopted an independent region of interest (ROI) approach. For VBM analyses, three ROIs were defined using the automated anatomical labeling (AAL) WFU Pick-Atlas toolbox: bilateral prefrontal cortex (including orbitofrontal cortex and anterior cingulate cortex), right and left amygdala. For VBM ROI analysis, we corrected for multiple comparisons using small-volume correction (SVC) in each ROI, with a Gaussian random field threshold set at $\alpha = 0.05$, corrected, and an extent of at least 10 contiguous voxels (see Mueller et al., 2013). Significant peak voxels ($p < .05$, family-wise error rate [few]-corrected) were extracted and analyzed with SPSS v.20 (Armonk, NY) (see Mueller et al., 2013). For FreeSurfer analysis, cortical thickness of rostral anterior cingulate cortex and of medial and lateral orbitofrontal cortex were extracted and analyzed with SPSS v.20 (Armonk, NY). Moreover, a whole-brain VBM analysis was performed for the reader's interest, but was not discussed. For whole-brain VBM analysis, we corrected for multiple comparisons using small-volume correction, with a Gaussian random field threshold set at $\alpha = 0.05$, corrected, and an extent of at least 10 contiguous voxels. Significant peak voxels ($p < .05$, Family-Wise Error correction (FWE)-corrected) were reported.

A 2×2 analysis of covariance (ANCOVA) with harsh parenting (high vs. low) and anxiety symptoms (high vs. low) levels as the between-subjects factors, and age, sex, SES, and total brain volume as covariates of no interest, was performed in SPSS v.20 (Armonk, NY). Bonferroni's corrections for multiple comparisons were applied with a significance level of $p < .01$ ($p < .05/5$ number of comparisons) to cortical and subcortical volume and thickness (orbitofrontal cortex volume, medial, and lateral orbitofrontal cortex thickness, rostral anterior cingulate cortex thickness, and amygdala volume). When an Anxiety×Parenting interaction was

Table 1. Demographic and clinical characteristics of youth, separately for high and low harsh parenting practices, and high and low anxiety levels^a

	High harsh parenting practices		Low harsh parenting practices		<i>p</i>		
	High anxiety	Low anxiety	High anxiety	Low anxiety	A	H	A×H
N	21	22	23	22			
Sex (female/male) ^b	11/10	11/11	14/9	10/12	.40	.84	.77
Age ^c	13.81 (0.14)	13.36 (0.14)	13.35 (0.14)	13.64 (0.14)	.58	.50	.01^f
Tanner stage ^c	4.05 (0.16)	4.00 (0.16)	3.85 (0.15)	3.75 (0.16)	.56	.12	.41
Verbal IQ (PPVT-R) ^c	105 (2.82)	108 (2.76)	109 (2.70)	111 (2.76)	.31	.18	.68
SES ^{c,d}	44.43 (2.46)	38.21 (2.40)	35.59 (2.40)	34.75 (2.40)	.15	.01	.27
<u>Current anxiety (SCARED-R)</u>							
SCARED-R (child) ^b	19.96 (2.03)	19.30 (1.99)	19.85 (1.94)	17.00 (1.99)	.51	.58	.74
SCARED-R (parent) ^b	15.46 (1.94)	10.74 (1.84)	12.75 (1.76)	8.16 (1.89)	.008	.14	.96
Current PP (mean) ^b	2.06 (0.11)	2.10 (0.11)	1.53 (0.11)	1.73 (0.11)	.30	.001	.50
Total brain volume ^{c,e}	1189261 (20106)	1198173 (19644)	1215514 (19212)	1188470 (19644)	.65	.68	.36

Note: N, number of participants; PPVT-R, Peabody Picture Vocabulary Test – Revised; SES, socioeconomic status; SCARED-R, Screen for Child Anxiety Related Emotional Disorders – Revised; A, Main effect of anxiety; H, Main effect of Harsh parenting; A×H, interaction between anxiety and harsh parenting levels.

^aMeans and standard deviations are reported.

^bChi-squares for quantitative measures.

^cTwo-way ANOVAs with harsh parenting (high vs. low) and anxiety (high vs. low) levels as the between-subjects factors.

^dHollingshead 2 factors index: higher score corresponds to lower socioeconomic status

^eTBV was calculated as the sum of the volumes of gray matter and white matter.

