Corticolimbic circuit structure moderates an association between early life stress and later trait anxiety

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A B S T R A C T

Childhood adversity is associated with a wide range of negative behavioral and neurodevelopmental consequences. However, individuals vary substantially in their sensitivity to such adversity. Here, we examined how individual variability in structural features of the corticolimbic circuit, which plays a key role in emotional reactivity, moderates the association between childhood adversity and later trait anxiety in 798 young adult university students. Consistent with prior research, higher self-reported childhood adversity was significantly associated with higher self-reported trait anxiety. However, this association was attenuated in participants with higher microstructural integrity of the uncinate fasciculus *and* greater thickness of the orbitofrontal cortex. These structural properties of the corticolimbic circuit may capture a neural profile of relative resiliency to early life stress, especially against the negative effects of childhood adversity on later trait anxiety.

1. Introduction

Developmental neuroscience reveals widespread effects of childhood adversity on brain development, with a focus on neural systems that are responsible for the experience and regulation of negative emotions (Tottenham, 2014). Human neuroimaging studies have reported associations between childhood adversity and alterations in the functional activity, intrinsic connectivity, and structure of the corticolimbic circuit (Burghy et al., 2012; Dannlowski et al., 2012; Gold et al., 2016; Hanson et al., 2010; Kelly et al., 2013; Malter Cohen et al., 2013). The corticolimbic circuit, particularly the dynamic interactions between the amygdala and prefrontal cortex, is central to the emergence and regulation of emotion and anxiety (Casey et al., 2011; Kim et al., 2011; Ochsner and Gross, 2005). As research on childhood adversity and adult internalizing symptoms converges on the corticolimbic circuit recent studies have shifted their attention to elucidating neural mechanisms for the later emergence of anxiety or depression following childhood adversity (Casey et al., 2011; Gorka et al., 2014; Nusslock and Miller, 2016).

Two structural magnetic resonance imaging (MRI) measures have been frequently featured in this converging research: (a) the degree of structural connectivity between the amygdala and prefrontal cortex represented by the microstructural integrity of the uncinate fasciculus (UF), and (b) the thickness of the orbitofrontal cortex (OFC). In general,

reduced OFC thickness and UF integrity are associated with increased internalizing symptoms and related behavioral/physiological characteristics, such as lesser fear extinction memory or greater trait anxiety (Eden et al., 2015; Greening and Mitchell, 2015; Hartley, 2011; Kim and Whalen, 2009; Kühn et al., 2011; Milad et al., 2005; but also see Ducharme et al., 2014 for age-dependent effects). A dual processing framework is often used to explain these findings, such that limbic areas of the brain (e.g., amygdala) communicate with the prefrontal cortical regions (e.g., OFC) via direct and indirect reciprocal neural pathways (Aggleton et al., 2015; Ghashghaei et al., 2007). Dynamic communication along these pathways in turn supports patterns of emotional reactivity (Bishop et al., 2007; Kim et al., 2011; Ochsner and Gross, 2005; Quirk and Beer, 2006). It has been suggested that this circuit is responsible for managing and regulating negative emotions. Specifically, prefrontal systems provide top-down, regulatory input on subcortical bottom-up, emotion-generative systems that include the amygdala (Ochsner and Gross, 2005). Relatedly, stronger connectivity between the amygdala and the prefrontal cortex may represent a better capacity for the transmission of such signals, which in turn could lead to beneficial outcomes in terms of anxiety (Kim et al., 2011). As such, abnormalities of the corticolimbic circuit lead to an imbalance between the amygdala and the prefrontal cortex, which is proposed to be an underlying neural mechanism for exaggerated internalizing symptoms seen in affective disorders (Grupe and Nitschke, 2013; Helm et al.,

2018; Shin and Liberzon, 2010). Indeed, studies suggest perturbations of the corticolimbic circuit may be a hallmark of many clinical disorders, including social anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder, and major depressive disorder (Johnstone et al., 2007; LeWinn et al., 2014; Phan et al., 2009; Sadeh et al., 2016; Tromp et al., 2012).

