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Effects of sensitivity to life stress on uncinate fasciculus segments in early adolescence

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Abstract

Previous research suggests that exposure to early life stress (ELS) affects the structural integrity of the uncinate fasciculus (UF), a frontolimbic white matter tract that undergoes protracted development throughout adolescence. Adolescence is an important transitional period characterized by the emergence of internalizing psychopathology such as anxiety, particularly in individuals with high levels of stress sensitivity. We examined the relations among sensitivity to ELS, structural integrity of the UF, and anxiety symptoms in 104 early adolescents. We conducted structured interviews to assess exposure to ELS and obtained subjective and objective ratings of stress severity, from which we derived an index of ELS sensitivity. We also acquired diffusion MRI and conducted deterministic tractography to visualize UF trajectories and to compute measures of structural integrity from three distinct segments of the UF: frontal, insular, temporal. We found that higher sensitivity to ELS predicted both reduced fractional anisotropy in right frontal UF and higher levels of anxiety symptoms. These findings suggest that fibers in frontal UF, which are still developing throughout adolescence, are most vulnerable to the effects of heightened sensitivity to ELS, and that reduced structural integrity of frontal UF may underlie the relation between early stress and subsequent internalizing psychopathology.

Key words: early life stress; diffusion tensor imaging; uncinate fasciculus; adolescence; orbitofrontal cortex; medial prefrontal cortex

Introduction

The sustained effects of early life stress (ELS) on neural circuitry have been posited to be a major contributing risk factor for adverse psychological and behavioral outcomes, particularly during adolescence. Adolescence is a key transitional period characterized by significant neurodevelopmental maturation, environmental changes, and the onset of various clinical disorders, particularly internalizing disorders (Andersen & Teicher, 2008; Lee et al., 2014). In this context, researchers have examined the effects of ELS on gray matter volumes and white matter connections in brain regions implicated in stress responses and emotion regulation, including subcortical structures such as the amygdala and hippocampus, and cortical structures, including the medial prefrontal cortex (mPFC) and orbitofrontal cortex [OFC; (Hanson *et al.*, 2010; Hanson *et al.*, 2012; Dannlowski *et al.*, 2012; Hanson *et al.*, 2014; Teicher *et al.*, 2016]. Seven samples thus far have examined the broad effects of ELS on white matter microstructure in early adolescents and young adults (Eluvathingal *et al.*, 2006; Govindan *et al.*, 2009; Choi *et al.*, 2011; Huang *et al.*, 2012; Kumar *et al.*, 2014; Bick *et al.*, 2015; Hanson *et al.*, 2015); however, all but one of these studies used an extreme-group approach comparing maltreated youth with

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non-exposed controls and had relatively small samples ($n = 16$–26 individuals with childhood maltreatment versus $n = 13$–27 controls). Perhaps not surprisingly, there has been little convergence among these studies except in identifying reduced white matter organization in frontolimbic tracts in the maltreated group. While an extreme-group approach is helpful in identifying broad areas of white matter that may be affected by severe stress, there are specific aspects of the ELS beyond simple indices of exposure that warrant investigation with brain structure.

In this context, *stress sensitivity*, which refers to the stable tendency for individuals to respond more or less strongly to stress, is a particularly important factor to consider in risk for psychopathology (Hammen, 2015). Indeed, persistently heightened responses to environmental stress are posited to lead to structural changes in brain regions associated with emotion regulation (McEwen, 2012); almost no work, however, has directly related individual differences in sensitivity to life stressors to structural changes in the human brain. Only one study to date has examined the association between dimensions of ELS and the structural integrity of white matter tracts; that study, however, focused on the effects of ELS in young adulthood rather than in adolescence (Hanson *et al.*, 2015). These researchers found that reduced fractional anisotropy (FA), a measure of the degree of directional preference in water diffusion and a proxy for white matter integrity, in the uncinate fasciculus (UF) was associated both with greater severity of childhood maltreatment and with higher levels of anxiety following recent stress. The UF is a component of the limbic system that connects temporal and frontal cortices, and is implicated in affective cognition, including emotion regulation, memory and learning (Von Der Heide *et al.*, 2013; Olson *et al.*, 2015)—processes that are critical for adaptively responding to environmental stress. In addition to being implicated in stress responses, protracted plasticity of the UF may render this tract especially vulnerable to the effects of environmental stressors occurring across childhood and adolescence, given that PFC systems during this time are not fully mature and are unable to regulate heightened limbic responses to environmental stimuli as efficiently as they are in adults (Ernst *et al.*, 2006; Somerville and Casey, 2010). Such heightened stress sensitivity can lead to anxious symptoms or clinical disorder later in life; indeed, anxiety is often considered the initial pathophysiological response to stress, and anxiety in particular is noted for having an onset during periods of marked developmental change, such as during early adolescence (Last *et al.*, 1996). Therefore, stress-related changes in microstructure in the UF may represent a neural mechanism of dysregulated emotional responses to the environment that underpin early symptoms of anxiety.