^fParticipants *High harsh parenting practices/High anxiety* were significantly older than the *High harsh parenting practices/Low anxiety* ($F_{1,84} = 5.37, p = .023$) and *Low harsh parenting practices/High anxiety* participants ($F_{1,84} = 4.90, p = .03$).

significant, findings were decomposed using pairwise comparisons with a Bonferroni correction for multiple comparisons in SPSS v.20 (Armonk, NY). For all significant results, we calculated and reported effect sizes (Cohen's partial η^2) (Cohen, 1973) and post hoc power (calculated using G*Power 3.1) (Faul, Erdfelder, Lang, & Buchner, 2007) in addition to *p* values.

Results

Participants

As we can see in Table 1, groups differed significantly in age and SES. Although there were no significant group differences in terms of sex and total brain volume, these variables were used as covariates of no interest in cerebral analysis, with age and SES, to ensure that they did not account for any of the findings, as these variables were previously reported to be linked with brain anatomy (Burgaleta, Johnson, Waber, Colom, & Karama, 2014; Casey, Jones, & Somerville, 2011; Hanson et al., 2013; Welborn et al., 2009). IQ was not included as a covariate to avoid over-correction because of its significant correlation with SES ($r = .26, p = .02$). Analyses were performed with and without IQ as covariate, and results were the same. Brain differences were also the same with parental education levels instead of Hollingshead two factors index as a covariate to represent SES.

As expected, the ANOVAs comparing current harsh parenting and anxiety levels revealed that current levels of harsh parenting was significantly higher in the *high harsh parenting* relative to the *low harsh parenting* adolescents ($p = .001$) and that current anxiety levels, as measured by the Screen for Child Anxiety Related Emotional Disorders – Revised (parent ratings), were higher in the *high anxiety* compared to the *low anxiety* adolescents ($p = .008$). No differences between *high anxiety* and *low*

anxiety adolescents were observed when analyzing the child scores collected using the Screen for Child Anxiety Related Emotional Disorders – Revised (child ratings). It is important to note that youth anxiety symptoms levels (parent ratings) were not correlated to harsh parenting practices levels ($r = .1, p = .32$).

Main effect of parenting practices

Regions of interest (VBM volumes and FreeSurfer cortical thickness)

As shown in Figure 3, VBM analysis revealed smaller orbitofrontal cortex volumes in the right medial part [18, 16.5, −18] ($F_{1,80} = 23.28, p < .001$, FWE-corrected, $k = 299$, partial $\eta^2 = 0.23$, power = 0.99) and left lateral part [−42, 52.5, −9] ($F_{1,80} = 33.52, p < .001$, FWE-corrected, $k = 1956$, partial $\eta^2 = 0.30$, power = 0.99), and smaller right amygdala volume [21, 4.5, −18] ($F_{1,80} = 15.69, p < .001$, FWE-corrected, $k = 105$, partial $\eta^2 = 0.16$, power = 0.98) in youth with high levels of harsh parenting over time, relative to low scorers on harsh parenting dimension.

Whole-brain analysis (VBM volume)

Whole-brain VBM analyses revealed one clusters, in the left lateral orbitofrontal cortex, significantly smaller in youth with high levels of harsh parenting over time, relative to low scorers on harsh parenting dimension: [−42, 53, −9] ($F_{1,80} = 33.33, p = .004$, FWE-corrected, $k = 49399$, partial $\eta^2 = 0.31$, power = 0.99).

Main effect of subclinical anxiety symptoms

There were no significant results related to subclinical anxiety levels.