Thus far, the majority of studies in this area have not considered the link between childhood adversity and anxiety later in life through the concurrent utilization of both structural connectivity and cortical thickness measures. While it is generally suggested that stronger corticolimbic structural connectivity and thicker OFC is associated with reduced internalizing symptoms, the *interactions* between these neural measures are seldom investigated. Examining such interactions is important because they allow for approximating the extent to which the capacity for both local regulatory processing via the OFC and dynamic communication between the OFC and amygdala shape emotional reactivity. The present study aims to address this need and identify a neural profile of those most resilient to the detrimental effects of childhood adversity on trait anxiety. Such a profile could subsequently inform ongoing efforts to develop biomarkers of relative risk or resilience for psychopathology. Using data from 798 young adult university students through the Duke Neurogenetics Study, we specifically tested the hypothesis that individuals with higher microstructural integrity of the UF *and* thicker OFC would exhibit an attenuated link between childhood adversity and trait anxiety in adulthood.

2. Methods

2.1. Participants

Data were available from 798 undergraduate students (452 women, age range 18–22 years, mean age = 19.65 years) who successfully completed the Duke Neurogenetics Study (DNS) between January 25th, 2010 and November 12th, 2013 including structural and diffusion magnetic resonance imaging scans, as well as self-reported childhood stress and trait anxiety. All participants provided written informed consent according to the Duke University Medical Center Institutional Review Board. To be eligible for the DNS, participants were required to be free of the following conditions: 1) medical diagnoses of cancer, stroke, head injury with loss of consciousness, untreated migraine headaches, diabetes requiring insulin treatment, chronic kidney, or liver disease; 2) use of psychotropic, glucocorticoid, or hypolipidemic medication; and 3) conditions affecting cerebral blood flow and metabolism (e.g., hypertension).

As the DNS seeks to examine broad variability in multiple behavioral phenotypes related to psychopathology, participants were not excluded based on diagnosis of past or current Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 1994) Axis I or select Axis II (borderline and antisocial personality) disorder. However, all participants were not taking psychotropic medications for a minimum of 14 days before study initiation. Categorical diagnosis was assessed with the electronic Mini International Neuropsychiatric Interview (MINI; Lecrubier et al., 1997) and Structured Clinical Interview for the DSM-IV subtests (SCID; First et al., 1996). Of the total sample reported here, 153 participants (19%) met criteria for at least one current or past DSM-IV diagnosis. Detailed summary of diagnoses is presented in Supplemental Table S1 in the Supplemental Materials. We note that DNS participants did not provide informed consent to have any of their data posted publicly. However, data can be requested by qualified investigators from the corresponding author. Requests require a concept paper describing the purpose of data access, ethical approval at the applicants' university, and provision for secure data access. Additional details can be found at https://www.haririlab.com/projects/procedures.html.

2.2. Self-report questionnaires

The State-Trait Anxiety Inventory-Trait Version (STAI-T) was used to assess self-reported levels of trait anxiety (Spielberger et al., 1988). The Childhood Trauma Questionnaire (CTQ) was used to assess exposure to childhood stress in five categories: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect (Bernstein et al., 1997). CTQ items were summed to create a total score for childhood adversity.

2.3. Image acquisition

Each participant was scanned using one of the two identical research-dedicated GE MR750 3T scanner equipped with high-power high-duty-cycle 50-mT/m gradients at 200 T/m/s slew rate, and an eight-channel head coil for parallel imaging at high bandwidth up to 1 MHz at the Duke-UNC Brain Imaging and Analysis Center. Following an ASSET calibration scan, diffusion-weighted images were acquired across two consecutive 2-min 50-s providing full brain coverage with 2 mm isotropic resolution and 15 diffusion-weighted directions (echo time (TE) = 84.9 ms, repetition time (TR) = 10,000 ms, b value = 1000 s/mm^2, field of view (FOV) = 240 mm, flip angle = 90°, matrix = 128 × 128, slice thickness = 2 mm. High-resolution anatomical T1-weighted MRI data were obtained using a 3D Ax FSPGR BRAVO sequence (TE = 3.22 ms, TR = 8.148 ms, FOV = 240 mm, flip angle = 12°, 162 sagittal slices, matrix = 256 × 256, slice thickness = 1 mm with no gap).