The UF is composed of three distinct segments: a temporal segment, an insular segment, and a frontal extension (Ebeling and von Cramon, 1992; Kier *et al.*, 2004; Peltier *et al.*, 2009). The temporal segment originates at the temporal pole/anterior temporal lobe (BA 20/38), uncus (BA 35), and the cortical nuclei of the amygdala (BA 28/34/36). The fibers then pass over the lateral nucleus of the amygdala, arch around the Sylvian fissure, through the limen insula and then become two smaller white matter tracts, the external and extreme capsules (Catani *et al.*, 2002; Mori and van Zijl, 2002). The UF fibers then extend into orbital regions of the frontal lobe (BA 11/47), where they split into a smaller medial branch that terminates in the frontal pole (BA 10) encompassing portions of mPFC, and a larger ventrolateral branch that terminates in the lateral OFC (Klingler and Gloor, 1960; Thiebaut de Schotten *et al.*, 2013). Converging evidence across human and animal studies indicates that development along the UF tract is not uniform; more specifically, projections from frontal regions to limbic structures emerge later than do projections from limbic structures to frontal regions (Bouwmeester *et al.*, 2002; Bouwmeester *et al.*, 2002; Lebel *et al.*, 2012). It is unclear, however, whether ELS disrupts white matter broadly within the UF, or alternatively, whether segments of the UF that are still undergoing maturation are especially susceptible to the effects of ELS. In particular, the fibers in the frontal segment of the UF that terminate in mPFC and OFC undergo dramatic change during adolescence (Casey *et al.*, 2008; Hasan *et al.*, 2009; Lebel *et al.*, 2012). This segment of the UF, therefore, may be especially vulnerable during adolescence to the effects of ELS, and may be implicated specifically in increased risk for adolescent-onset disorders that are characterized by heightened reactivity to the environment, such as anxiety disorders. Indeed, prior work has demonstrated that greater severity of ELS is associated with reduced white matter volume and microstructure, as well as with anxious phenotypes (Gorka *et al.*, 2014; Hanson *et al.*, 2015). Investigating whether ELS affects development in segments of the UF that mature during adolescence is important for identifying mechanisms underlying the relation between stress sensitivity and internalizing psychopathology, and will increase our understanding of why and how adolescence is a period of heightened risk for disorders such as anxiety.

In the present study, therefore, we tested the formulation that heightened sensitivity to ELS is associated with structural anomalies in the UF, an important emotion regulation white matter tract, in early adolescence. Importantly, we capitalized on the increased precision of recent innovative tractography methods to investigate FA within the temporal, insular, and frontal segments in order to determine whether sensitivity to ELS is associated with UF either globally or, alternatively, selectively within specific segments that are still undergoing major developmental changes during early adolescence. Although our principal diffusion measure of interest in this study was FA, given that it is a summary and non-specific measure of microstructural integrity (Song *et al.*, 2002), we also examined axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD) in order to interpret the effects that we obtain in this study with greater specificity. We hypothesized that frontal regions of the UF are particularly more vulnerable to the effects of heightened sensitivity to ELS and, further, that reduced structural integrity (as measured by FA) of this portion of the UF underlies the increased risk for onset of anxiety in this age group. Given prior work demonstrating associations among ELS, white matter macrostructure and microstructure, and anxious phenotypes (Gorka *et al.*, 2014; Hanson *et al.*, 2015), we also tested whether reduced FA in segments of the UF that were found to be associated with ELS sensitivity predicted greater anxiety symptoms, and whether FA of the UF mediated the relation between ELS sensitivity and anxiety symptoms.

Materials and methods

Participants and procedures

Participants were native English speakers from the surrounding San Francisco Bay Area and were recruited through a combination of media and online advertisements. A total of 104 participants (64 females; mean ± SD age: 11.41 ± 1.21 years) were included in the final analysis. This study was approved by the Stanford University Institutional Review Board; all participants provided informed assent and a parent/legal guardian provided

informed consent in accordance with the Declaration of Helsinki. Please see "Participants and Procedures" in the Supplement for details on exclusion criteria.

Assessment of ELS

Participants were interviewed about their lifetime exposure to 30+ types of stressful experiences using a modified version of the Traumatic Events Screening Inventory for Children (see Supplementary Table S1; (Ribbe, 1996). For each type of ELS that the participant endorsed, interviewers followed up with specific questions to characterize the severity of the stressful experience (e.g., nature of relationship between the participant and the offending person, duration of the experience, the participant's perception of consequences ensuing from the experience). In addition, for each type of stressor that the participant endorsed, the participant provided subjective severity ratings of how helpless, confused, or scared s/he felt at the time of the experience on a 4-point scale (0 = *not scared*; 3 = *extremely scared*). A panel of three coders, blind to the children's subjective severity ratings and reactions and behaviors during the interview, then rated the objective severity of each type of stressor endorsed using a modified version of the UCLA Life Stress Interview coding system (Rudolph *et al*., 2000). Coders made objective severity ratings on a 5-point scale (0 = *non-event or no impact* (e.g., witness debris from car crash); 4 = *extremely severe impact* (e.g., sexually abused); ICC = 0.99). Following coding, we z-scored and summed child subjective and panel objective severity ratings, creating standardized indices of cumulative subjective and objective ELS severity, respectively (King et al., 2016). To summarize, we collected two indicators of life stress: subjective severity (based on participant ratings) and objective severity (based on panel ratings). Using these data, we computed a third, distinct, measure capturing *ELS sensitivity* that we used in all primary analyses (see below).

Operationalizing ELS sensitivity

We operationalized ELS sensitivity as the residual variance in children's cumulative subjective stress severity (SSS) after accounting for cumulative objective stress severity (OSS). Using this method, ELS sensitivity reflects the subjective response of children to their ELS experiences beyond the objective severity of these experiences. Specifically, for each child, we used the standardized residual values from the following linear regression:

$$SSS = 0.792 * OSS - 0.186$$

Positive values for a child indicate higher ELS sensitivity or a tendency toward a heightened response to stress. Negative values for a child indicate lower ELS sensitivity or a tendency toward a reduced response to stress.

