

Individual Variation in White Matter Microstructure is Related to Better Recovery from  
Negative Stimuli

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Conflict of Interest Statement

R.J.D. serves on the board of directors for the non-profit organization Healthy Minds  
Innovations. The other authors report no perceived or real conflicts of interest.

### Abstract

The uncinate fasciculus is a white matter tract that may facilitate emotion regulation by carrying connections from the prefrontal cortex to regions of the temporal lobe, including the amygdala. Depression and anxiety are associated with reduced uncinate fasciculus fractional anisotropy (FA) – a diffusion tensor imaging measure related to white matter integrity. In the current study, we tested whether FA in the uncinate fasciculus is associated with individual differences in emotional recovery measured with corrugator supercillii electromyography in response to negative, neutral, and positive images in 108 participants from the Midlife in the US (MIDUS; <http://midus.wisc.edu>) Refresher study. Corrugator activity is linearly associated with changes in affect, and differentiated negative, neutral, and positive emotional responses. Higher uncinate fasciculus FA was associated with lower corrugator activity 4-8 seconds after negative image offset, indicative of better recovery from negative provocation. In an exploratory analysis, we found a similar association for the inferior fronto-occipital, inferior longitudinal and superior longitudinal fasciculi. These results suggest that the microstructural features of the uncinate fasciculus, and these other association white matter fibers, may support emotion regulatory processes with greater white matter integrity facilitating healthier affective functioning.

## Individual Variation in White Matter Microstructure is Related to Better Recovery from Negative Stimuli

The uncinate fasciculus is a white matter fiber bundle carrying projections from the orbitofrontal cortex to the anterior temporal lobe (Bracht et al., 2009; Petrides & Pandya, 2007), and is hypothesized to facilitate top-down emotion regulation by carrying projections from the orbitofrontal cortex to the amygdala (d'Arbeloff et al., 2018; Zuurbier et al., 2013). The amygdala contributes to affective processing and plays a central role in detecting and responding to threatening and negative stimuli (Davis & Whalen, 2001; Fox & Shackman, 2017). Inhibition of the amygdala via both the orbitofrontal cortex and dorsolateral prefrontal cortex is thought to mediate emotion regulation of responses to threatening or negatively-valenced stimuli (Delgado et al., 2008; Diekhof et al., 2011; Roy et al., 2012; Shiba et al., 2017). The dorsolateral prefrontal cortex may regulate amygdala activity, in part, through connections with the orbitofrontal cortex, which in turn projects to the amygdala via uncinate fasciculus fibers (d'Arbeloff et al., 2018; Delgado et al., 2008).

Past studies have investigated how individual differences in affective functioning are related to the microstructure of the uncinate fasciculus using diffusion tensor imaging (DTI) measures such as fractional anisotropy (FA). FA is the degree to which diffusion is directionally dependent, with higher FA indicating greater diffusion anisotropy, and is highly sensitive to the underlying tissue microstructure (Alexander et al., 2011; Chanraud et al., 2010). Depressed patients have lower uncinate fasciculus FA (Bhatia et al., 2018; Bracht et al., 2015; de Kwaasteniet et al., 2013; A. Zhang et al., 2012). Low uncinate fasciculus FA has been related to trait anxiety (Kim et al., 2016; Kim & Whalen, 2009) and anxiety disorders (Hettema et al., 2012; Liao et al., 2014; Phan et al., 2009). However, Modi et al. (2013) found a positive

correlation between trait anxiety and uncinata fasciculus FA, while Montag et al. (2012) found a similar association for males, but not females. Similarly, in a sample containing young, middle-aged, and older adults, Clewett et al. (2014) found a positive relationship between trait anxiety and amygdala-vPFC FA (using an ROI that included the uncinata fasciculus). Higher uncinata fasciculus FA has been associated with greater self-reported use of the emotion regulation strategy of cognitive reappraisal, particularly in women (Zuurbier et al., 2013). Higher uncinata fasciculus FA is also related to decreased amygdala activation to emotional faces in children and adolescents (Swartz et al., 2014), and greater amygdala habituation to fearful faces (Hein et al., 2018). In addition, individuals with high uncinata fasciculus FA exhibit a stronger negative relationship between self-reported cognitive reappraisal and symptoms of depression and anxiety (d'Arbeloff et al., 2018).

While past studies have investigated how uncinata fasciculus FA relates to anxiety and depression (Bhatia et al., 2018; Bracht et al., 2015; de Kwaasteniet et al., 2013; Greenberg et al., 2021; Hettema et al., 2012; Liao et al., 2014; Phan et al., 2009; A. Zhang et al., 2012) and amygdala reactivity (Swartz et al., 2014), whether uncinata fasciculus FA is related to the behavioral response to emotional provocation is not clear. Examining this relationship may provide insights into how the microstructure of the uncinata fasciculus is related to basic affective functioning and how alterations in this microstructure may confer risk for mood and anxiety disorders. To examine how the microstructure of the uncinata fasciculus relates to emotional responses to affective stimuli, we investigated whether individual differences in uncinata fasciculus FA were associated with the response to affective images, as measured by electromyography of the corrugator supercillii, the muscle involved in brow furrowing. Corrugator activity increases in response to negatively valenced stimuli, and decreases to

positively valenced stimuli, and this modulation correlates reliably with participants' valence ratings of the stimuli (Cacioppo et al., 1986; Larsen et al., 2003; Lee et al., 2009; Tan et al., 2012). We also tested whether uncinete fasciculus microstructure correlated with activity of the zygomaticus major, the muscle involved in smiling. Zygomaticus activity increases in response to positively valenced stimuli, but is not sensitive to negative stimuli (Larsen et al., 2003; Tan et al., 2012). This allowed us to use the zygomaticus as a control region, to determine whether electromyographic activity to negative stimuli was specific to the corrugator or more widespread, which could indicate an effect due to an artifact or a process that is not specific to negative affect.