2.4. Diffusion MRI analysis

All diffusion MRI data were preprocessed in accordance with the protocol developed by the Enhancing Neuro Imaging Genetics through Meta-Analysis consortium (ENIGMA; http://enigma.ini.usc.edu/protocols/dti-protocols). As these are standardized procedures made available by the ENIGMA consortium and further documented in our previously published work (Kim et al., 2019), a full description of diffusion MRI data preprocessing steps are provided in the Supplemental Methods available online. All diffusion-weighted images were visually inspected for artifacts, distortions and major head motions to ensure quality. Following preprocessing, *a priori* pathways-of-interest were taken from the Johns Hopkins University DTI-based white matter atlas, adhering to the ENIGMA protocol (Wakana et al., 2007). These pathways-of-interest were used to mask each participant's FA skeleton maps, and then the average FA values were extracted on an individual participant basis. Our primary pathway-of-interest was the uncinate fasciculus (Fig. 1A). As the UF included in this atlas only represents a very small intermediary segment of the pathway, we used another UF pathway-of-interest with better coverage of the entire tract using the Johns Hopkins University White Matter Tractography Atlas (Mori et al., 2005). The left and right UF pathways were binarized in order to extract mean FA values for each participant. Since we did not have *a priori* predictions regarding inter-hemispheric differences and to reduce the number of statistical tests, the extracted FA values were averaged across left and right hemispheres for further statistical analyses to protect against false positives.

2.5. Cortical thickness analysis

To generate cortical thickness measures, T1-weighed images from all participants were first skull-stripped using ANTs (Klein et al., 2009), then submitted to FreeSurfer v.5.3 (http://surfer.nmr.mgh.harvard.edu)'s automated surface-based pipeline, *recon-all* (Dale et al., 1999; Fischl et al., 1999). For quality assurance, montages of brain images were created within the preprocessing pipeline. All of the images were visually inspected for artifacts and distortions to ensure quality. Each brain volume's surface underwent reconstruction and cortical