Anxiety symptoms

Several measures were administered as part of a larger longitudinal study on the effects of ELS on neurodevelopment (Humphreys, Kircanski, Colich, & Gotlib, 2016). Given prior work demonstrating associations among ELS, white matter volumes and microstructure, and anxious phenotypes (Gorka *et al*., 2014; Hanson *et al*., 2015) in this study we examined scores on the Multidimensional Anxiety Scale for Children 2nd edition [MASC; (March *et al*., 1997)]. The MASC assesses a wide range of anxiety symptoms and is considered the strongest psychometric measure of broadband anxiety for early adolescents (March and Sullivan, 1999; Baldwin and Dadds, 2007). To reduce participant burden, only the Social Anxiety and Physical Symptoms scales of the MASC were administered. Given both that the onset of social anxiety coincides with the age of our participants, and that it is among the most common anxiety disorders in adolescence (Beesdo *et al*., 2010), our primary behavioral outcome was scores on the MASC Social Anxiety scale. We also selected the Physical Symptoms scale from the MASC to administer given that items from this scale explain the most variance in MASC total scores (March *et al*., 1997). Moreover, the Physical Symptoms scale also has higher reliability than does the Harm Avoidance scale (March *et al*., 1997), and reflects symptoms that are more relevant to individuals in this age group than are symptoms assessed with the Separation Anxiety Scale, which is more appropriate for younger children (March *et al*., 1997; Kessler *et al*., 2005). One participant failed to complete the MASC scales and was therefore excluded from all analyses involving these measures.

MRI scanning acquisition

MRI scans were acquired at the Center for Cognitive and Neurobiological Imaging (CNI) at Stanford University using a 3T Discovery MR750 (GE Medical Systems, Milwaukee, WI) equipped with a 32-channel head coil (Nova Medical). For all participants, T1-weighted images were acquired using a SPGR sequence (TR/TE/TI = 6.24/2.34/450 ms; flip angle = 12°; sagittal slices; 0.9 mm isotropic voxels) and a diffusion-weighted EPI sequence (TR/TE = 8500/93.5 ms; b = 2000 mm^2/s, 64 axial slices, 2 mm isotropic voxels; 60 gradient directions, and 6 b = 0 images acquired at the beginning of the scan).

Diffusion MRI preprocessing

Diffusion MRI data were processed using the open-source mrVista software distribution developed by the VISTA lab (Stanford Vision and Imaging Science and Technology). See 'Image Processing and Diffusion Tensor Calculation' in the Supplement for more details. For more information on the software used for diffusion MRI preprocessing, please see http://vistalab.stanford.edu/software.

Automatic fiber quantification

Deterministic tractography was performed to identify the UF bilaterally in each individual brain (see Figure 1 for renderings of bilateral UF from a representative participant). While tractography can provide spatially-specific estimates of tract integrity, investigators often summarize tract integrity by averaging

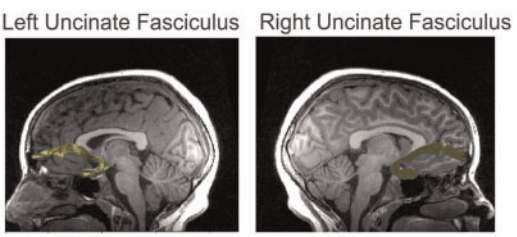

Fig. 1 Bilateral uncinate fasciculus from a representative participant. Visualization of tractography results reveals the trajectory of the uncinate fasciculus, which starts in the lateral nucleus of the amygdala, passes through the insula and then terminates in mPFC and lateral OFC.

diffusion characteristics across the full length of the tract. Diffusion characteristics in fact vary along the trajectory of white-matter tracts, and specific segments of tracts may be particularly sensitive in development (Lebel *et al.*, 2012; Yeatman *et al.*, 2012). One solution is to first localize the white-matter tract in individual brains, followed by summarizing diffusion measurements at nodes along the length of the tract. This approach allows researchers to investigate targeted segments of white matter tracts that may be altered by stressful life experiences.

In the present study, we used Automatic Fiber Quantification [AFQ; (Yeatman *et al.*, 2012] to identify and characterize each individual bilateral UF. AFQ is an automated clustering method that provides lower bias and higher efficiency relative to manual tracing methods. Briefly, whole-brain deterministic tractography was initiated from each white matter voxel and streamlines were traced from the seed point in both directions along the principal diffusion axis. Streamlines that passed through two planar waypoint regions of interest (ROIs), one near the temporal pole and one near the frontal pole, were identified as candidate UF fibers. Each candidate fiber was then scored based on its spatial proximity to a probabilistic fiber-tract map (Wakana *et al.*, 2007), and fibers with high probability scores were retained. Outlying streamlines were removed from the UF based on each their length and Mahalanobis distance from the core fiber estimate. Streamlines with length longer than five standard deviations above the mean, or Mahalanobis distance greater than four standard deviations from the uncinate spatial core were removed (Hall *et al.*, 2016). Every individual's UF was visually checked for quality assurance, and streamlines that deviated substantially from known pathways were omitted. We conservatively excluded participants for whom both right and left tracts did not adequately resolve due to poor positioning of the automated waypoint ROIs. See 'Automatic Fiber Quantification' in the Supplement for more details. For more information on AFQ, see: https://github.com/jyeatman/AFQ.