As the uncinete fasciculus may be involved in emotion regulation (d'Arbeloff et al., 2018; Delgado et al., 2008), we expected that the microstructure of this pathway would be associated with recovery processes following stimulus offset. Emotional recovery – how long the emotional response persists following the offset of an emotional provocation – is an important constituent of an individual's affective style. For example, less amygdala recovery is associated with inhibited temperament (Blackford et al., 2009), anxiety (Lau et al., 2012), depression, (Siegle et al., 2002) and neuroticism (Schuyler et al., 2014), and emotion regulation can decrease the duration of the amygdala response (Waugh et al., 2016). Individual differences in the time-course of corrugator activity are also associated with an individual's affective style (for review see Schaefer et al., 2018). Greater corrugator activity during the recovery from negative provocation suggests emotion regulation difficulties, because corrugator activity is sensitive to voluntary emotion regulation (Lee et al., 2009). In the absence of emotion regulation instructions, better corrugator recovery may index implicit emotion regulation – emotion regulation processes that operate automatically and without conscious effort (Mauss et al., 2007).

Greater corrugator activity after negative picture offset, indicative of poorer recovery, has been associated with lower levels of conscientiousness and self-control (Javaraš et al., 2012). In addition, persistent marital stress is related to higher corrugator activity following positive images (indicative of blunted positive emotional responses), with corrugator activity mediating the relationship between marital stress and depression symptoms (Lapate et al., 2014).

We predicted that greater FA of the uncinat fasciculus would be associated with reduced corrugator activity following negative image offset, indicating better recovery from emotional provocation. Based on past evidence that uncinat fasciculus FA is related to the regulation of negative emotions (d'Arbeloff et al., 2018; Hein et al., 2018), we expected relations between uncinat FA and corrugator and zygomaticus activity in response to positive images to be negligible. We also explored whether uncinat fasciculus FA was related to self-reported trait anxiety and negative affect, anxiety and depression symptomatology, and typical use of emotion regulation strategies.

While we chose the uncinat fasciculus as an a priori ROI, at the request of a reviewer, we also explored relationships between FA in each of the major fiber bundles and both the corrugator response to emotional images and affect-related self-report. There is little research linking these tracts to either affective responses or to the function of the amygdala, as most of this work has focused on the uncinat fasciculus (Hein et al., 2018; Swartz et al., 2014). However, studies investigating which tracts exhibit microstructural changes in anxiety disorders and anxiety-related traits are heterogeneous, with many major fiber bundles implicated, but often inconsistently across studies: Reduced FA in the uncinat fasciculus, cingulum bundle, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and superior longitudinal fasciculus has been implicated in generalized anxiety disorder (Adluru et al., 2017; Hettema et al., 2012; W.

Wang et al., 2016). However, while some past studies implicate reduced uncinate fasciculus FA in trait anxiety (Kim et al., 2016; Kim & Whalen, 2009), others have found a positive relationship between trait anxiety and FA in the uncinate fasciculus and fornix (Modi et al., 2013), as well as in the cingulum bundle, inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus and the superior longitudinal fasciculus in males, but not females (Montag et al., 2012). Meanwhile, Westlye et al. (2011) reported that harm avoidance – a trait related to anxiety – was associated with reduced FA in widespread white matter regions, extending into virtually all major tracts. Several studies have reported reduced FA in obsessive compulsive disorder, including the uncinate fasciculus, the cingulum bundle, the inferior occipital fasciculus, the inferior longitudinal fasciculus, and superior longitudinal fasciculus (Koch et al., 2014; Peng et al., 2012; Piras et al., 2013). In a meta-analysis, Jenkins et al. (2016) found that compared to healthy controls, participants with mood and anxiety disorders had reduced FA in the uncinate fasciculus, inferior fronto-occipital fasciculus, forceps minor, and superior longitudinal fasciculus. Thus, given the heterogenous nature of these past results, we explored relationships between the corrugator response to negative images and FA in each of the major fiber bundles, including the cingulum bundle, the inferior fronto-occipital fasciculus, the inferior frontal fasciculus, the superior longitudinal fasciculus, the corticospinal tract, the forceps major, the forceps minor, and the fornix.

## **Method**

### **Participants**

Participants were enrolled in the Midlife in the United States study (MIDUS; <http://midus.wisc.edu>), a national longitudinal study of health and well-being across the lifespan. Data came from the MIDUS refresher sample, a group of participants enrolled in the MIDUS

study beginning in 2011 to refresh the original MIDUS cohort. Random digit dialing was the primary method of recruitment for the MIDUS refresher cohort, although a sample of primarily African American participants recruited in Milwaukee, WI, by door-to-door solicitation was also included. Data for the current analysis came from the MIDUS Refresher Neuroscience Project, which included a psychophysiology session and an MRI session completed on consecutive days. While we previously reported that higher resting-state connectivity between the central amygdala and bed nucleus of the stria terminalis is related to greater corrugator reactivity to affective images using the MIDUS refresher dataset (Pedersen et al., 2020), relationships between structural connectivity (i.e. diffusion weighted imaging data) and the response to affective stimuli remain untested in this sample.