A

B

C
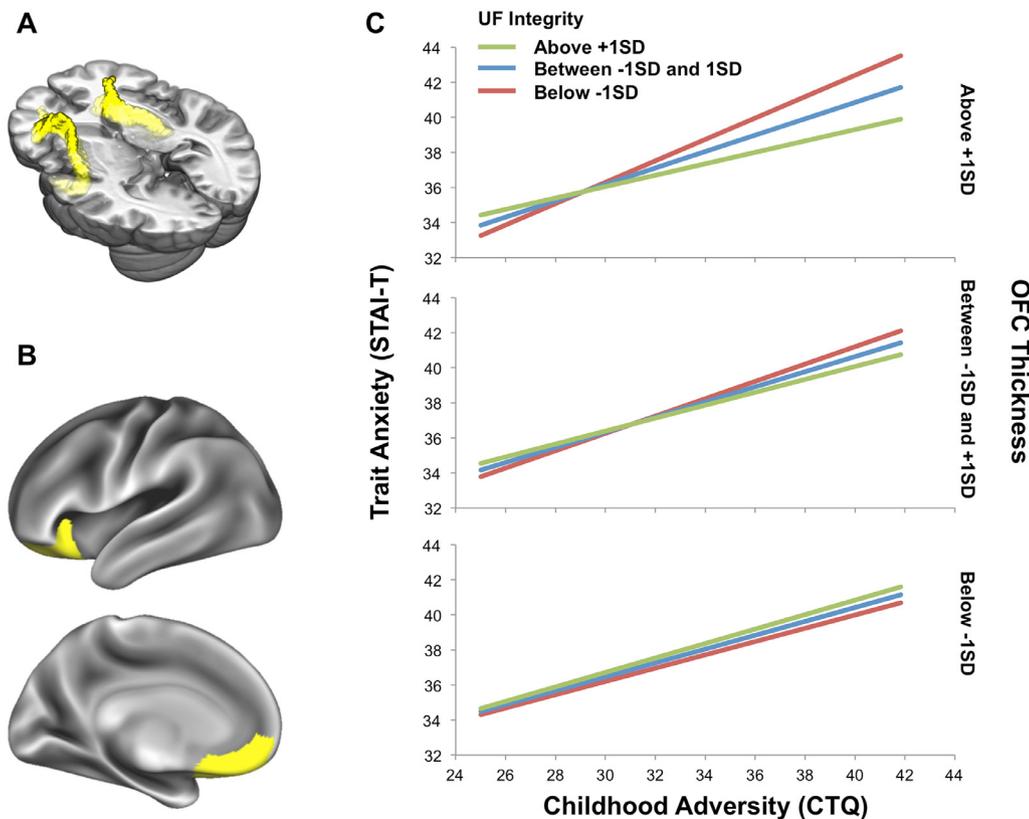
Fig. 1. Corticolimbic circuit structure moderates the association between childhood adversity and trait anxiety in adulthood. (A) The uncinate fasciculus (UF), a major white matter pathway that connects corticolimbic circuit nodes, notably the amygdala and OFC, is depicted in yellow. Mean fractional anisotropy (FA) values were used to estimate the microstructural integrity of the uncinate fasciculus. (B) The orbitofrontal cortex is overlaid on a medial and lateral surface of an inflated brain image. Mean cortical thickness measures were estimated from these regions. (C) A significant three-way interaction was observed such that the microstructural integrity of the uncinate fasciculus and orbitofrontal cortical thickness jointly moderated the association between childhood adversity and adult trait anxiety. Attenuation of a usually robust association between childhood adversity and trait anxiety (bottom and middle panel) was observed in individuals with stronger microstructural integrity of the uncinate fasciculus *and* thicker orbitofrontal cortex (i.e., decreased slope of the green lines in the top panel).

parcellation (Klein and Tourville, 2012). From the reconstructed surface, cortical thickness was estimated from the distance between the gray/white matter boundary and the gray matter/cerebral spinal fluid boundary at each vertex (Fischl and Dale, 2000). Based on the *a priori* hypothesis, our primary region-of-interest was the orbitofrontal cortex. As the Desikan-Killany-Tourville atlas (Klein and Tourville, 2012) provides medial and lateral OFC (mOFC and lOFC, respectively) parcellations separately, cortical thickness of the OFC was computed as the average of the left and right mOFC and lOFC (Fig. 1B). *Post hoc* analyses were performed using cortical thickness measures derived from the mOFC and lOFC separately, to ensure the effects observed with the average OFC were not dependent on either subregion specifically. Codes that were used to preprocess and analyze the structural and diffusion MRI data are available at our website (https://github.com/HaririLab/pipeline2.0_DNS/tree/4c95cd0ffb44fed2de7ede2c91c2193540636d1f).