UF *tract profiles*

FA tract profiles of left and right UF were calculated by cross-sectioning each tract into 100 equidistant nodes. FA was computed at each node by averaging FA of all streamlines in the node, but weighting FA by the Mahalanobis distance of each fiber estimate from the spatial core, such that streamlines closer to the spatial core of the UF contributed more to the mean FA estimate. We computed tract profiles in this manner because the method has been validated by other reports in this participant age range (Yeatman *et al.*, 2012; Johnson *et al.*, 2013;; Hall *et al.*, 2016).

Segmenting the UF *tract*

We computed the mean FA tract profile in UF in both hemispheres for all participants and then computed the first order derivatives along each node of the mean UF tract profile to identify local maxima for the purposes of segmenting UF into temporal, insular, and frontal segments (see Supplementary Figure S1). We identified the first 30 nodes as 'temporal,' the subsequent 42 nodes as 'insular,' and the remaining 28 nodes as 'frontal' and we used these same locations for each participant when partitioning their individual UF tracts. The results we report here nevertheless do not change if we use alternative, albeit less data-driven, methods for defining UF segments (e.g., splitting the tract into thirds or quarters). For each participant, we computed mean FA for each of the three segments for each hemisphere and used these values in our subsequent regression models (see below).

Statistical analyses

All statistical analyses reported below were two-tailed tests ($\alpha = 0.05$) conducted in *R* v.3.3.1.

Associations between ELS sensitivity and FA in UF

To examine whether ELS sensitivity differentially predicted FA in the three segments of the UF, we conducted separate linear regression models with mean FA within the temporal, insular, and frontal segments of UF (left and right separately) as the respective outcome variables, and ELS sensitivity as the predictor:

$$FA_{\text{temporal UF}} = \beta_{\text{stress sensitivity}} + \beta_0$$

$$FA_{\text{insular UF}} = \beta_{\text{stress sensitivity}} + \beta_0$$

$$FA_{\text{frontal UF}} = \beta_{\text{stress sensitivity}} + \beta_0$$

We also tested whether ELS sensitivity predicted mean FA across the entire UF (left and right separately):

$$FA_{\text{UF}} = \beta_{\text{stress sensitivity}} + \beta_0$$

Associations between ELS sensitivity and anxiety symptoms

To examine whether greater ELS sensitivity predicted anxiety symptoms, we conducted linear regression models predicting MASC Social Anxiety and MASC Physical Symptoms scores (separately) from ELS sensitivity:

$$MASC_{\text{social anxiety}} = \beta_{\text{stress sensitivity}} + \beta_0$$

$$MASC_{\text{physical symptoms}} = \beta_{\text{stress sensitivity}} + \beta_0$$

Associations between FA in UF *and anxiety symptoms*

Based on our findings (described below), we tested whether reduced FA within the frontal segment of the right UF predicted MASC Social Anxiety and MASC Physical Symptoms scores (separately) using linear regression:

$$MASC_{\text{social anxiety}} = \beta_{\text{right frontal UF FA}} + \beta_0$$

$$MASC_{\text{physical symptoms}} = \beta_{\text{right frontal UF FA}} + \beta_0$$

As a follow-up analysis, we also tested whether reduced FA within the frontal segment of the right UF predicted MASC Social Anxiety using linear regression above and beyond FA from the other segments of right UF:

$$MASC_{\text{social anxiety}} = \beta_{\text{right frontal UF FA}} + \beta_{\text{right insular UF FA}} + \beta_{\text{right temporal UF FA}} + \beta_0$$

Mediation analysis

Based on our findings (described below), we tested the possibility that FA within the frontal segment of right UF statistically mediated the association between ELS sensitivity and MASC Social Anxiety scores. Specifically, we conducted a single mediation model with ELS sensitivity as the treatment variable (*X*), mean FA within the frontal segment of right UF as the mediator (*M*), and MASC Social Anxiety scores as the outcome variable (*Y*):

We performed a series of bootstrapped regressions to test the significance of the total effect of the model, and also the indirect (mediation) effect. We estimated 95% confidence intervals for the total effect and indirect effect using Monte Carlo simulations with 10,000 chains implemented in the RMediation package in R. Significant mediation is indicated if the confidence intervals for both effects do not contain 0.

Specificity of ELS sensitivity

To clarify the unique significance of ELS sensitivity in vulnerability of the UF and risk for anxiety symptoms, we also tested whether objective ELS severity predicted diffusivity measures in the frontal segment of the UF and social anxiety using the linear models described above except with the cumulative objective severity score as a predictor:

$$FA_{\text{right frontal UF}} = \beta_{\text{objective ELS severity}} + \beta_0$$

$$MASC_{\text{social anxiety}} = \beta_{\text{objective ELS severity}} + \beta_0$$

Results

Participant characteristics

Demographic and clinical characteristics of the participants are presented in Table 1. Neither age, pubertal stage, nor sex was significantly related to FA in the UF, or to MASC Social Anxiety, or to MASC Physical Symptoms scores (see Supplementary Table S2 for more details). Therefore, in order to preserve model parsimony, we did not include these demographic variables as covariates in the linear regression models (reported below).

Table 1. Demographics of participants

Age (years)	11.41 ± 1.12 (9.19-13.98)
Sex (M/F)	40/64
Ethnicity (Caucasian/African American /Hispanic/Asian/Native American /Pacific Islander/Other)	41/8/9/11/2/1/31 [1]
Tanner Stage	2.05 ± 0.75 (1–4)
Number of stressful life events (Child)	4.15 ± 3.18 (0–16)
Number of types of stressful events reported	3.69 ± 2.70 (0–12)
Subjective ELS Severity (Child)	5.68 ± 4.64 (0–20)
Objective Stress Severity (Coder-rated)	5.85 ± 4.57 (0.5–19)
Stress Sensitivity (Residual)	0 ± 4.35 (−16.09 to 15.51)
MASC Social Anxiety Scale	9.47 ± 6.16 (0–26) [1]
MASC Physical Symptoms Scale	10.13 ± 5.82 (0–25) [1]

All characteristics are reported in mean ± SD (range) unless otherwise noted. Numbers in [ ] indicate the number of individuals with missing data from the measure.

