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RESEARCH ARTICLE

WILEY AGGRESSIVE BEHAVIOR

Microstructural integrity of white matter moderates an association between childhood adversity and adult trait anger

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Abstract

Amongst a number of negative life sequelae associated with childhood adversity is the later expression of a higher dispositional tendency to experience anger and frustration to a wide range of situations (i.e., trait anger). We recently reported that an association between childhood adversity and trait anger is moderated by individual differences in both threat-related amygdala activity and executive control-related dorsolateral prefrontal cortex (dlPFC) activity, wherein individuals with relatively low amygdala and high dlPFC activity do not express higher trait anger even when having experienced childhood adversity. Here, we examine possible structural correlates of this functional dynamic using diffusion magnetic resonance imaging data from 647 young adult men and women volunteers. Specifically, we tested whether the degree of white matter microstructural integrity as indexed by fractional anisotropy modulated the association between childhood adversity and trait anger. Our analyses revealed that higher microstructural integrity of multiple pathways was associated with an attenuated link between childhood adversity and adult trait anger. Amongst these pathways was the uncinate fasciculus (UF; $\Delta R^2 = 0.01$), which not only provides a major anatomical link between the amygdala and prefrontal cortex but also is associated with individual differences in regulating negative emotion through top-down cognitive reappraisal. These findings suggest that higher microstructural integrity of distributed white matter pathways including but not limited to the UF may represent an anatomical foundation serving to buffer against the expression of childhood adversity as later trait anger, which is itself associated with multiple negative health outcomes.

KEYWORDS
childhood adversity, corticolimbic, dMRI, trait anger, white matter

1 | INTRODUCTION

Experiencing adversity during childhood has multiple consequences on brain development, particularly that associated with the experience of negative affect (Tottenham, 2014). Functional and structural neuroimaging studies have highlighted corticolimbic brain regions associated with childhood adversity including exaggerated amygdala activity to threat-related facial expressions (Dannlowski et al., 2012), decreased intrinsic functional connectivity between the amygdala and ventromedial prefrontal cortex (Burghy et al., 2012), decreased orbitofrontal cortex volume (Hanson et al., 2010), and increased amygdala volume accompanied by elevated anxious temperament (Kuhn et al., 2016). This study to date has largely focused on the neural correlates of childhood adversity associated with the later

experience of depression and anxiety (Casey et al., 2011; Nusslock & Miller, 2016). Childhood adversity also begets cognitive consequences associated with such disorders, as depressed individuals with a greater number of adverse experiences during childhood exhibited poorer general knowledge, slower processing speed, and impaired executive functions (Dannehl, Rief, & Euteneuer, 2017).

In contrast, considerably fewer studies have examined brain regions that may link childhood adversity with the later expression of trait anger, which reflects an individual's dispositional propensity for having a low threshold for feeling anger and perceiving a wide range of situations as frustrating (Spielberger, 1991). As such, trait anger has broad societal impact including increased risk for physical and mental illness, such as coronary heart disease and reactive aggression/violence, respectively (Bettencourt, Talley, Benjamin, & Valentine, 2006; Chida & Steptoe, 2009). Neuroimaging research has suggested that dysfunction in the corticolimbic circuit also may underpin trait anger and aggression (Rosell & Siever,2016). For example, reduced functional connectivity between the amygdala and the prefrontal cortex has been mapped onto aggressive behavioral traits (Coccaro, McCloskey, Fitzgerald, & Phan, 2007; Passamonti et al., 2008, but see also Beyer, Münte, Wiechert, Heldmann, & Krämer, 2014). Furthermore, a task-based activation study by our group has reported a positive correlation between trait anger and amygdala activity to angry facial expressions in men who are also high in trait anxiety, a pattern consistent with reactive aggression (Carré, Fisher, Manuck, & Hariri, 2012).