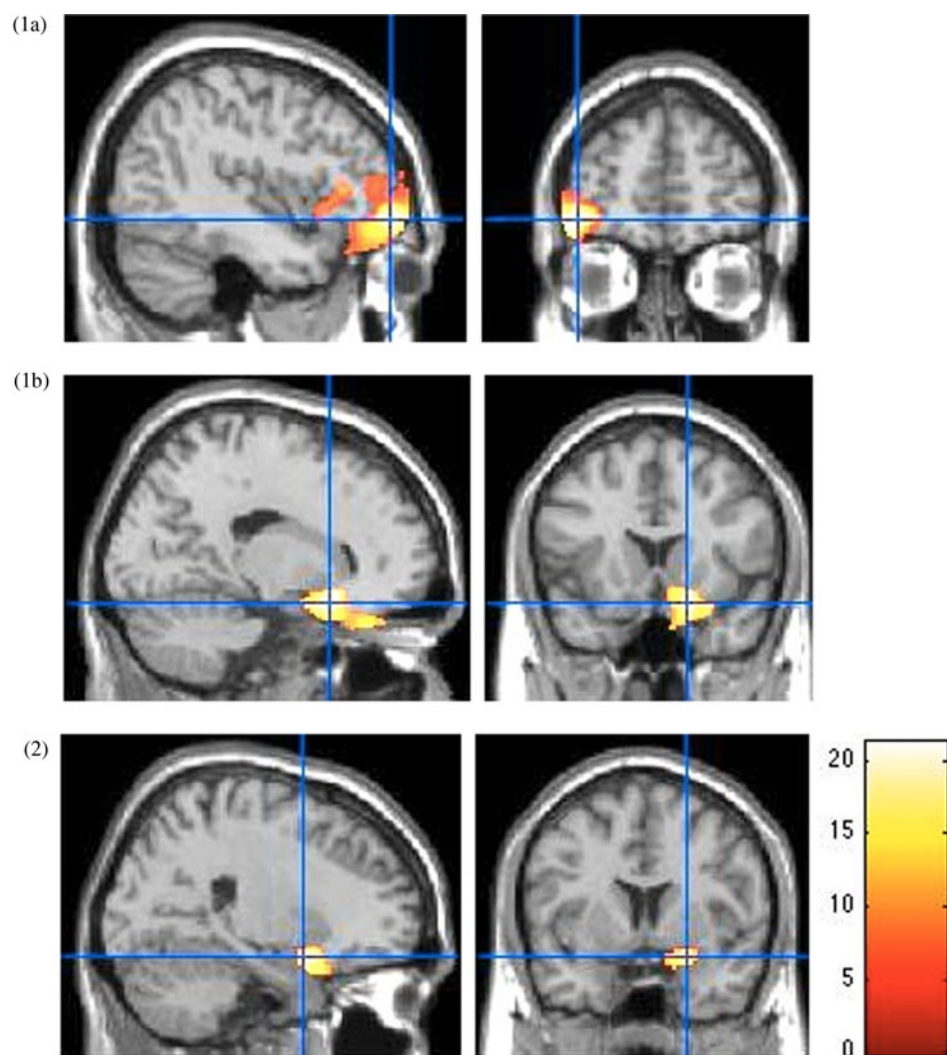


Figure 3. Smaller prefrontal cortex and amygdala volumes in high, compared to low scorers on the harsh parenting dimension. Main effect of parenting for the lateral orbitofrontal cortex (1a), the medial orbitofrontal cortex (1b) and the amygdala (2) from the voxel-based morphometry (VBM) analysis. All $p < .05$, family-wise error rate (few)-corrected at a peak level. Color bar shows F statistics. Results are displayed on a Montreal Neurological Institute (MNI) T1 brain template, at a threshold of $p < .005$.

Parenting by anxiety symptoms interaction

Regions of interest (VBM volumes and FreeSurfer cortical thickness)

In VBM analysis, a Parenting \times Anxiety interaction emerged in left amygdala [$-28.5, -6, -15$] ($F_{1,80} = 12.13, p < .001$, FWE-corrected, $k = 303$, $\text{partial } \eta^2 = 0.23$, $\text{power} = 0.99$). In youth with low subclinical anxiety symptoms levels, high harsh parenting practices levels were associated with smaller amygdala volume ($F_{1,80} = 7.31, p < .01$). In youth with high subclinical anxiety symptoms levels, high harsh parenting practices levels were associated with greater amygdala volume ($F_{1,80} = 7.31, p < .01$). In youth with low harsh parenting levels, high subclinical anxiety symptoms levels were associated with smaller amygdala volume ($F_{1,80} = 5.16, p < .05$). In youth with high harsh parenting levels, high subclinical anxiety symptoms levels were associated with greater amygdala volume ($F_{1,80} = 5.16, p < .05$) (see Figure 4).