2.6. Statistical analysis

PROCESS (model 3) for SPSS (Hayes, 2013) was utilized within SPSS 21 (IBM Corp., Armonk, NY, USA) to test whether an interaction between microstructural integrity of UF and cortical thickness of the OFC jointly moderated the association between CTQ (independent variable) and STAI-T scores (dependent variables). Bootstrapping was performed using 5000 samples, and variables were mean-centered in the model. Age, sex, and head movement during the diffusion MRI scans were included in the model as covariates. The latter was included as a covariate as it has been suggested that head motion may induce spurious correlations between diffusivity- or anisotropy-related metrics with behavioral measures (Yendiki et al., 2013). Current or past diagnosis of DSM-IV disorders was also included as a covariate, due to our interests in assessing the interactions among related variables that include trait anxiety and corticolimbic structures. This covariate was binary coded (0 = *no history of psychopathology*, 1 = *current or past psychopathology*). *Post hoc* analyses included the following. In addition to the UF, the

cingulum bundle was used as a control pathway-of-interest to test the moderation model with the same parameters to assess the possibility that the observed effects may be due to the variance associated with limbic white matter tracts in general. In a similar manner, the rostral anterior cingulate cortex was used as a control region-of-interest to examine the possibility that the observed effects may be due to limbic cortical thickness in general. Furthermore, OFC and amygdala volume, derived from FreeSurfer's automated segmentation pipeline, was entered as one of the moderators in the model to test the possibility that the results are driven by cortical and subcortical structural variation. For these *post hoc* analyses, the significance threshold was corrected for multiple comparisons using a false discovery rate approach (Benjamini and Hochberg, 1995). Finally, all of the analyses detailed above were repeated in participants without current or past DSM-IV diagnoses (*n* = 645).

3. Results

3.1. Self-Report measures of childhood adversity and trait anxiety

Descriptive statistics (mean ± standard deviation; min-max) of the self-report measures are summarized as follows: STAI-T (37.84 ± 9.19; 20–73) and CTQ (33.42 ± 8.4; 25–75). Internal consistency for the self-reported questionnaires from the present sample was assessed using McDonald's omega (McDonald, 1999): STAI-T ($\omega_h = 0.67$, $\omega_t = 0.93$) and CTQ ($\omega_h = 0.62$, $\omega_t = 0.93$). Mean scores for the CTQ subscales were as follows: emotional abuse (7.13 ± 2.73; 5–22), physical abuse (6.06 ± 1.98; 5–21), sexual abuse (5.28 ± 1.49; 5–18), emotional neglect (8.44 ± 3.55; 5–23), and physical neglect (6.51 ± 2.24; 5–17). As expected, a significant positive correlation was observed between CTQ and STAI-T ($r = 0.42$, $p < 0.00001$). This association remained after controlling for age, sex, and diagnosis of DSM-IV disorders, using hierarchical regression analysis with CTQ as an independent variable that was added in the second step and STAI-T as the dependent variable (first step: $R^2 = 0.037$, $F(3794) = 10.28$,

$p < 0.000001$; second step: $\Delta R^2 = 0.162$, $\Delta F(1793) = 160.71$, $\beta = 0.41$, $p < 0.000001$). Correlation matrix for the main variables is provided in Supplemental Table S2.