Diffusion tensor imaging (DTI) data were collected for 118 participants. Two participants were excluded from analysis because they were missing psychophysiology data, and 8 more were excluded due to excessive noise in their corrugator electromyography data. As a result, data from 108 participants (59 female, 49 male) with a mean age of 48.6 (range: 26-76) years were used in our primary analyses. Twelve participants had excessive noise in their zygomaticus electromyography data. Because of this, analyses involving zygomaticus data include data from 104 participants. When participants were asked their main racial origins, 70 endorsed White, 31 endorsed Black or African American, 2 endorsed Native American or Alaskan Native, and 1 endorsed Asian and 4 endorsed “other”. One participant was missing data for trait anxiety, emotion regulation strategy use and negative affect, with an additional subject missing data for emotion regulation strategy use only, and another missing data for symptoms of anxiety and depression. Additional demographic information can be found in Table 1.

### **Image Acquisition**



MRI scanning was performed on a 3-Tesla MR750 General Electric scanner (Waukesha, WI) using an 8-channel head coil. Diffusion weighted images were collected using a Stejskal-Tanner (Stejskal & Tanner, 1965) diffusion prepared single-shot echo-planar imaging pulse sequence. Sixty-five axial slices of 2 mm thickness were acquired with 6 diffusion-encoding directions at  $b=400$  s/mm<sup>2</sup> and 70 diffusion encoding directions at  $b=1200$  s/mm<sup>2</sup>, in addition to 4 baseline images ( $b=0$  s/mm<sup>2</sup>). Images were acquired with an in-plane matrix of 128 mm  $\times$  128 mm, resulting in a 2 mm  $\times$  2 mm resolution (FOV=256 mm, TR=7000 ms, TE=68.7 ms, partial Fourier [62.5%], ASSET [SENSE]  $\times$  2).

### **Diffusion Weighted Image Processing and Tractography**

The software package MRtrix3 (v. 3.0; Tournier et al., 2019) was used to denoise the data (Veraart et al., 2016), and correct Gibbs ringing artifacts (Kellner et al., 2016). The FMRIB Software Library (FSL v. 5.0.11) ‘eddy’ tool was used to correct for eddy current-induced distortions and subject movements (Andersson & Sotiropoulos, 2016), and to skull-strip the data (Smith, 2002). Weighted least squares was used to fit the tensors at each voxel using the Diffusion Imaging In Python package (v. 0.14.0; Garyfallidis et al., 2014). The Advanced Normalization Tools software package (v. 2.2.0; Avants, Tustison, & Song, 2009) was used to create a study specific FA template, and to normalize each participant’s images to this template. Tensors from individual subjects were reoriented to preserve the principal orientations (which is important for tractography) when spatially transforming to the template, and a population-averaged tensor template was generated using the reoriented tensor maps using the Diffusion Tensor Imaging ToolKit (v. 2.3.3; Zhang, Yushkevich, Rueckert, & Gee, 2007).

ROIs from the Illinois Institute of Technology (IIT) Human Brain Atlas (v. 4.1; S. Zhang & Arfanakis, 2018) were warped to our study-specific template (Avants et al., 2009). ROIs from

the IIT atlas warped to our study-specific template can be seen in Supplementary Figure 1. The alignment between each participant's normalized FA map and the normalized atlas was visually inspected to ensure accuracy. For each participant FA values were extracted for each tract in the IIT atlas. A white matter mask with voxels whose FA values was greater than 0.2 was created for each participant. Mean FA values within these masks were extracted for each subject to provide a measure of total white matter FA. We also extracted mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) from these maps for additional analyses presented in the Supplementary Table 1.

### **Self-Report Measures**

Participants completed self-report questionnaires including the State-Trait Anxiety Inventory – Trait Form (STAI-X2; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), the Positive and Negative Affect Schedule – General (PANAS; Watson, Clark, & Tellegen, 1988), the Mood and Anxiety Symptoms Questionnaire (MASQ; Watson & Clark, 1991), and the Emotion Regulation Questionnaire (ERQ; Gross & John, 2003). Trait anxiety scores used in analyses were mean scores for the STAI-X2, while mean scores for the negative affect subscale of the PANAS-General were used as trait negative affect scores. Sums for the Anxious Arousal and General Distress – Anxiety subscales of the MASQ were computed and averaged to obtain an estimate of anxiety symptoms. Similarly sums for the Loss of Interest and General Distress – Depression subscales of the MASQ were computed and averaged to produce an estimate of depression symptoms. Mean scores from the ERQ expressive suppression and cognitive reappraisal subscales were used as measures of the two emotion regulation styles. Scores were excluded from analysis for a given subject when fewer than 50% of items were completed. One participant was missing data for the STAI-X2, ERQ and the PANAS, with an additional subject

missing data for the ERQ, and another missing data on the MASQ. Descriptive statistics for self-reported measures can be found in Table 2.

### **Data Sharing**

EMG and self-report data can be downloaded through the MIDUS-Colectica Portal (<https://midus.colectica.org>) or the Inter-university Consortium for Political and Social Research data archive (visit <https://doi.org/10.3886/ICPSR36901> for data from the MASQ questionnaire, and <https://doi.org/10.3886/ICPSR37094> for all other self-report and EMG data). Diffusion-weighted data (and other raw imaging data collected in MIDUS) are available by contacting SMS.