UF *tract profiles*

On average, participants showed typical tract profiles in FA, AD, RD and MD in right and left UF (Yeatman *et al.*, 2012). See Figure 2 for FA tract profiles and Supplementary Figure S2 in the Supplement for AD, RD and MD tract profiles in right and left UF. See Table 2 for a summary of FA in right and left UF and Supplementary Table S3 for a summary of AD, RD and MD in right and left UF.

Associations between ELS sensitivity and FA in UF

Greater ELS sensitivity was significantly associated with reduced FA in the frontal segment of right UF ($B = -0.0024 \pm 0.001$, $t_{96} = -2.25$, $P = 0.027$, $R^2 = 0.05$; see Figure 3A), and marginally associated with reduced FA within the insular segment of right UF ($B = -0.0017 \pm 0.001$, $t_{96} = -1.859$, $P = 0.067$; $R^2 = 0.035$) and entire right UF ($B = -0.0014 \pm 0.0007$, $t_{96} = -1.86$, $P = 0.066$, $R^2 = 0.035$), respectively, (see Table 3). ELS sensitivity was not associated with FA in the temporal segment of right UF (see Table 3) or in any of the segments of the left UF (see Table 4). See Figure 3A for more details and Table 3 for a summary of the regression results with stress sensitivity predicting UF FA.

Associations between ELS sensitivity and anxiety symptoms

Greater ELS sensitivity significantly predicted higher MASC Social Anxiety scores ($B = 0.333 \pm 0.14$, $t_{95} = 2.36$, $P = 0.02$, $R^2 = 0.090$; see Figure 3B) and higher MASC Physical Symptoms scores ($B = 0.349 \pm 0.13$, $t_{95} = 2.65$, $P = 0.01$, $R^2 = 0.067$).

Associations between FA in UF and anxiety symptoms

Reduced FA in the frontal segment of the right UF was significantly associated with higher MASC Social Anxiety scores ($B = -34.09 \pm 12.14$, $t_{101} = -2.808$, $P = 0.006$; $R^2 = 0.072$; see Figure 3C)

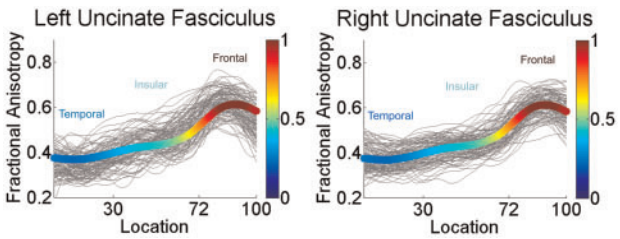

Fig. 2 Tract profiles of left and right uncinate fasciculus. FA tract profiles for each participant (in gray) were plotted by cross-sectioning 100 nodes along the length of the tract. Nodes 1–30 comprised the temporal segment, nodes 31–72 comprised the insular segment, and nodes 73–100 comprised the frontal segment of the uncinate fasciculus (see Supplementary Figure S1 for details on this procedure). Overlaid in color is mean FA across subjects.

Table 2. Summary of FA in the uncinate fasciculus

UF Location (FA)	Left UF	Right UF	Difference
Temporal	0.355 ± 0.04	0.376 ± 0.04	t_{103}=5.127, $P < 0.001$*
Insular F	0.455 ± 0.05	0.439 ± 0.04	t_{103}=−3.562, $P = 0.001$*
Frontal	0.593 ± 0.05	0.587 ± 0.05	t_{103}=−1.438, $P = 0.154$
Whole Tract	0.463 ± 0.03	0.461 ± 0.03	t_{103}=−0.813, $P = 0.418$

All measures are reported as mean ± SD. Lateralization differences in FA in each UF segment were assessed using paired *t*-tests.

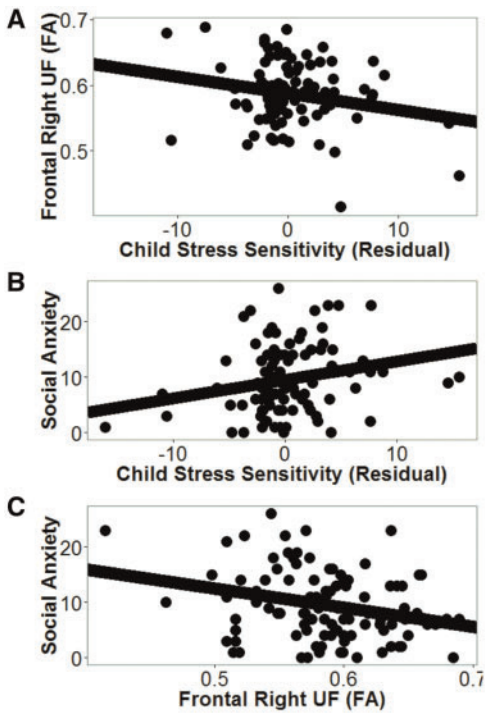

Fig. 3 Associations between stress sensitivity, fractional anisotropy of frontal right uncinate fasciculus, and anxiety symptoms. Higher levels of stress sensitivity predicted (A) reduced FA of frontal segment of right UF ($B = -0.002 \pm 0.001$, $t_{96} = -2.25$, $P = 0.027$) and (B) social anxiety ($B = 0.333 \pm 0.140$, $t_{95} = 2.36$, $P = 0.020$), and (C) reduced FA of frontal segment of right UF predicted higher levels of social anxiety ($B = -34.09 \pm 12.14$, $t_{101} = -2.808$, $P = 0.006$).