FreeSurfer cortical thickness measurements revealed a Parenting \times Anxiety interaction in the left rostral anterior cingulate cortex thickness ($F_{1,80} = 6.47, p = .01$, $\text{partial } \eta^2 = 0.08$, $\text{power} = 0.78$). In youth with low subclinical anxiety symptoms levels, high harsh parenting practices levels were associated with greater anterior cingulate cortex thickness ($F_{1,80} = 3.9, p = .05$); the association was nonsignificant for youth with high subclinical anxiety

symptoms levels. In youth with low harsh parenting levels, high subclinical anxiety symptoms levels were associated with greater anterior cingulate cortex thickness ($F_{1,80} = 12.26, p = .001$); the association was nonsignificant for youth with high harsh parenting levels (see Figure 4).

Whole-brain analysis (VBM volume)

There were no significant whole-brain volume differences concerning Parenting \times Anxiety interaction.

Discussion

This study compared gray matter volume and cortical thickness in healthy youth (12–16 years old) who experienced high or low harsh parenting practices over time and high or low subclinical anxiety symptoms levels over time, between 2.5 and 9 years old. The key findings from this study are the smaller prefrontal cortex and amygdala volumes among youth who have experienced early high levels of harsh parenting over time during childhood, compared to those who have not. The second most important findings are significant interactions between harsh parenting and subclinical anxiety symptoms levels for amygdala volume and rostral anterior cingulate cortex thickness. Youth with high subclinical

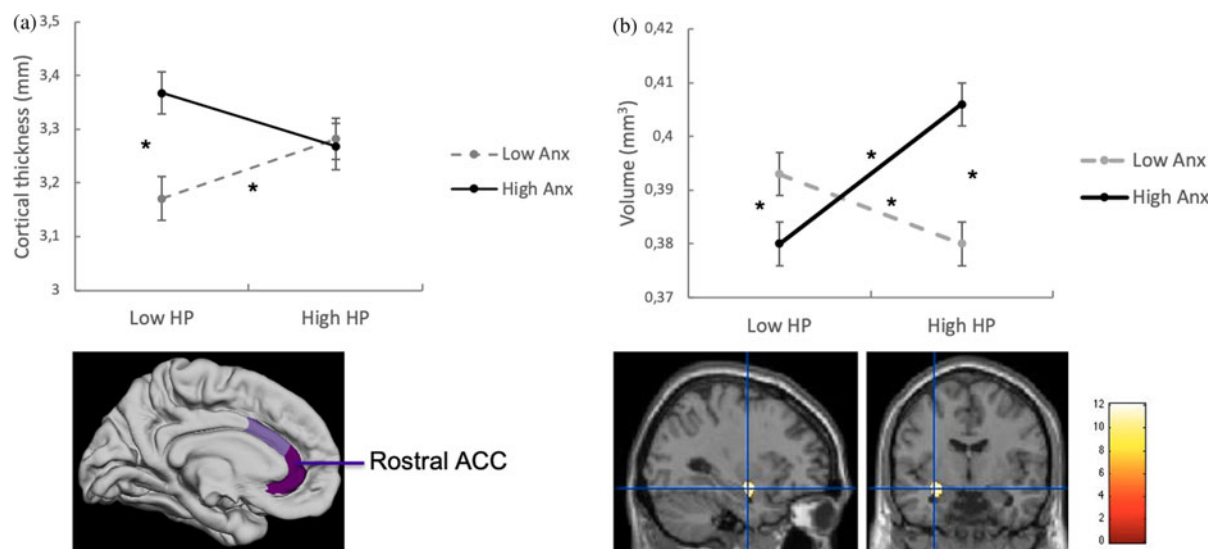


Figure 4. Significant Parenting \times Anxiety interactions for (a) left rostral anterior cingulate cortex (ACC) thickness from FreeSurfer analysis and (b) left amygdala volume from voxel-based morphometry (VBM) analysis. * $p < .05$, family-wise error rate (few)-corrected at a peak level for VBM results and Bonferroni corrected for FreeSurfer and VBM analysis. Color bar shows F statistics. Results are displayed on a Montreal Neurological Institute (MNI) T1 brain template, at a threshold of $p < .005$ for VBM results. Anx, Anxiety; HP, Harsh parenting.

anxiety symptoms, compared to youth with low subclinical anxiety symptoms, presented (a) lower amygdala volume and (b) greater rostral anterior cingulate cortex thickness, when harsh parenting was low; greater amygdala volume without significant rostral anterior cortex thickness difference, when harsh parenting was high. Youth with high harsh parenting over time, compared to youth with low harsh parenting, presented (a) lower amygdala volume and (b) greater rostral anterior cingulate cortex thickness, when subclinical anxiety symptoms were low; greater amygdala volume without significant rostral anterior cortex thickness difference, when subclinical anxiety symptoms were high.