### **Experimental Design and Statistical Analysis**

**Facial electromyography task.** Participants viewed 30 negative, 30 neutral, and 30 positive images from the International Affective Picture System (Lang et al., 2008). Trials consisted of a 1 s fixation period followed by an image displayed for 4 s and were separated by a random 14-18 s intertrial interval. For the first .5 seconds of image presentation, images were surrounded by a yellow or purple border. To promote attention to the images, participants were asked to report the color of the border with a button press. Ag-AgCl Touchproof shielded electrodes were used to measure activity from the corrugator supercilii and zygomaticus major muscles.

BIOPAC hardware amplified raw electromyography signals, which were sampled at 1000 Hz using Acknowledge software. A 60 Hz notch filter was applied to the corrugator data. Artifacts were then removed, following visual inspection. Spectral power density ( $\mu\text{V}^2/\text{Hz}$ ) in the 30-200 Hz frequency band was estimated for 1 s epochs (extracted through Hanning windows with 50% overlap) of artifact-free data using a Fast Fourier Transform. The data were

then log-transformed and used to create 12 baseline-corrected, one-second epochs for each valence condition, using the 1 second fixation period preceding image presentation as the baseline. Data were *z*-scored within subject and averaged to create estimates for three 4-second time windows for each valence condition, including an early time window representing activity during image presentation, a middle time window (0-4 seconds after image offset) and a late time window (4-8 seconds after image offset). Further information concerning the collection and processing of this data can be found in the Inter-university Consortium for Political and Social Research data archive ([doi.org/10.3886/ICPSR37094](https://doi.org/10.3886/ICPSR37094)) or see Van Reekum et al. (2011).

### **Statistical analysis.**

*Effects Tested.* Statistical analysis was performed in R v. 3.6 (Team, 2018). Linear regression was used to test whether greater FA values in each ROI were associated with altered corrugator recovery following negative images across two epochs: early recovery (0-4 s after image offset), and late recovery (4-8 s after image offset).

As a point of comparison, we also tested whether FA in each of the major fiber bundles was related to corrugator reactivity, i.e., corrugator activity during the 4 second image presentation. In the case of a significant relationship, the correlation for the corrugator response to neutral and positive images, as well as the zygomaticus responses to negative, neutral, and positive images for the same epoch was tested. Next relationships for FA values in each tract with trait anxiety and negative affect, as well as typical use of the emotion regulation strategies of cognitive reappraisal and expressive suppression were tested.

Both standardized and unstandardized beta-coefficients are reported, along with semi-partial correlation (*sr*) for regressions involving more than one independent variable. All regressions were checked for outliers using a Cook's D cutoff of .1. Except where noted,

removing outliers had no impact on whether an effect was significant, and all data points are used in the reported analyses.

Whether relationships between FA values in each tract and a given dependent variable varied for the left and right hemisphere was tested using difference tests for dependent correlations with the `paired.r` function in the R package, “psych” (v. 1.8.12; Revelle, 2018). None of our dependent variables exhibited a significantly different correlation with FA values coming from the left and right hemisphere for any of tracts investigated for any reported effects after correcting for multiple comparisons (all p-values > .06). Because of this, mean FA values averaged across hemisphere were used in all analyses.

*Covariates.* Starting with middle age, aging is associated with a decline in white matter microstructure (Kochunov et al., 2012; Yeatman et al., 2014). Age is also often accompanied by changes in emotion functioning, with older adults reporting less negative emotion and stable levels of positive emotion (Carstensen et al., 2000; Charles et al., 2001; Charles & Carstensen, 2010; Schneider, 2018). Furthermore, Cotter et al. (2020) found that older adults with declining FA report worsening mood over time, while those with stable FA report improved mood. Therefore, age could cause a spurious relationship between FA and corrugator recovery by acting as a confounding variable. However, controlling for age may be an overly conservative standard, as age could also drive variability in the white matter microstructure in a given tract, which could in turn affect corrugator activity. Separate regressions were first run with an interaction term for FA for a given ROI with age and sex, respectively. When no significant interactions were found, the interaction term was dropped and demographic variables were instead included as additional covariates to test whether effects remained while controlling for age, sex, and race, as well as global FA. If an effect remains significant after including global FA, it suggests that the effect

was specific to the tract in question, and not driven by global changes in white matter microstructure such as those expected to accompany aging (Kochunov et al., 2012; Yeatman et al., 2014) .

### **Correction for Multiple Comparison.**

*Uncinate Fasciculus.* Regressions testing relationships between uncinate fasciculus and corrugator activity were Bonferroni-corrected for two comparisons, representing the time windows of interest (early and late recovery). For consistency, this same correction was applied to regressions relating uncinate fasciculus FA and the corrugator reactivity time-window, which were included as a point of comparison. Regressions between self-reports of depression and anxiety related traits or symptoms were controlled for four comparisons (trait anxiety, trait negative affect, anxiety symptoms, depression symptoms), while analyses involving self-reported dispositional use of emotion regulation strategies were controlled for two comparisons (expressive suppression and cognitive reappraisal). Reported p-values have been adjusted accordingly using Bonferroni correction. This correction scheme was applied for main effects, as well as effects involving interactions with sex and age. For tables reporting diffusion measures other than FA, the same correction scheme was applied within each diffusion measure.