More recently, we reported that threat-related amygdala activity and executive control-related dorsolateral prefrontal cortex (dlPFC) activity jointly moderate a link between childhood adversity and trait anger in young adults, such that this association was attenuated for individuals with a combination of relatively low amygdala and high dlPFC activity (Kim et al., 2018). Here, we aimed to expand upon these findings by utilizing diffusion magnetic resonance imaging (dMRI), which enables the quantification of the microstructural integrity of white matter fiber tracts (Basser & Pierpaoli, 1996). Based on the findings from the aforementioned research, we hypothesized that higher microstructural integrity of the uncinate fasciculus (UF), a major white matter fiber pathway connecting the prefrontal cortex with limbic areas including the amygdala (Ebeling & von Cramon, 1992), would buffer against the expression of higher trait anger associated with the experience of childhood adversity. Our hypothesis further reflects earlier work finding that higher microstructural integrity of the UF is associated with more frequent use of cognitive reappraisal to regulate negative emotions (Eden et al., 2015; Zuurbier, Nikolova, Åhs, & Hariri, 2013), which reflects the top-down inhibition of amygdala activity by prefrontal circuits (Buhle et al., 2014). As a test of specificity, we performed exploratory analyses on other major white matter pathways across the whole brain.

2 | METHOD

2.1 | Participants

A total of 647 undergraduate students (385 women, age range 18–22 years, mean age = 19.6 years) who successfully completed the Duke Neurogenetics Study (DNS) between January 25th, 2010 and November 12th, 2013 had available dMRI (two scans) and self-reported questionnaire data for our analyses. These participants were free of past or current diagnosis of a DSM-IV Axis I or select Axis II (borderline and antisocial personality) disorder assessed with the electronic Mini International Neuropsychiatric Interview (Lecrubier et al., 1997) and Structured Clinical Interview for the DSM-IV subtests (First, Spitzer, Gibbon, & Williams, 1996), respectively. The DNS aims to assess the associations among a wide range of behavioral, neural, and genetic variables in a large sample of young adults. For the present study, we specifically focused on trait anger and its association with childhood adversity.

Before data collection, informed consent in accordance with the Duke University Medical Center Institutional Review Board was obtained from all participants. To be eligible for the DNS, all participants were free of the following conditions: (a) medical diagnoses of cancer, stroke, head injury with loss of consciousness, untreated migraine headaches, diabetes requiring insulin treatment, chronic kidney, or liver disease; (b) use of psychotropic, glucocorticoid, or hypolipidemic medication; and (c) conditions affecting cerebral blood flow and metabolism (e.g., hypertension).

2.2 | Self-report questionnaires

The Childhood Trauma Questionnaire (CTQ) was used to assess exposure to childhood adversity in five categories: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect (Bernstein, Ahluvalia, Pogge, & Handelsman, 1997). The State-Trait Anger Expression Inventory (STAXI) was used to index trait anger (Spielberger, 1991). In addition to total scores, the two subscales of STAXI—angry temperament or the propensity to experience anger without being provoked and angry reaction or the propensity to experience anger in response to negative events—were also calculated. Trait anxiety was measured using the State-Trait Anxiety Inventory-Trait Version (STAI-T), to test whether or not the present findings were specific to trait anger (Spielberger, Gorsuch, & Lushene, 1988).

2.3 | Image acquisition

Diffusion-weighted and high-resolution anatomical T1-weighted magnetic resonance imaging scans were acquired using an 8-channel head coil for parallel imaging on one of the two identical research-dedicated GE MR750 3T scanners (GE Healthcare, Chicago, IL) 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] = 84.9ms, repetition time [TR] = 10,000ms, b value = 1,000 s/mm^2, field of view [FOV] = 240 mm, flip angle = 90°, matrix = 128 × 128, and 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, and slice thickness = 1 mm with no gap).