Results linked to high levels of harsh parenting over time (regardless of anxiety levels) are in agreement with literature on child severe adversity (Baker et al., 2012; De Brito et al., 2013; Edmiston et al., 2011; Hanson et al., 2010, 2015; Hodel et al., 2015; Kelly et al., 2013; Korgaonkar et al., 2013; McLaughlin et al., 2014). It has been suggested that smaller amygdala and prefrontal cortex volumes in maltreated children (implicated in emotional processing and regulation, respectively), could be associated with a variety of behavioral problems (e.g., impulsive, anxious, and depressive behaviors) and poorer social functioning, and may be related to increased psychiatric vulnerability (De Brito et al., 2013; Edmiston et al., 2011; Hanson et al., 2010; Kelly et al., 2013; Korgaonkar et al., 2013).

Results from interactions between the two factors (harsh parenting and subclinical anxiety symptoms) levels are particularly interesting. Greater rostral anterior cingulate cortex thickness in youth with high anxiety and youth with high harsh parenting over time (compared to those with low anxiety and low harsh parenting over time, respectively) is significant only when the second risk factor is low. This is in accordance with the study of Ducharme et al. (2013) in youth without an anxiety disorder (Ducharme et al., 2013). In that longitudinal study, ventromedial prefrontal cortex thickness (including the rostral anterior cingulate cortex) was increased along with subclinical anxiety levels between 15 and 22 years (Ducharme et al., 2013).

Ducharme et al. (2013) proposed two hypotheses to explain increased medial prefrontal cortex thickness with subclinical anxiety level in healthy youth: (a) this is a biological compensatory mechanism for an overly active limbic system, potentially preventing onset of mood and anxiety disorders (Ducharme et al., 2013). (b) Knowing that prefrontal cortex thickness normal development is to decrease during adolescence (Mills, Goddings, Clasen, Giedd, & Blakemore, 2014), this increase would be related to a delayed maturation of these structure with anxiety symptoms. This maturational delay could be a precursor to a pathological decrease in cortical thickness associated with risk or onset of a disorder (Ducharme et al., 2013). A recent longitudinal study in 120 youth has also demonstrated a link between negative maternal behavior and attenuated cortical thinning in prefrontal cortex regions (Whittle et al., 2014), which is consistent with the second hypothesis advanced by Ducharme et al. (2013).

Greater anterior cingulate cortex thickness linked to high levels of harsh parenting over time (without anxiety) and to high levels of subclinical anxiety symptoms over time (without harsh parenting) could therefore represent a compensatory mechanism to avoid development of an internalized disorder and / or a delay in this brain structure maturation. Absence of thicker anterior cingulate cortex in youth who have two risk factors (i.e., who have a more severe condition) in this study, and smaller rostral anterior cingulate cortex thickness in youth with subclinical anxiety symptoms and at least one of whose parents had anxiety disorder (Suffren et al., 2019), could thus be explained by an absence of compensatory mechanism and/or by the beginning of an anterior cingulate cortex thickness decrease, which makes these youth closer to develop an anxiety disorder. Longitudinal studies will be required to answer this question.

Amygdala volume in youth with high anxiety and youth with high harsh parenting (compared to those with low anxiety and low harsh parenting, respectively) is significantly smaller when the second risk factor is low and greater when the second risk

factor is high. This result could explain discrepancies observed in studies on amygdala volume linked to anxiety and adversity (Mueller et al., 2013). Lack of comparison with a group of participants with a history of adversity but who do not have anxious symptoms, or who conversely have anxious symptoms without a history of adversity, limits the ability to determine whether observed cerebral differences are linked more specifically to adversity or anxiety in the literature (Hart & Rubia, 2012; McCrory et al., 2011). These results are in accordance with studies showing increased amygdala volume with subclinical anxiety symptoms (Juranek et al., 2006; Qin et al., 2014) and exposure to maternal depressive symptomatology (Lupien et al., 2011).