*Exploratory Tracts.* Regressions testing relationships between the exploratory tracts and corrugator activity were corrected across the 9 tracts for regressions involving the reactivity time window and across the 9 tracts and 2 time points (i.e. 18 comparisons) for regressions including the 2 recovery time windows. This correction was applied using the Benjamini-Hochberg procedure for false discovery rate (FDR). FDR correction was also applied across the 9 tracts and 4 depression and anxiety self-report measures (36 comparisons), as well as the 9 tracts and the 2 emotion regulation self-report measures (18 comparisons). This correction scheme was applied

for main effects, as well as effects involving interactions with hemisphere, sex and age. For tables reporting diffusion measures other than FA, the same correction scheme was applied within each diffusion measure.

## Results

### Manipulation Check

Consistent with expectations, greater corrugator activity was observed in response to negative vs. neutral images for the reactivity,  $t(107)=8.312$ , 98.3% CI[.52, .94],  $p<.001$ , early recovery,  $t(107)=6.055$ , 98.3% CI[.36, .85],  $p<.001$ , and late recovery time windows,  $t(107)=2.495$ , 98.3% CI[.01, .48],  $p=.042$ . Greater corrugator activity was also observed in response to negative vs. positive (reactivity:  $t(107)=11.904$ , 98.3% CI[.91, 1.37],  $p<.001$ ; early recovery:  $t(107)=9.826$ , 98.3% CI[.7, 1.16],  $p<.001$ ; late recovery:  $t(107)=4.758$ , 98.3% CI[.24, .74],  $p<.001$ ), and neutral vs. positive images (reactivity:  $t(107)=5.035$ , 98.3% CI[.21, .6],  $p<.001$ ; early recovery:  $t(107)=3.517$ , 98.3% CI[.1, .54],  $p=.002$ ; late recovery:  $t(107)=2.644$ , 98.3% CI[.02, .48],  $p=.028$ ) for all time windows (Figure 1). These results suggest that corrugator activity indexed affective reactions as expected, with higher activity for negative than neutral images, and lower activity for positive than neutral images.

Zygomaticus activity was significantly larger on positive vs. neutral image trials for the reactivity,  $t(103)=4.919$ , 98.3% CI[.26, .77],  $p<.001$ , early recovery,  $t(103)=3.338$ , 98.3% CI[.1, .63],  $p=.004$ , but not late recovery time-windows,  $t(103)=1.419$ , 98.3% CI[-.12, .45],  $p=.477$ . Zygomaticus activity was also higher for positive vs. negative image trials for the reactivity,  $t(103)=5.732$ , 98.3% CI[.34, .84],  $p<.001$ , and early recovery,  $t(103)=3.852$ , 98.3% CI[.17, .73],  $p<.001$ , but not late recovery time-windows,  $t(103)=1.2$ , 98.3% CI[-.14, .41],  $p=.69$ . There was no difference for negative vs. neutral image trials for any time-window (all  $p$ -values  $> .1$ ). These

results align with past findings that zygomaticus activity is sensitive to positive affect, in comparison to both negative and neutral, but insensitive to negative vs. neutral affect (Tan et al., 2012).

## **FA and Electromyography**

### *Uncinate Fasciculus*

Mean uncinat fasciculus FA did not significantly interact with age (all  $p$ -values  $> .39$ ) for any reported effects using electromyographic measures as outcome variables. Mean uncinat fasciculus FA was not related to the corrugator response during negative images,  $B=4.76$ ,  $\beta=0.13$ ,  $t(106)=1.3$ ,  $p=0.392$ , or during early recovery from negative images,  $B=-4.03$ ,  $\beta=-0.12$ ,  $t(106)=-1.2$ ,  $p=0.467$ . However, greater uncinat fasciculus FA was associated with lower late recovery corrugator activity following negative images,  $B=-14.72$ ,  $\beta=-0.35$ ,  $t(106)=-3.89$ ,  $p<0.001$  (Figure 2), and this effect remained when controlling for overall white matter FA,  $B=-18.57$ ,  $\beta=-0.45$ ,  $sr=-0.3$ ,  $t(105)=-3.35$ ,  $p=0.002$ , as well as when controlling for race, age and sex,  $B=-11.19$ ,  $\beta=-0.27$ ,  $sr=-0.23$ ,  $t(100)=-2.55$ ,  $p=.024$ . In contrast, we did not detect a relationship between uncinat fasciculus FA and late recovery corrugator activity following neutral,  $B=-3.58$ ,  $\beta=-0.1$ ,  $t(106)=-1.05$ ,  $p=.596$ , or positive images,  $B=-6.11$ ,  $\beta=-0.16$ ,  $t(106)=-1.67$ ,  $p=0.197$ , or late zygomaticus activity to negative,  $B=3.73$ ,  $\beta=0.1$ ,  $t(102)=1.02$ ,  $p=.623$ , or positive images,  $B=-2.91$ ,  $\beta=-0.08$ ,  $t(102)=-0.83$ ,  $p=.814$ . We did find an interaction between late zygomaticus activity following neutral images and sex,  $B=20.44$ ,  $\beta=.23$ ,  $t(100)=2.34$ ,  $p=.043$ , with a positive relationship between late recovery zygomaticus activity and uncinat fasciculus FA in men,  $B=19.23$ ,  $\beta=.39$ ,  $t(44)=2.82$ ,  $p=.014$ , but not women,  $B=-1.21$ ,  $\beta=-.03$ ,  $t(56)=-.22$ ,  $p=1$ . Although, this interaction was no longer significant after the removal of one outlying observation (cook's  $D = .39$ ),  $B=19.77$ ,  $\beta=.22$ ,  $t(99)=2.26$ ,  $p=.052$ . No other effects reported in this section interacted



with sex (all  $p$ -values  $> .15$ ). Table 3 presents results for relationships between the corrugator response and additional DTI measures, including mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD).