2.4 | Diffusion MRI analysis

All dMRI 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/). Raw diffusion-weighted images were corrected for eddy current and aligned to the non-diffusion-weighted (b0) image using linear registration to correct for head motion. Volume-by-volume head motion was quantified by calculating the root mean square (RMS) deviation of the six motion parameters (three translation and three rotation components), for each pair of consecutive diffusion-weighted brain volumes. The resulting volume-by-volume RMS deviation values were averaged across all images, yielding a summary statistic of head motion for each participant, which were used as a covariate of no interest in all subsequent group-level analyses. Next, following skull stripping, diffusion tensor models were fit at each voxel using the Diffusion Toolbox in FSL (Behrens et al., 2003; Smith et al., 2004), generating a whole-brain fractional anisotropy (FA) image for each participant. For each participant, an average of the FA images from each of the two scans was produced to increase the signal-to-noise ratio of the data (e.g., Chavez & Heatherton, 2017). These images were then subjected to a tract-based spatial statistics (TBSS) in FSL (Smith et al., 2006). TBSS analysis entails the realignment of each individual FA image to a standard FA template in Montreal Neurological Institute space using nonlinear registration (FNIRT). Then, individual FA images were projected onto the ENIGMA-DTI FA skeleton, searching for maximal FA values perpendicular to the skeleton. The resulting individual FA skeletons were used to extract average FA values for our a priori pathways of interest (POIs).

2.5 | Pathways-of-interest analysis

A priori POIs were taken from the Johns Hopkins University DTI-based white matter atlas, adhering to the ENIGMA protocol (Wakana et al., 2007). These POIs were used to mask each participant's FA skeleton maps, and then the average FA values were extracted on a subject-by-subject basis. As the UF included in this atlas only represents a very small intermediary segment of the pathway, we used a UF POI with better coverage of the entire tract using the Johns Hopkins University White Matter Tractography Atlas (Mori, Wakana, van Zijl, & Nagae-Poetscher, 2005). The left and right UF POIs were binarizedto extract mean FA values from the left UF and right UF for each participant. Since we did not have a priori predictions regarding interhemispheric 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 further protect against false positives (see Table 1 for a full list of the 24 POIs).

TABLE 1 Moderating effects of white matter pathway strength on the association between childhood adversity on trait anger, controlling for the effects of age, sex, and head motion

Tract	*b*(SE)	95% CI	ΔR^2	$F_{(1,640)}$	*p*
ACR	−2.57 (0.77)	(−4.09, −1.05)	0.017	11.04	0.0009*
UF	−3.10 (1.02)	(−5.10, −1.10)	0.014	9.25	0.0024*
SLF	−2.81 (0.95)	(−4.68, −0.94)	0.013	8.68	0.0033*
GCC	−2.45 (0.88)	(−4.20, −0.76)	0.012	8.00	0.0048*
EC	−3.14 (1.11)	(−5.33, −0.96)	0.012	8.00	0.0048*
SFO	−1.83 (0.66)	(−3.12, −0.53)	0.012	7.71	0.0056*
SCC	−2.57 (0.95)	(−4.43, −0.72)	0.011	7.40	0.0067*
SS	−1.99 (0.75)	(−3.46, −0.52)	0.011	7.06	0.0081*
PTR	−1.52 (0.65)	(−2.80, −0.24)	0.008	5.41	0.0204*
ALIC	−2.09 (0.93)	(−3.92, −0.26)	0.008	5.02	0.0254
RLIC	−1.56 (0.78)	(−3.09, −0.03)	0.006	3.98	0.0464
PCR	−1.72 (0.88)	(−3.45, 0.01)	0.006	3.82	0.0511
SCR	−2.13 (1.11)	(−4.30, 0.04)	0.006	3.73	0.0539
BCC	−1.69 (0.89)	(−3.43, 0.05)	0.006	3.64	0.0567
CP	1.42 (1.28)	(−1.10, 3.95)	0.002	1.23	0.2679
CGC	−0.63 (0.61)	(−1.83, 0.57)	0.002	1.06	0.3040
ML	−0.54 (0.62)	(−1.75, 0.68)	0.001	0.75	0.3878
CGH	−0.44 (0.56)	(−1.54, 0.67)	<0.001	0.60	0.4383
FXST	0.50 (0.78)	(−1.02, 2.02)	<0.001	0.42	0.5189
FX	0.23 (0.49)	(−0.72, 1.19)	<0.001	0.23	0.6318
CST	0.29 (0.71)	(−1.10, 1.68)	<0.001	0.17	0.6811
PLIC	−0.45 (1.14)	(−2.67, 1.78)	<0.001	0.15	0.6952
ICP	−0.23 (0.72)	(−1.65, 1.18)	<0.001	0.10	0.7467
SCP	0.05 (0.70)	(−1.32, 1.42)	<0.001	0.01	0.9423