3.2. Moderation analysis

The overall model was significant in predicting trait anxiety from childhood adversity, microstructural integrity of the UF, and cortical thickness of the OFC ($R^2 = 0.21$, $F_{(11, 786)} = 19.23$, $p < 0.0001$). Importantly, a significant three-way interaction among CTQ total scores, UF FA, and OFC cortical thickness predicted STAI-T scores ($b = -26.58$, standard error (SE) $= 10.76$, 95% confidence interval (CI) $= [-47.71, -5.45]$, $\Delta R^2 = 0.006$, $t = -2.47$, $p = 0.014$; full results are summarized in Supplemental Table S3). Follow-up simple slopes analysis showed that the interaction was primarily driven by individuals with relatively high UF FA and thicker OFC, for whom the association between CTQ and STAI-T scores was attenuated ($b = 0.32$, SE $= 0.08$, CI $= [0.18, 0.47]$, $t = 4.29$, $p < 0.0001$; Fig. 1C). Specifically, the Johnson-Neyman technique indicated that the interaction between CTQ total scores and UF FA was significantly associated with STAI-T only when OFC cortical thickness was 0.09 standard deviations above the mean or greater (Supplemental Table S4). We note that an unexpected increase in the association between CTQ and STAI-T scores was observed in individuals with relatively low UF FA and thicker OFC, which also contributed to this interaction. Conditional effects of CTQ on STAI-T at below -1 SD, between -1 SD and $+1$ SD, and above $+1$ SD of UF FA and OFC cortical thickness are summarized in Supplemental Table S5 in the Supplemental Material available online. This interaction was robust to the inclusion of global FA (i.e., grand mean FA of all voxels in the whole brain) as an additional covariate in the model ($b = -26.63$, SE $= 10.78$, CI $= [-47.78, -5.48]$, $\Delta R^2 = 0.006$, $t = -2.47$, $p = 0.014$), or the use of state anxiety as a dependent variable instead of trait anxiety (see Supplemental Results). When the cingulum bundle was used as a moderator variable instead of the UF, the three-way interaction was no longer statistically significant ($b = -14.55$, SE $= 8.14$, $t = -1.79$, $p = 0.07$), regardless of the inclusion of the global FA covariate. Similarly, when the rostral anterior cingulate cortex thickness was used as a moderator variable instead of OFC, the three-way interaction was no longer statistically significant ($b = -1.37$, SE $= 8.75$, $t = -0.16$, $p = 0.88$), regardless of the inclusion of the global FA covariate. We note here that the differences across these interaction effects were not significant, when using the method described by Cumming (2009) in which 50% overlap between independent confidence intervals is used as a guideline to determine statistical significance of the difference between regression coefficients. In other words, while a statistically significant three-way interaction was only observed for the model in which UF FA and OFC thickness served as moderators, this effect was not significantly different from the interaction effects from the models in which control brain regions were used as moderators. When OFC volume was used as a moderator variable instead of OFC thickness, with intracranial volume as an additional covariate, the three-way interaction was no longer significant ($b = 0.004$, SE $= 0.002$, $t = 1.68$, $p = 0.09$). When amygdala volume was entered into the models as one of the moderators (replacing UF FA or OFC thickness, respectively) with intracranial volume as an additional covariate, the three-way interactions were no longer significant ($b = -0.001$, SE $= 0.001$, $t = -0.93$, $p = 0.35$; $b = 0.013$, SE $= 0.008$, $t = 1.6$, $p = 0.11$). Finally, when moderation models were generated using only one of the two proposed moderators, the interaction was no longer significant (model with UF FA: $b = 1.39$, SE $= 1.45$, $t = -0.96$, $p = 0.34$; model with OFC thickness: $b = 0.2$, SE $= 0.24$, $t = 0.82$, $p = 0.41$), indicating that both UF FA and OFC thickness were necessary to observe a moderating effect. None of the *post hoc* control analyses yielded significant interaction effects after correcting for multiple comparisons. Removing head motion parameters, current or past diagnosis of DSM-IV disorders, or both as

covariates from the analyses did not change the results.

Similar findings were observed when cortical thickness was estimated separately for the mOFC and lOFC. In brief, significant three-way interactions among CTQ total scores, UF FA, and medial/lateral OFC cortical thickness predicted STAI-T scores (model using mOFC: $b = -21$, SE $= 10.33$, CI $= [-41.28, -0.72]$, $\Delta R^2 = 0.004$, $t = -2.03$, $p = 0.043$; model using lOFC: $b = -23.91$, SE $= 9.41$, CI $= [-42.38, -5.44]$, $\Delta R^2 = 0.007$, $t = -2.54$, $p = 0.011$). In both cases, follow-up simple slopes analysis showed that the interaction was primarily driven by individuals with relatively high UF FA and thicker OFC (model using mOFC: $b = 0.35$, SE $= 0.08$, CI $= [0.2, 0.51]$, $t = 4.46$, $p < 0.0001$; model using lOFC: $b = 0.31$, SE $= 0.07$, CI $= [0.16, 0.45]$, $t = 4.17$, $p < 0.0001$). The Johnson–Neyman technique indicated that the interactions between CTQ total scores and UF FA were significantly associated with STAI-T, only when mOFC thickness was 0.34 standard deviations above the mean or greater, or when lOFC cortical thickness was 0.1 standard deviations above the mean or greater. All of the results remained consistent when the analyses were limited to 645 individuals without current of past DSM-IV diagnoses. Detailed description of these findings is summarized in the Supplemental Results.