### ***Exploratory Tracts***

FA did not significantly interact with age (all  $p$ -values  $> .14$ ) or sex (all  $p$ -values  $> .25$ ) for any of the reported effects with EMG measures as outcome variables for any of the exploratory tracts. There were no significant relationships between corrugator activity during negative image presentation and mean FA in any of the exploratory tracts (all  $p$ -values  $> .18$ ).

There was a significant zero-order relation between early recovery corrugator activity and FA in the forceps major,  $B=-6.89$ ,  $\beta=-0.23$ ,  $t(106)=-2.48$ ,  $p=0.044$ , but this relationship was no longer significant when controlling for either age, sex and race,  $B=-6.31$ ,  $\beta=-0.21$ ,  $sr=-0.2$ ,  $t(100)=-2.13$ ,  $p=.106$ , or global white matter FA,  $B=-8.29$ ,  $\beta=-0.28$ ,  $sr=-0.21$ ,  $t(105)=-2.2$ ,  $p=0.136$ . There were no other significant relationships between FA and corrugator activity during negative images in the early recovery time window ( $p>.08$ ).

Table 4 contains results for relationships between FA in each of the exploratory tracts and late recovery corrugator activity following negative images with no covariates, while controlling for age, sex and race, and while controlling for global FA. There was a zero-order relation between corrugator activity following negative images in the late recovery time window and FA in the hippocampal portion of the cingulum bundle, corticospinal tract, forceps major, forceps minor, inferior-frontal occipital fasciculus, inferior longitudinal fasciculus and superior longitudinal fasciculus, but not the cingulate portion of the cingulum bundle or fornix. For the corticospinal tract, this effect was no longer significant after removing one outlier (Cook's  $D=.13$ ),  $B=-11.26$ ,  $\beta=$ ,  $t(105)=-2.27$ ,  $p=.057$ . Despite these significant zero-order relationships,

only inferior longitudinal fasciculus FA was significantly related to late recovery corrugator activity following negative images when controlling for age, sex and race. In addition, mean FA in the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus and superior longitudinal fasciculus was significantly related to late recovery corrugator activity following negative images when controlling for global FA. In contrast, there were no significant relationships between inferior longitudinal fasciculus, inferior fronto-occipital fasciculus or superior longitudinal fasciculus FA and late recovery corrugator activity following positive (inferior longitudinal fasciculus:  $B=-4.72$ ,  $\beta=-0.12$ ,  $t(106)=-1.19$ ,  $p=0.423$ ; inferior fronto-occipital fasciculus:  $B=-5.16$ ,  $\beta=-0.12$ ,  $t(106)=-1.28$ ,  $p=0.423$ ; superior longitudinal fasciculus:  $B=-5.45$ ,  $\beta=-0.12$ ,  $t(106)=-1.25$ ,  $p=0.423$ ) or neutral images (inferior longitudinal fasciculus:  $B=3.26$ ,  $\beta=-0.09$ ,  $t(106)=-0.89$ ,  $p=0.506$ ; inferior fronto-occipital fasciculus:  $B=-4.15$ ,  $\beta=-0.11$ ,  $t(106)=-1.11$ ,  $p=0.407$ ; superior longitudinal fasciculus:  $B=-5.61$ ,  $\beta=-0.13$ ,  $t(106)=-1.39$ ,  $p=0.272$ ). Similarly, FA in these tracts was not significantly associated with late recovery zygomaticus activity following negative (inferior longitudinal fasciculus:  $B=4.55$ ,  $\beta=0.11$ ,  $t(102)=1.16$ ,  $p=0.415$ ; inferior fronto-occipital fasciculus:  $B=4.82$ ,  $\beta=0.12$ ,  $t(102)=1.21$ ,  $p=0.415$ ; superior longitudinal fasciculus:  $B=7.02$ ,  $\beta=0.16$ ,  $t(102)=1.64$ ,  $p=.415$ ), positive (inferior longitudinal fasciculus:  $B=-2.71$ ,  $\beta=-0.07$ ,  $t(102)=-0.72$ ,  $p=0.91$ ; inferior fronto-occipital fasciculus:  $B=-1.54$ ,  $\beta=-0.04$ ,  $t(102)=-0.4$ ,  $p=0.91$ ; superior longitudinal fasciculus:  $B=-2.7$ ,  $\beta=-0.06$ ,  $t(102)=-0.65$ ,  $p=0.91$ ) or neutral images (inferior longitudinal fasciculus:  $B=8.77$ ,  $\beta=0.18$ ,  $t(102)=1.86$ ,  $p=.183$ ; inferior fronto-occipital fasciculus:  $B=8.13$ ,  $\beta=0.16$ ,  $t(102)=1.69$ ,  $p=.184$ ; superior longitudinal fasciculus:  $B=11.05$ ,  $\beta=0.21$ ,  $t(102)=2.14$ ,  $p=.183$ ).