Note. ACR: anterior corona radiata; ALIC: anterior limb of the internal capsule; BCC: body of the corpus callosum; CGC: cingulum-cingulate gyrus; CGH: cingulum-hippocampus; CI: confidence interval; CP: cerebral peduncle; CST: corticospinal tract; EC: external capsule; FX: fornix; FXST: fornix-stria terminalis; GCC: genu of the corpus callosum; ICP: inferior cerebellar peduncle; ML: medial lemniscus; PCR: posterior corona radiata; PLIC: posterior limb of the internal capsule; PTR: posterior thalamic radiation; RLIC: retrolenticular part of the internal capsule; SCC: splenium of the corpus callosum; SCP: superior cerebellar peduncle; SCR: superior corona radiata; SE: standard error; SFO: superior fronto-occipital fasciculus; SLF: superior longitudinal fasciculus; SS: sagittal stratum; UF: uncinate fasciculus.

*$q < 0.05$ when whole brain FA was included as a covariate.

2.6 | Study design and statistical analysis

PROCESS for SPSS (Hayes, 2013) was utilized within SPSS 21 (IBM Corp., Armonk, NY) to test whether FA values of white matter pathways moderated the association between CTQ and STAXI scores (independent and dependent variables, respectively), while including age, sex, and head motion as covariates. We also report the changes in the main findings when global FA (i.e., average FA across all white matter tracts) was also included as a covariate. As per our a priori hypothesis, the initial moderation analysis focused on the UF; subsequently, the remaining 23 POIs were analyzed using identical

procedures. Since 24 major fiber pathways were tested separately (i.e., 24 independent moderation models), a false discovery rate correction was imposed on the significance threshold ($q < 0.05$) to correct for multiple statistical tests (Benjamini & Hochberg, 1995). Importantly, the same false discovery rate-corrected significance threshold was also applied when testing the UF, as we believe it is important to protect against Type I error not only for the POIs that were a part of exploratory analyses but also for our a priori target. Finally, to assess the specificity of the present findings to trait anger, an additional set of post hoc analyses were performed with trait anxiety (STAI-T scores) as the dependent variable in the moderation models.

3 | RESULTS

3.1 | Self-report questionnaire results

Means and standard deviations for the self-report measures were as follows: STAXI (15.77 ± 4.19), CTQ (33.06 ± 7.88), and STAI-T (37.07 ± 8.6). Scores for the STAXI subscales were as follows: angry temperament (5.24 ± 1.81) and angry reaction (7.87 ± 2.47). Scores for the CTQ subscales were as follows: emotional abuse (7.01 ± 2.54), physical abuse (5.98 ± 1.82), sexual abuse (5.24 ± 1.44), emotional neglect (8.34 ± 3.47), and physical neglect (6.48 ± 2.19). As expected, STAXI total scores were positively correlated with CTQ total scores ($r = 0.15$; $p < 0.001$).

3.2 | dMRI results

A total of 5 out of 24 pathways examined showed significant negative correlations between FA and CTQ at $p < 0.05$, after controlling for age, sex, and head motion. These included the UF ($r = -0.1$; $p = 0.011$) as well as the superior cerebellar peduncle ($r = -0.15$; $p = 0.0002$), medial lemniscus ($r = -0.14$; $p = 0.0006$), inferior cerebellar peduncle ($r = -0.09$; $p = 0.018$), and anterior corona radiata ($r = -0.08$; $p = 0.041$). However, the only association for the superior cerebellar peduncle and medial lemniscus ($qs < 0.05$) remained significant after correction for multiple comparisons. Three out of 24 pathways showed significant correlations with STAXI at $p < 0.05$ (posterior thalamic radiation: $r = -0.12$; $p = 0.002$, sagittal striatum: $r = -0.1$; $p = 0.016$, and splenium of the corpus callosum: $r = -0.08$; $p = 0.034$), but none survived correction for multiple comparisons (both $qs > 0.05$).