4. Discussion

Our findings offer further evidence that the link between the experience of childhood adversity and later trait anxiety is influenced by structural characteristics of the corticolimbic circuit. By leveraging two distinct structural properties of the corticolimbic circuit in the form of microstructural integrity of the UF and cortical thickness of the OFC, we observed a modest but significant three-way interaction among these two measures and childhood adversity with respect to trait anxiety. Unpacking this interaction revealed that, while the association between childhood adversity and trait anxiety was generally robust, it was relatively attenuated in individuals who had both stronger microstructural integrity of the UF and thicker OFC. We also observed a relative increase in the association between childhood adversity and trait anxiety in individuals with weaker UF and thicker OFC, which was an unexpected finding that would need to be replicated in future studies in order to establish its reliability. Further, this moderating effect may be potentially non-specific to the UF and OFC.

These patterns may be able to inform neuroscience research that seeks to elucidate the developmental pathways through which the experience of childhood adversity may later emerge as differences in mood and affect. Cortical thinning of the OFC has been associated with maltreatment in children (Kelly et al., 2013), and reduced OFC thickness has been reported in adolescents who experienced childhood abuse (Gold et al., 2016). Relatedly, reduced volume of the OFC measured during adulthood has been associated with childhood adversity (Clausen et al., 2019; Dannlowski et al., 2012). Consistent with these individual findings, a voxel-wise meta-analysis of data from 693 children, adolescents, and adults found evidence of reduced OFC volume as a function of childhood maltreatment (Lim et al., 2014). A common implication from these findings is that structural properties of the OFC – and more generally, the corticolimbic circuit – could represent biomarkers of vulnerability to stress and, conversely, a neural architecture for resilience. The potential for OFC thickness is further supported by the observation that temperamental characteristics related to behavioral inhibition measured as early as 4 months of age are associated with thinner OFC in young adulthood (Schwartz et al., 2010). It is worth noting here that another study with a similar design failed to observe such an association between temperament at 4 months of age and later OFC thickness (Sylvester et al., 2016). Perhaps it may be useful to consider OFC thickness in conjunction with other corticolimbic structural characteristics, such as microstructural integrity of the UF, at least in the context of childhood adversity and anxiety.

Our findings expand upon this proposal by showing how a generally

robust association between childhood adversity and trait anxiety is moderated by the cortical thickness of the OFC, along with the microstructural integrity of the UF – another promising structural risk biomarker (Eden et al., 2015; Greening and Mitchell, 2015; Kim and Whalen, 2009; see Mincic, 2015 for review). The present findings extend this existing literature by demonstrating that OFC thickness and UF integrity may need to be considered simultaneously to realize the value of corticolimbic circuit structure as a potential biomarker of relative risk or resiliency to the negative effects of childhood adversity. One potential explanation of this buffering account is that the link between childhood adversity and trait anxiety may be attenuated by a fully developed neural platform – in this case, stronger structural integrity of the uncinate fasciculus and thicker orbitofrontal cortex – that enables better regulation of negative emotions such as anxiety (Casey et al., 2011; Ochsner and Gross, 2005). That being said, we note here that the frequency of use of emotion regulation strategies in the present sample, measured with the Emotion Regulation Questionnaire (ERQ; Gross and John, 2003), did not explain the moderating effects of the neural measures on the association between childhood adversity and trait anxiety (see Supplemental Results). While it still may be the case that the present findings could reflect some aspects of emotion regulation other than self-reported usage of reappraisal or suppression, future studies can help determine this possibility.