## Self-Reports

### *Uninate Fasciculus*

There were no significant interactions between uncinat fasciculus FA and either age (all  $p$ -values  $>.76$ ) or sex (all  $p$ -values  $>.52$ ) on any of the self-reported measures. There was no significant relationship between uncinat fasciculus FA and self-reported anxiety symptoms,  $B=-25.77$ ,  $\beta=-0.13$ ,  $t(105)=-1.35$ ,  $p=.724$ , depression symptoms,  $B=-29.9$ ,  $\beta=-0.14$ ,  $t(105)=-1.48$ ,  $p=.572$ , trait anxiety,  $B=-1.79$ ,  $\beta=-0.08$ ,  $t(105)=-0.78$ ,  $p=1$ , or trait negative affect,  $B=0.49$ ,  $\beta=0.02$ ,  $t(105)=0.21$ ,  $p=1$ . We also did not detect any associations between uncinat fasciculus FA and the dispositional use of the emotion regulation strategies of expressive suppression,  $B=7.7$ ,  $\beta=0.12$ ,  $t(104)=1.26$ ,  $p=.424$ , or cognitive reappraisal,  $B=-1.01$ ,  $\beta=-0.02$ ,  $t(104)=-0.22$ ,  $p=1$ . Supplementary Table 1 contains results for other diffusion measures, including MD, RD, and AD.

### ***Exploratory Tracts***

There were no significant interactions between FA and either age (all  $p$ -values  $>.98$ ) or sex (all  $p$ -values  $>.75$ ) for any of the self-reported measures in any of the exploratory tracts. There were no significant associations between FA and self-reported anxiety symptoms (all  $p$ -values  $>.72$ ), depression symptoms (all  $p$ -values  $>.72$ ), trait anxiety (all  $p$ -values  $>.73$ ), trait negative affect (all  $p$ -values  $>.72$ ), expressive suppression (all  $p$ -values  $>.61$ ) or cognitive reappraisal (all  $p$ -values  $>.61$ ) in any of the exploratory tracts.

### **Discussion**

Our hypothesis that the white matter microstructure of the uncinat fasciculus would be related to better recovery from negative provocation was supported. Higher FA in this tract was related to lower corrugator activity 4-8 s following negative image offset while controlling for global FA, suggesting that these effects were not driven by global differences in FA. In a sample of children and adolescent participants, Swartz et al. (2014) found that uncinat fasciculus FA is

associated with less amygdala activation to emotional faces, suggesting higher FA within the uncinata fasciculus may indicate white matter microstructure that facilitates neural communication underlying regulation of the amygdala via signals from the prefrontal cortex. Thus, our findings are consistent with the hypothesis that the uncinata fasciculus facilitates top-down regulation signals from the prefrontal cortex to the amygdala, resulting in greater recovery following affective provocation. While past research has demonstrated that greater FA in the uncinata fasciculus is associated with more amygdala habituation to fearful faces (Hein et al., 2018), to our knowledge this is the first study to demonstrate that uncinata fasciculus FA is associated with individual differences in the time-course of the affective response, specifically mean recovery 4-8 s after offset, to individual negative stimuli.

In an exploratory analysis, we found that higher FA in the inferior fronto-occipital, inferior longitudinal and superior longitudinal fasciculi was also related to reduced corrugator activity in the late recovery time window when controlling for global FA. This effect was also significant in the inferior longitudinal fasciculus while controlling for sex, race, and age. In the inferior fronto-occipital and superior longitudinal fasciculi this effect was at trend level when controlling for sex, race, and age. These findings suggest that these tracts may participate in the emotional response to negative images and support the disengagement of emotional processing following the offset of emotional stimuli.

Both the inferior longitudinal and inferior fronto-occipital fasciculi are thought to support the modulation of visual processing for emotionally salient stimuli (Latini, 2015; Pessoa & Adolphs, 2010; Rudrauf et al., 2008). The inferior longitudinal fasciculus originates in the dorsolateral occipital cortex, cuneus, fusiform gyrus and lingual gyrus and projects to anterior temporal cortex (Latini et al., 2017). This tract is thought to support the transmission of

information from early visual cortices to the amygdala (Latini, 2015). This connection enables the amygdala to rapidly detect affective stimuli and modulate visual processing through projections that run back to the visual cortex (Pessoa & Adolphs, 2010; Rudrauf et al., 2008), which also likely run through the inferior longitudinal fasciculus. This is supported by studies finding that damage to the inferior longitudinal fasciculus is related to impaired recognition of emotional facial expressions (Crespi et al., 2014; Genova et al., 2015; Philippi et al., 2009). As such, our finding that low FA in the inferior longitudinal fasciculus leads to sustained responses to negative stimuli may be tied to its role in modulating the processing of affective stimuli, although further research is needed to elucidate the exact mechanism for this effect.