3.3 | Moderation analysis results

The overall model including childhood adversity and microstructural integrity of the UF was significant in predicting trait anger ($R^2 = 0.04$; $F(6, 640) = 4.4$; $p = 0.0002$). A significant interaction effect indicated that the FA of the UF moderated the association between CTQ and STAXI ($b = -3.1$; 95% confidence interval [CI] = [−5.1, −1.1]; $\Delta R^2 = 0.01$; $p = 0.0024$). Follow up simple slopes analysis showed that the interaction was primarily driven by individuals with the relatively higher FA of the UF, for whom the association between CTQ and STAXI total scores was attenuated ($b = 0.01$; 95% CI = [−0.52, 0.72]; $p = 0.75$). The Johnson–Neyman calculation indicated that childhood adversity was significantly associated with trait anger only when UF FA was less than 0.41 standard deviations above the mean. However, a similar pattern was also found in seven other pathways even when applying a false discovery rate-corrected threshold for multiple comparisons ($q < 0.05$; Figure 1 and Table 1). These pathways were the anterior corona radiata (ACR; $\Delta R^2 = 0.02$), superior longitudinal fasciculus (SLF; $\Delta R^2 = 0.01$), genu of the corpus callosum (GCC; $\Delta R^2 = 0.01$), external capsule (EC; $\Delta R^2 = 0.01$), superior fronto-occipital fasciculus (SFO; $\Delta R^2 = 0.01$), septum of the corpus callosum (SCC; $\Delta R^2 = 0.01$), and sagittal striatum (SS; $\Delta R^2 = 0.01$). The ACR showed the strongest moderating effect ($b = -2.57$; 95% confidence interval = [−4.09, −1.05]; $\Delta R^2 = 0.02$; $p < 0.001$; see Table 1 for statistics for all pathways). These interactions were robust to the inclusion of global FA as a covariate in the model (i.e., the same eight pathways remained significant, along with the posterior thalamic radiation). Finally, when the moderation models were tested with trait anxiety as the dependent variable, none of the 24 POIs showed a significant effect (all $qs > 0.05$).

4 | DISCUSSION

Consistent with prior research and our primary hypothesis, from a sample of high functioning young adults, we found that an association between childhood adversity and trait anger in young adulthood is moderated by the microstructural integrity of the UF, a corticolimbic pathway between the prefrontal cortex and amygdala also associated with the typical use of top-down cognitive reappraisal strategies to regulate negative emotion (Eden et al., 2015; Zuurbier et al., 2013). Surprisingly, however, 8 of the 24 white matter pathways examined yielded similarly significant effects, such that higher microstructural integrity attenuated the association between childhood adversity and trait anger. Notably, several of these other pathways including ACR, SLF, and GCC also reflect prefrontal structural connections. These effects were relatively specific to trait anger, as none of the white matter pathways moderated the link between childhood adversity and trait anxiety; in other words, unlike trait anger, trait anxiety was strongly linked with childhood adversity regardless of the microstructural integrity of white matter pathways.

It is worth noting that the largest moderation effect was observed for the ACR, which is a major white matter pathway with reciprocal connections between the thalamus and the cerebrum that covers the prefrontal cortex and the anterior cingulate cortex, and has been suggested to support multiple forms of information processing (Catani, Howard, Pajevic, & Jones, 2002; Kelly et al., 2017; Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004). Of particular relevance, studies have shown that individual differences in the microstructural integrity of the ACR are associated with executive control-related function such as (a) cognitive control, as measured by reaction times from a go/no-go task (Liston et al., 2006) or a modified Stroop task (Seghete, Herting, & Nagel, 2013);