Table 3. Regression results from linear models with stress sensitivity predicting right UF FA

UF location (FA)	Beta	*t*-statistic	*P* value
R Temporal	$B = 0.0002 \pm 0.001$	$t_{96} = 0.16$	$P = 0.087$
R Insular	$B = -0.0014 \pm 0.001$	$t_{96} = -1.86$	$P = 0.067$
R Frontal	$B = -0.002 \pm 0.001$	$t_{96} = -2.25$	$P = 0.027^*$
R whole tract	$B = -0.0017 \pm 0.001$	$t_{96} = -1.86$	$P = 0.066$

Only the model predicting right frontal UF FA was statistically significant at $P < 0.05$ (as noted by *). See Supplementary Table S5 for regression results with stress sensitivity predicting AD, RD and MD in right UF.

but not higher MASC Physical Symptoms scores ($B = 9.91 \pm 11.88$, $t_{101} = -0.836$, $P = 0.405$). Using multiple linear regression to predict MASC social anxiety scores with all three FA measurements (temporal, insular, frontal) as predictors still yielded a significant effect of frontal UF on social anxiety ($B = -34.02 \pm 13.60$, $t_{99} = -2.501$, $P = 0.014$; $R^2 = 0.079$). See Figure 3C for more details and Table 4 for a summary of the regression results with FA from the other UF segments as predictors.

Mediation analysis

Although the total effect of our mediation model was significant (95% CI: 0.034–0.579, $P = 0.027$), FA of the frontal segment of right UF did not significantly account for the association between stress sensitivity and MASC Social Anxiety scores (95% CI: −0.015 to 0.161, $P = 0.104$).

Table 4. Regression results from linear models with stress sensitivity predicting left UF FA

UF location (FA)	Beta	*t*-statistic	*P*-value
L Temporal	$B = 0.0005 \pm 0.001$	$t_{96} = 0.555$	$P = 0.580$
L Insular	$B = -0.0015 \pm 0.001$	$t_{96} = -1.38$	$P = 0.171$
L Frontal	$B = 0.0005 \pm 0.001$	$t_{96} = 0.388$	$P = 0.700$
L whole tract	$B = -0.0004 \pm 0.0008$	$t_{96} = -0.46$	$P = 0.650$

All beta estimates from these regressions were not statistically significant at $P < 0.05$. See Supplementary Table 5 for regression results with stress sensitivity predicting AD, RD and MD in left UF.

Specificity of ELS sensitivity

Objective stress severity did not significantly predict FA, AD, RD or MD in the frontal segment of right UF or anxiety symptoms. See Supplementary Table S4 for more details.

Follow-up analyses with other diffusivity measures

ELS sensitivity was marginally associated with greater RD in the frontal segment of right UF ($B = 0.0015 \pm 0.0008$, $t_{101} = 1.889$, $P = 0.062$, $R^2 = 0.004$), which in turn was significantly associated with increasing MASC Social Anxiety scores ($B = 36.31 \pm 16.82$, $t_{101} = 2.159$, $P = 0.032$, $R^2 = 0.044$). See Supplementary Table S5 for a summary of the regression analyses of ELS sensitivity predicting UF AD, RD and MD, and Supplementary Table S6 for a summary of these diffusivity measures predicting anxiety symptoms.

Discussion

In this study, we tested whether the tendency to respond more strongly to real-life stressors is associated with structural anomalies in an emotion regulation tract in early adolescents. Specifically, we examined whether ELS sensitivity is selectively associated with structural integrity (as measured by FA) in the limbic, temporal, and frontal segments of the UF. We found that ELS sensitivity was significantly associated with both reduced FA within the frontal segment of right UF (Figure 3A) and increased levels of social anxiety (Figure 3B). Moreover, reduced FA within the frontal segment of right UF significantly predicted higher levels of social anxiety (Figure 3C). Our results extend previous investigations comparing white matter microstructure in adolescents with and without histories of maltreatment by demonstrating that heightened sensitivity to ELS contributes to reduced FA in fibers tracts in the UF that are still undergoing developmental changes. Specifically, we identified that stress sensitivity was associated with reduced FA in the frontal segment of the UF, which terminates in OFC and mPFC, and that both of these variables were associated with greater social anxiety symptoms. Our findings may potentially reflect stress-related reduced PFC regulation of limbic responsivity, and thus, greater vulnerability to future stressors and risk for internalizing psychopathology, particularly social anxiety.

Early adolescents with social anxiety have also been shown to be at increased risk for developing additional anxiety or depressive disorders during later adolescence and adulthood (Stein *et al.*, 2001). Given the high rates of anxiety comorbid with depression in adolescents (Avenevoli *et al.*, 2001) and evidence that anxiety symptoms and disorders—particularly social anxiety—often precede adolescent-onset depression (Rice *et al.*, 2004), it is not surprising that reduced FA in the UF has also been documented in adolescent depression (Cullen *et al.*, 2010;

Table 5. Regression results from linear models with right UF FA predicting MASC social anxiety scores (top) and physical symptoms (bottom).