Considering the suggested protective role of stronger corticolimbic structural connectivity, it is noteworthy that the three-way interaction may also have been influenced by individuals with weaker UF integrity and thicker OFC. We observed an attenuated link between childhood adversity and trait anxiety in individuals with weaker microstructural integrity of the UF and thicker OFC (red line in the top panel of Fig. 1C and Supplemental Figure S1). Individuals with such patterns of corticolimbic structure contributed to the observed effects by showing a steeper slope between childhood adversity and trait anxiety. Although the cross-sectional nature of the present data limits our ability to draw definitive conclusions, we speculate that one possibility is that corticolimbic structural connectivity may serve a protective role against childhood adversity, which is activated only when the OFC has not sufficiently matured. Of course, future investigations, ideally with longitudinal designs, are required to test such predictions. This speculation is inferred from evidence for age-related monotonic decline in cortical thickness across the brain (Walhovd et al., 2017). This particular prediction would benefit from future studies employing a longitudinal approach.

Our study, of course, is not without limitations. First, due to a crosssectional design, childhood adversity was measured retrospectively and relied on self-report. Thus, participants may have been subject to biased recall of their childhood experiences and their self-report influenced by current mood. This line of research can greatly benefit from future studies with a longitudinal design, such as sampling prospective measures of childhood adversity from multiple sources. Differentiation of prospective and retrospective measures of childhood maltreatment is important. A recent meta-analysis reported poor overall agreement between the two assessment strategies, especially when retrospective measures of childhood adversity are based on questionnaires (Baldwin et al., 2019). Second, as our data were sampled from high functioning young adult university students, the generalizability of the findings reported here remains to be determined, especially with regard to those who have endured severe early life stress (e.g., institutionalization, abuse). Third, it should be noted that corticolimbic white matter pathways, including the UF, are amongst the slowest to mature, continuing to develop until well into the third decade of life (Lebel et al., 2008). Since the present sample consisted entirely of young adults between 18 and 22 years of age, the structural properties of the UF may still be changing. As such, our findings should be interpreted within such constraints in mind. Fourth, the STAI-T, despite its namesake, has met with some criticism that it may reflect the tendency to experience both anxiety and depression (Watson et al., 1995).

Thus, when interpreting STAI-T, it may be useful to consider it as representing a general negative emotion (Grupe and Nitschke, 2013). Fifth, it should be noted that we were unable to assess inter-rater reliability of the MINI and the SCID from the present sample. Sixth, there was insufficient evidence to support the possibility that the present three-way interaction may be specific to UF and OFC, since direct comparisons across this effect and those from models using control brain regions yielded statistically nonsignificant differences. For this reason, we are careful to suggest the moderating effect observed here may be non-specific to the UF and OFC. However, *a priori* evidence (Burghy et al., 2012; Casey et al., 2011; Dannlowski et al., 2012; Hanson et al., 2010; Malter Cohen et al., 2013) suggests that the corticolimbic circuit, which includes the UF and OFC, may still be key in supporting the effects of early life adversity in the context of anxiety. Lastly, independent replication is necessary if these features of corticolimbic circuit structure are to be further considered as risk biomarkers. This is particularly important with regard to 1) relatively small effect size and 2) the unexpected increased association between childhood adversity and trait anxiety in those with thicker OFC and lower UF integrity.

These limitations notwithstanding, our current findings build upon and extend the literature on identifying neuroimaging-derived moderators of potentially long-term, detrimental effects of childhood adversity. Our work further offers the testable hypothesis that a pattern of corticolimbic circuit structural properties may capture a neural profile of resiliency to the negative impact of childhood adversity on trait anxiety. More generally, our findings demonstrate that simultaneously considering qualitatively distinct structural measures, such as microstructural integrity of white matter pathways and thickness of cortical gray matter, may be useful in elucidating the nature of known associations among experiential and behavioral phenomena.

Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nicl.2019.102050.

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