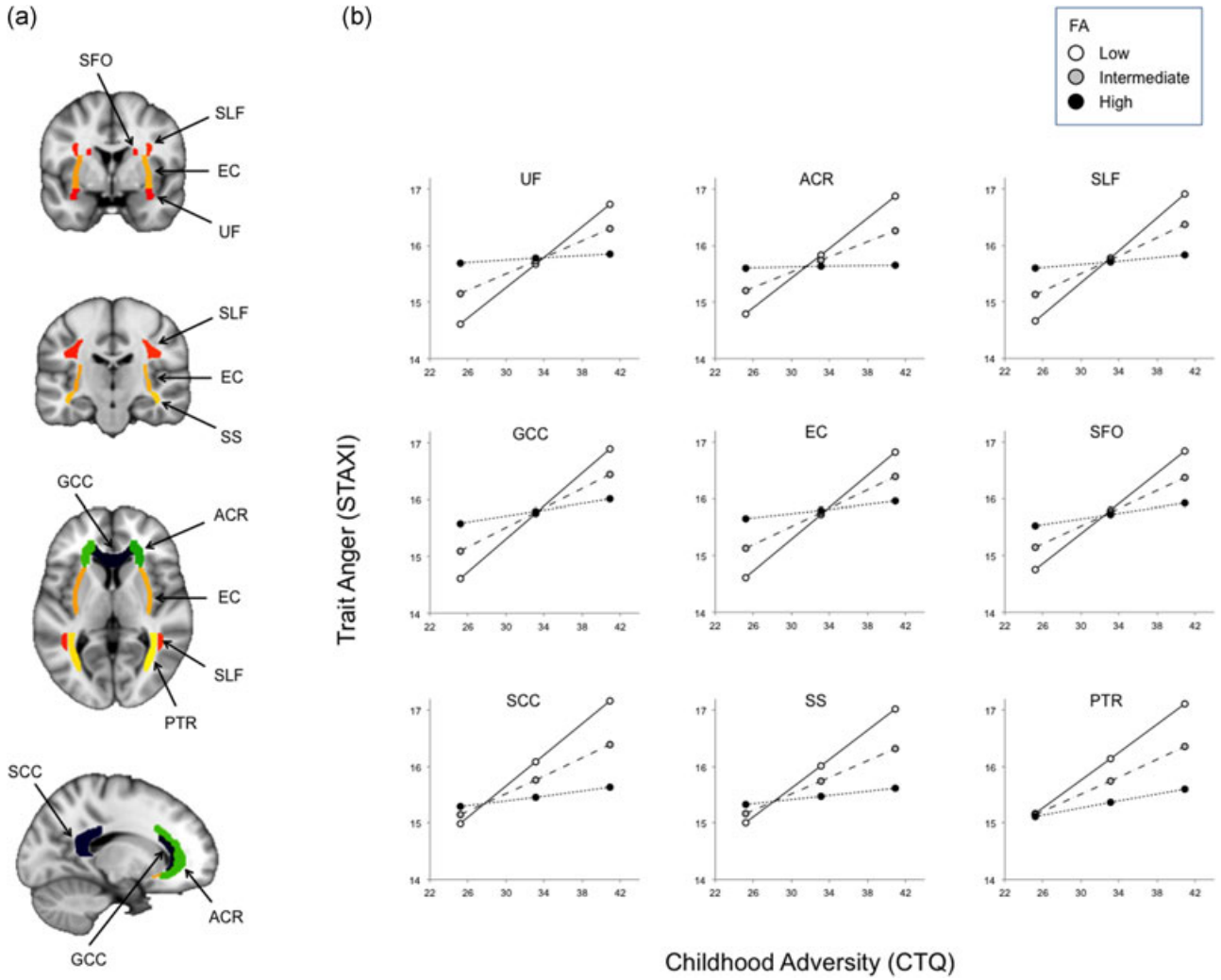

FIGURE 1 Widespread white matter pathway microstructural integrity as assessed with dMRI moderates an association between childhood adversity and later trait anger. (a) The major fiber pathways exhibiting significant moderating effects (all *q*s < 0.05). (b) Positive association between childhood adversity and trait anger was attenuated in individuals with relatively higher microstructural integrity (i.e., FA) in these white matter pathways (black circles/dotted lines). PTR became significant when whole brain FA was included as a covariate. ACR: anterior corona radiata; dMRI: diffusion magnetic resonance imaging; EC: external capsule; FA: fractional anisotropy; GCC: genu of the corpus callosum; PTR: posterior thalamic radiation; SCC: splenium of the corpus callosum; SFO: superior fronto-occipital fasciculus; SLF: superior longitudinal fasciculus; SS: sagittal stratum; UF: uncinate fasciculus

(b) executive attention, as measured by the time spent on resolving conflict during an attention network test (Niogi, Mukherjee, Ghajar, & McCandliss, 2010; Tang et al., 2010); and (c) working memory, as measured by the performance on the Memory for Digits subtest of the Wechsler Abbreviated Scale of Intelligence (Niogi & McCandliss, 2006). Furthermore, a recent large-scale meta-analysis across 4,322 individuals reported that the microstructural integrity of the ACR showed the largest deficits in schizophrenia, corroborating the findings from previous functional neuroimaging and behavioral studies demonstrating prefrontal executive function-related abnormalities in schizophrenia (Kelly et al., 2017).