UF location (FA)	Beta	*t*-statistic	*P*-value
social anxiety			
R Temporal	$B = -17.11 \pm 15.02$	$t_{101} = -1.14$	$P = 0.257$
R Insular	$B = -20.42 \pm 15.79$	$t_{101} = -1.29$	$P = 0.199$
R Frontal	$B = -34.09 \pm 12.14$	$t_{101} = -2.81$	$P = 0.006^*$
R whole tract	$B = -44.44 \pm 19.03$	$t_{101} = -2.34$	$P = 0.022^*$
UF location (FA)	Beta	*t*-statistic	*P* value
physical symptoms			
R Temporal	$B = 33.67 \pm 13.90$	$t_{101} = 2.42$	$P = 0.017^*$
R Insular	$B = 2.63 \pm 15.06$	$t_{101} = 0.18$	$P = 0.860$
R Frontal	$B = 9.93 \pm 11.88$	$t_{101} = 0.84$	$P = 0.410$
R whole tract	$B = 25.24 \pm 18.31$	$t_{101} = 1.378$	$P = 0.171$

All beta estimates were non-significant except for right frontal UF FA and R UF FA across the entire tract predicting Social Anxiety scores, and right temporal UF FA predicting Physical Symptom scores (as noted by *). See Supplementary Table 6 for regression results with AD, RD and MD from right UF predicting MASC scores.

Table 6. Regression results from linear models with left UF FA predicting MASC social anxiety scores (top) and physical symptoms (bottom).

UF location (FA)	Beta	*t*-statistic	*P*-value
social anxiety			
L Temporal	$B = 23.45 \pm 15.16$	$t_{101} = 1.55$	$P = 0.125$
L Insular	$B = -15.82 \pm 12.97$	$t_{101} = -1.22$	$P = 0.225$
L Frontal	$B = -14.00 \pm 12.15$	$t_{101} = -1.15$	$P = 0.252$
L whole tract	$B = -11.86 \pm 18.30$	$t_{101} = -0.64$	$P = 0.519$
UF location (FA)	Beta	*t*-statistic	*P*-value
physical symptoms			
L Temporal	$B = 22.90 \pm 5.13$	$t_{101} = 1.60$	$P = 0.113$
L Insular	$B = 8.52 \pm 12.33$	$t_{101} = 0.69$	$P = 0.491$
L Frontal	$B = 18.21 \pm 11.42$	$t_{101} = 1.59$	$P = 0.114$
L whole tract	$B = 28.34 \pm 17.12$	$t_{101} = -1.66$	$P = 0.101$

All beta estimates from these regressions were not statistically significant at $P < 0.05$. See Table Supplementary Table S6 for regression results with AD, RD and MD from left UF predicting MASC scores.

LeWinn *et al.*, 2014). Reduced FA in the UF, particularly in the frontal fibers, may represent a neural mechanism of dysregulated emotional responses to environmental stimuli that manifest early as social anxiety symptoms and then, through adolescence onward, as depressive symptoms. Our observation of significant associations with ELS sensitivity, white matter microstructure in frontal UF, and symptoms of social anxiety, but not symptoms of physical anxiety, is consistent with this formulation.

Importantly, no studies to date have examined neural correlates of stress sensitivity, that is, the tendency to respond more or less strongly to environmental stress. Stress sensitivity may be especially important for understanding effects of ELS on brain development, which are posited to be explained by psychobiological responses to stress exposure. Indeed, in the current study we found no significant associations between the objective severity of exposure to ELS and white matter microstructure of the UF, highlighting the importance of directly assessing children's responses to their experiences and the role of perceived stress in structural integrity of the UF. In larger samples (Gorka *et al.*, 2014; Hanson *et al.*, 2015), investigators have found effects of ELS exposure on the UF, in addition to reduced white and gray matter volumes in regions connected by the UF (Dannlowski *et al.*,; Hanson *et al.*, 2010). The fact that our findings were unique to ELS sensitivity and not to simple cumulative stress may be due to the fact that the children, who were recruited from the community, were heterogeneous in their exposure to ELS. Variability in ELS sensitivity is likely to be reduced in the context of exposure to extreme stressors, with all individuals experiencing heightened responses and exposure alone predicting atypical neurodevelopment. It will be important for future studies with both community and high-risk samples of children to integrate assessment of stress sensitivity with careful characterization of tract profiles for all relevant white matter tracts.

In our sample, associations among ELS sensitivity, white matter microstructure, and anxiety were statistically significant only in the right UF. Of the previous studies examining FA of the UF as a function of ELS severity and exposure, two reported reduced FA only in the left UF (Eluvathingal *et al.*, 2006; Hanson *et al.*, 2015) and two reported reduced FA in bilateral UF (Govindan *et al.*, 2010; Kumar *et al.*, 2014; although it should be noted that the sample reported by Eluvathingal and colleagues is a subset of that reported by Kumar and colleagues). Interestingly, Govindan and colleagues demonstrated that reduced FA in right UF only correlated significantly with duration of orphanage care (Govindan *et al.*, 2010). The discrepancies among our studies could be due to differences in the samples in these studies (young adults as in the case of Hanson *et al.*, 2015 and severely socioemotionally deprived children as in the cases of Eluvathingal *et al.*, 2006; Kumar *et al.*, 2014; Govindan *et al.*, 2010), and/or to methodological differences (e.g., these previous studies relied on voxel-based methods). Our results in right UF are nevertheless consistent with recent evidence that stress responses in the central nervous system are lateralized (for a review, see Ocklenburg *et al.*, 2016). Specifically, neuronal firing rates in right PFC have been shown to control stress hormones in animals and to be active primarily in response to stressors (Sullivan and Gratton, 1999; Lee *et al.*, 2015; Ocklenburg *et al.*, 2016). In contrast, activity in left PFC is posited to counteract this ramping up of stress-induced activity through interhemispheric inhibition (Lee *et al.*, 2015; Ocklenburg *et al.*, 2016). It is possible that the lateralization of stress regulatory systems promotes efficient regulation of stress and emotions (Sullivan, 2004). Other researchers have posited that interhemispheric transmission is also implicated in the interplay of stress and structural and functional lateralization (Ocklenburg *et al.*, 2016). Future research, particularly in animals where lesion techniques can be applied, is needed to examine these issues more explicitly and systematically.