Whittle et al. (2013) reported delayed amygdala development linked to maltreatment, and accelerated amygdala development in youth who have experienced maltreatment and who have developed psychopathology, compared to youth who have not developed psychopathology (Whittle et al., 2013). However, we do not know about youth with subclinical anxiety levels in that study. These results suggest that, during adolescence, the amygdala is larger when youth are at high risk to develop a disorder and smaller when youth have a disorder. It seems important to follow these youth in coming years in order to answer this question.

It is important to keep in mind that we cannot infer causality here, because of correlational and cross-sectional design of this study. Even if structural abnormalities could be the result of early-life stress, it could also be a pre-existing risk factor for vulnerability to adversity exposure, psychological trauma and stress-related disorders that would be induced by genetics (Gilbertson et al., 2002; Lupien, McEwen, Gunnar, & Heim, 2009). Even if the animal literature tends to confirm that some structural abnormalities follow stress exposure (Qin et al., 2014; Yan, 2012), future studies in humans should try to extend longitudinal studies across the human lifespan.

Lack of data on the mother during pregnancy (e.g., alcohol, drugs, stress) and on parents' psychiatric health are also limits to this study, since we know that these factors influence brain and emotional development (Jones et al., 2019; Kolb, Harker, Mychasiuk, de Melo, & Gibb, 2017; Suffren et al., 2019). These factors should be taken into account in future studies.

Finally, parenting and anxiety data are parent-reported data, which raise the question of social desirability (Boivin et al., 2005) and parental perception of their own parenting and their child anxiety level (Gordo et al., 2018). Some studies support reliability of measure reported by the mother (Windham et al., 2004), and trajectories observed in our sample correspond to trajectories of parenting observed in another sample (Lansford et al., 2009). Moreover, only participants who had a persistent level over time were recruited, which may suggest that even though coercive parenting practices and/or anxiety levels were generally underestimated, those who reported a higher level actually had a higher level compared to those who reported a lower level. Moreover, parental perceptions of their own parenting and of their child anxiety level can be biased. For example, anxious parents may have negative perceptual or interpretive biases, may be inaccurately critical of their own parenting and see more anxiety behaviors in their children (Gordo et al., 2018). This may explain, in part, the absence of cerebral differences related to child anxiety levels in this study. It would have been interesting to add longitudinal measures of parenting and anxiety self-reported by youth.

Another limitation concerns VBM method. There are some inherent limitations to that method. In particular, data must be perfectly spatially aligned (Bookstein, 2001). In addition, the smoothing and blurring steps can be misleading when it comes to detect differences in small structures like amygdala (Grodin, Lin, Durkee, Hommer, & Momenan, 2013).

To conclude, this study has replicated and extended the relation between adversity (high levels of harsh parenting over time here), and smaller volumes of prefrontal cortex structures and amygdala to youth who did not experience severe adversity, who did not have anxiety disorder and who did not take medication. More interestingly, this study showed significant interactions between parental practices and subclinical anxiety symptoms concerning rostral anterior cingulate cortex thickness and amygdala volume. Youth with high subclinical anxiety symptoms, compared to youth with low subclinical anxiety symptoms, presented (a) lower amygdala volume and (b) greater rostral anterior cingulate cortex thickness, when harsh parenting was low; greater amygdala volume without significant rostral anterior cortex thickness difference, when harsh parenting was high. Youth with high harsh parenting, compared to youth with low harsh parenting, presented (a) lower amygdala volume and (b) greater rostral anterior cingulate cortex thickness, when subclinical anxiety symptoms were low; greater amygdala volume without significant rostral anterior cortex thickness difference, when subclinical anxiety symptoms were high. These results highlight the importance of taking into account these two risk factors and not just one when looking at the emergence of internalized disorders. Since we know that these structural abnormalities can contribute to an increase in psychiatric vulnerability later in life (McCrory, De Brito, & Viding, 2012), following these youth in the coming years may help identify brain markers of risk and resilience to psychopathology in adulthood.

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Conflicts of Interest. None.

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