The current finding with the ACR may be further relevant in the context of our previous functional neuroimaging study, where we observed that individuals with lower threat-related amygdala activity and higher executive control-related dlPFC activity had an attenuated association between childhood adversity and trait anger (Kim et al., 2018). One possible interpretation of these converging findings is that higher microstructural integrity of prefrontal white matter enables dlPFC to exert more efficient control over other prefrontal and limbic areas, including the amygdala, thereby buffering against the negative effect of childhood adversity on trait anger. As there are no direct anatomical connections between the dlPFC and the amygdala, functional communication between the two regions is likely mediated by the ventromedial prefrontal cortex (vmPFC). The vmPFC acts as an anatomical gateway between these brain regions, as it not only has direct connections with the dlPFC through prefrontal white matter tracts, but also with the amygdala via the UF (Delgado, Nearing, Ledoux, & Phelps, 2008; Von Der Heide, Skipper, Klobusicky, & Olson, 2013). While we were unable to test this idea directly as our previous fMRI data set (Kim et al., 2018) and current dMRI data sethave no

overlap in participants, future investigations using concurrent structural and functional neuroimaging data can build on our findings.

Relevant to our findings from healthy individuals, the UF has been associated with disorders characterized by aggressive behavior, such as psychopathy and conduct disorder. However, the results in the literature are somewhat mixed—whereas adult psychopathy is generally linked with decreased structural connectivity of the UF (Motzkin, Newman, Kiehl, & Koenigs, 2011; Sobhani, Baker, Martins, Tuvblad, & Aziz-Zadeh, 2015), aggressive behavior in adolescents is associated with both increased and decreased structural connectivity of the UF, depending on the study (Breeden, Cardinale, Lozier, VanMeter, & Marsh, 2015; Sarkar et al., 2013; see Waller, Dotterer, Murray, Maxwell, & Hyde, 2017 for review). As our findings from high functioning young adults are more in line with the former (i.e., stronger structural connectivity of the UF in adulthood is beneficial in the context of childhood adversity and trait anger), subsequent studies adopting a longitudinal design that routinely evaluates childhood adversity over the course of development would be able to help clarify the mixed findings in the latter.

In addition to the UF and ACR, which provide prefrontal structural connectivity, white matter pathways in other areas of the brain such as the external capsule and splenium of the corpus callosum also showed significant moderating effects, implying that widespread white matter alterations may be involved in the emergence of trait anger associated with childhood adversity. However, it is important to consider the moderating effects of each pathway based on the structure of the interaction (Figure 1a). All interactions are based on the differences in slopes across varying FA levels (i.e., for all eight pathways, the association between childhood adversity and trait anger was attenuated in individuals with greater FA). Interestingly, some interactions are mostly driven by trait anger differences in individuals with higher childhood adversity, whereas others are additionally influenced by differences in individuals with lower childhood adversity. For the SS, SCC, and posterior thalamic radiation, lower childhood adversity corresponded to lower trait anger regardless of the FA values in these pathways; as the level of childhood adversity increases, however, the relative integrity of these pathways becomes an important moderator. In this regard, these pathways fit the buffering account more so than others, as higher microstructural integrity appears to play a protective role against the association of childhood adversity and trait anger later in life. For the remaining pathways showing a significant moderating effect, the buffering account does not fully explain the observed interaction as individuals with higher microstructural integrity exhibited intermediate levels of trait anger, even when childhood adversity was low. Future studies utilizing a longitudinal design could further explore this unexpected effect, and therefore the present findings in these pathways should be interpreted with caution.