Although the present study is the largest human neuroimaging investigation to date examining the association of ELS and uncinate microstructure in adolescents, our results must be interpreted cautiously given important limitations. First, we conducted several regression models in addition to those testing our primary hypotheses, and did not apply formal corrections for multiple comparisons. Given that this is the first study to utilize innovative tract segmentation algorithms to investigate the effects of ELS on white matter microstructure of the uncinate, we view our analyses of multiple UF segments and inclusion of all diffusivity metrics as comprehensive. Although this is a clear strength of our study, the issue of multiple comparisons is inherent when including all of these measures. Second, the cross-sectional design of this study limits our causal interpretation that greater sensitivity to ELS results in or is reflected by reduced FA in the right UF, and that these processes subsequently lead to higher anxiety symptoms. Similarly, the cross-sectional design of this study may also explain why we did not find a significant mediation effect of frontal uncinate

microstructure in the relation between ELS sensitivity and social anxiety symptoms, as these fibers are still undergoing development. Third, the inherent limitations in understanding the molecular mechanisms that contribute to DTI metrics such as FA, particularly in human neuroimaging studies, temper our interpretations that greater stress sensitivity leads to demyelination of frontal UF. Indeed, FA alone cannot be used to determine whether the effects we obtained in this study were due to poorer myelination or to other factors such as axonal membrane integrity, density, and diameter, or crossing fibers (Beaulieu, 2002; Song and Gangstead, 2004). Animal research suggests that the combination of reduced FA and higher RD in the absence of change in AD is a biomarker of poor myelination (Song *et al.*, 2002). Although we report in the present study that ELS sensitivity is associated with higher RD in frontal right UF, which in turn is significantly associated with higher levels of social anxiety symptoms, the relation between ELS sensitivity and RD in frontal right UF was only marginally significant. Furthermore, the mapping of these diffusivity patterns with myelination processes has not yet been validated in humans. Finally, although our *a priori* hypotheses centered on finding that greater ELS sensitivity was associated with reduced FA in frontal UF and with higher anxiety symptoms, our study is limited in its exclusive focus on the UF. Researchers have identified reduced FA in other white matter tracts (Choi *et al.*, 2009; Choi *et al.*, 2011; Huang *et al.*, 2012; Bick *et al.*, 2015); nevertheless, we should emphasize that no study examined tract profiles, assessing instead diffusivity metrics averaged across the entire tract (although Huang and colleagues did attempt to examine FA within dorsal versus ventral segments of the superior longitudinal fasciculus in an exploratory follow-up analysis).

Future studies examining FA (and other diffusivity measures) should also carefully assess tract profiles in tracts other than the UF, particularly the cingulum hippocampus, which includes direct connections to the hippocampus which is a stress-sensitive structure, and the inferior fronto-occipital fasciculus and inferior longitudinal fasciculi, both of which are major visual-limbic pathways that overlap with the frontal segment of the UF that relays information to OFC (Ashtari, 2011). Additional longitudinal research is also needed to determine the extent to which heightened sensitivity to ELS reflects a dispositional susceptibility with adaptively dimorphic effects depending on environmental context (i.e., *differential susceptibility to the environment* as in (Ellis *et al.*, 2011) or a tendency toward heightened responses that develops over time as a consequence of exposure to early stressors (i.e., *stress sensitization* as in McLaughlin *et al.*, 2010). Within both the differential susceptibility and stress sensitization frameworks, however, exposure to ELS precedes the negative psychobiological consequences of heightened responses to ELS. In the context of these literatures, our results therefore support the formulation that these responses initially potentiate changes in brain development that set the stage for increased risk for clinical disorder. We do not know whether reduced FA in the UF during early adolescence, when rates of internalizing disorders are relatively low compared to mid or late adolescence, is a less informative predictor than is FA in the UF later in development. Indeed, it is possible that the *trajectory* of UF development is most predictive of vulnerability to psychopathology in the individuals we studied (Olson *et al.*, 2015; Gotlib and Ordaz, 2016). Finally, there are additional aspects of the experience of ELS that warrant further investigation. For example, the type and timing of exposure to stress may moderate the associations between ELS sensitivity and UF development (Teicher *et al.*, 2016). Longitudinal investigations with neuroimaging and in-depth stress and clinical assessments at multiple time points are needed to address these questions.

In summary, we provide novel evidence that white matter fibers within the frontal segment of the right UF are especially vulnerable to the effects of heightened sensitivity to ELS during early adolescence, a period of significant frontolimbic maturational changes, and that reduced structural integrity in frontal UF may reflect heightened sensitivity to stress. Moreover, we found that individual differences in white matter integrity of frontal right UF predicted concurrent levels of anxiety. Our results contribute in our understanding of why adolescence is a neurobiologically susceptible period for the onset of internalizing psychopathology by showing that varying responses to stressful life experiences are associated with changes in developing tracts of structures that support stress responses and emotion regulation.

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