It is worth noting that both the genu and the splenium of the corpus callosum moderated the association between childhood adversity and trait anger in young adulthood. The corpus callosum, the largest white matter tract in the human brain that serves to connect the left and right cerebral hemispheres, has been linked with anger and aggressive behavior (Schutter & Harmon-Jones, 2013). Specifically, the corpus callosum is proposed to be a neuroanatomical basis for frontal cortical asymmetries, which are predominantly associated with approach motivation—anger and aggression in particular (Schutter & Harmon-Jones, 2013). This view provides a possible interpretation of our corpus callosum findings, such that stronger interhemipsheric connectivity may serve to maintain optimal levels of frontal asymmetry, which in turn could buffer against the negative effects of childhood adversity on trait anger.

Our study, of course, is not without limitations that can be addressed in future research. First, as the data were collected via a cross-sectional design, causal inference is limited and interpretations of the findings should be accordingly tempered. Future work employing a longitudinal design would be able to mitigate the shortcomings associated with using retrospective reports to measure childhood adversity. Second, the data were acquired from a sample of high functioning university students, which limits the ability to generalize the findings to a broader population, especially to those with severe experiences of childhood adversity such as institutionalization, as well as those with pathological levels of anger or aggression. We urge caution in making broader inferences from our data, as our study sample was characterized by generally low scores on the childhood trauma and trait anger questionnaires (e.g., CTQ subscale scores from our sample are within the none or minimal category; Bernstein et al., 1997). The range of these scores was also relatively limited, but sufficiently variable to observe an expected positive correlation between childhood adversity and trait anger. Thus, the present findings should be interpreted within the constraints of high functioning individuals. Those who experienced significant childhood adversity and still ended up as high functioning young adults, a general characteristic of individuals in a university study sample such as ours, may reflect their relative resilience to early life stress. Third, we note that as the fornix region is especially susceptible to partial volume effects (Pai, Soltanian-Zadeh, & Hua, 2011; Prakash & Nowinski, 2006), the interpretation of the null finding within this pathway should be made with caution until replicated. We also note that the relatively small effect sizes reported here are consistent with previous neuroimaging studies of individual differences related to emotion (Kim, Avinun, Knodt, Radtke, & Hariri, 2017; Murphy et al., 2013; Westlye, Bjørnebekk, Grydeland, Fjell, & Walhovd, 2011; Zuurbier et al., 2013), likely reflecting the complex nature of variability that manifests in brain and behavior, which in turn highlights the importance of considering multiple moderating variables in future research. Fourth, the regional variability associated with the neurodevelopmental trajectories of white matter tracts should be taken into consideration. Frontotemporal pathways, which include the UF, in particular, have been suggested to be amongst the slowest to reach maturation (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). Testing the generalizability of the present findings to individuals in midlife and beyond would be important, as our study sample consisted of young adults (18–22 years of age). Finally, future studies could improve the quality of dMRI data by acquiring them with a higher angular sampling

resolution (e.g., >60 diffusion-weighted directions). That being said, we note that the FA data derived from a 15-direction versus 61-direction dMRI data set were comparable to one another in the context of their association with trait anxiety (Kim et al., 2017).

In summary, we report that at least amongst relatively high functioning young adults an association between childhood adversity and trait anger later in life is moderated by individual differences the microstructural integrity of white matter pathways connecting multiple brain regions not limited to those within a corticolimbic circuit. Generally, higher white matter integrity was associated with an attenuated link between childhood adversity and trait anger. As such, the present findings provide further support for the importance of microstructural integrity of white matter pathways to mental health. While it is difficult to pinpoint a precise mechanism for the current findings without accompanying functional neuroimaging or longitudinal data, one possibility is that stronger structural connectivity allows for more flexible and efficient functional communication among a network of brain regions that are implicated in aggressive behavior and emotion regulation, thereby offering increased resiliency against adversity and stress. If future investigations, especially those employing longitudinal designs, are able to replicate and extend these patterns to more diverse populations, such measures of white matter microstructural integrity may become a reliable and useful biomarker of an individual's relative risk or resiliency to the experience of childhood adversity.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interests.

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