The inferior fronto-occipital fasciculus originates in the visual cortex, including the lingual gyrus, posterior fusiform, cuneus and polar occipital cortex, and travels through the temporal stem and external/extreme capsules terminating in the inferior frontal gyrus, fronto-orbital region and frontal pole (Forkel et al., 2014). This pathway may enable the orbitofrontal cortex to extract affective salience from early visual areas and to modulate visual processing via projections back to the occipital lobe (Pessoa & Adolphs, 2010; Rudrauf et al., 2008). While the orbitofrontal cortex has been implicated in the attentional bias toward negatively-valenced stimuli (Hartikainen et al., 2012; Murphy & Bachevalier, 2020), it is also involved in emotion regulation (Dixon et al., 2017; Goldin et al., 2008). Hooker and Knight (2006) argue that the lateral orbitofrontal cortex inhibits the processing of task-irrelevant affective stimuli by down-regulating their processing in sensory regions, including the visual cortex (Bishop, 2008; Vuilleumier et al., 2001). This suggests that connections facilitated by the inferior fronto-occipital fasciculus may be important for emotion regulation, including disengaging attention from negatively valenced stimuli. If so, high white matter integrity of the inferior fronto-occipital

fasciculus may contribute to greater emotion regulation following negatively valenced stimuli by allowing more efficient disengagement of attention from them.

The superior longitudinal fasciculus connects the frontal lobe with the parietal lobe and temporoparietal junction region (Kamali et al., 2014; Makris et al., 2005; X. Wang et al., 2016). This tract is thought to play an important role in language, the regulation of motor behavior, as well as visuospatial attention and working memory (Koshiyama et al., 2020; Nakajima et al., 2020). Connections between the prefrontal and posterior parietal cortices may play a role in preventing salient distractors from entering working memory (Jacob & Nieder, 2014; Lanssens et al., 2020; Minamoto et al., 2012) and disengaging attention from threat-related stimuli (De Raedt et al., 2010; Mulckhuyse et al., 2017). In addition, both the prefrontal cortex and posterior parietal regions are involved in the emotion regulation strategy of cognitive reappraisal (Buhle et al., 2014; Morawetz et al., 2017). It is thought that dorsolateral prefrontal cortex connections with posterior parietal cortex support cognitive reappraisal by directing attention and working memory to select a reappraisal strategy that will achieve a given regulatory goal (Silvers & Guassi Moreira, 2019). As such, high integrity in the superior longitudinal fasciculus may result in lower corrugator activity following emotional stimuli by facilitating connections between regions important for disengaging from negatively valenced stimuli (De Raedt et al., 2010; Mulckhuyse et al., 2017), and emotion regulation (Silvers & Guassi Moreira, 2019).

Our results demonstrate that the neural mechanisms related to variation in reactivity to and recovery from emotional provocation are distinct. Affective processes are dynamic, and individual differences in how these processes unfold over time constitute important aspects of affective style. Sustained responses to negative affective provocation are related to mood dysphoria (Taubitz et al., 2013), trait hostility (Fredrickson et al., 2000), low conscientiousness

(Javaras et al., 2012), and lower well-being (Schaefer et al., 2013) and may indicate reduced capacity for emotion regulation (Lee et al., 2009; Schaefer et al., 2018). Further research is needed to investigate how variation in uncinate, inferior longitudinal, inferior fronto-occipital and superior longitudinal fasciculi white matter microstructure is related to personality and other aspects of affective style.

White matter microstructure was not significantly related to symptoms of anxiety and depression, trait anxiety, trait negative affect, or dispositional use of the emotion regulation strategies of cognitive reappraisal and expressive suppression for the tracts investigated in our community sample. This suggests that the time-course of participant's corrugator responses to images indexed a portion of their affective profile that was not accounted for in these self-report measures. Past research has demonstrated that corrugator activity 4-8 s after picture offset also corresponds to other affect-related individual differences, such as marital stress, symptoms of depression (Lapate et al., 2014), and conscientiousness (Javaras et al., 2012). Our results highlight the importance of measuring individual differences in affect in multiple ways, as differing methods may assess different constructs, and are susceptible to different sources of error variance (Mauss & Robinson, 2009). However, it remains unclear why past studies have found relationships between the uncinate fasciculus white matter microstructure and measures of depression and anxiety (d'Arbeloff et al., 2018; Hettema et al., 2012; Liao et al., 2014; Phan et al., 2009), while we did not. Many of these past studies recruited groups of participants with and without anxiety or mood disorders, while our sample was intended to be representative of the U.S. population (Ryff et al., 2015). As a result, our sample may have limited range of anxiety and depression symptoms, with fewer participants reporting clinically significant levels. Schalet et al. (2014) suggested that a score of 25 or higher on the General Distress – Anxiety subscale of

the MASQ may represent clinically-relevant anxiety symptomatology. In our sample, 5.6% of participants met this criterion. Breddmeier et al. (2010) suggested a cut-off of 23 or higher on the loss of interest subscale of the MASQ when screening for possible current major depressive episode. Two of our subjects (1.9%) reached this cut-off. While our results suggest a relationship between uncinat fasciculus FA and affective functioning in a relatively psychologically healthy sample, associations between self-reported anxiety and depression with white matter microstructure in this tract may be more likely to emerge when the sample includes a large proportion of participants with clinical levels of anxiety or mood disorders.

A major limitation to the current study is the correlational nature of our findings. While past studies demonstrating an association between uncinat fasciculus FA and both emotion regulation (Zuurbier et al., 2013) and amygdala reactivity (Swartz et al., 2014) suggest plausible mechanisms whereby the white matter microstructure of the uncinat fasciculus may affect emotional recovery, the current analysis cannot establish causality. Similarly, while past work on mood and anxiety disorders suggests that the inferior longitudinal, inferior fronto-occipital and superior longitudinal fasciculi may each play a role in affective processing (Jenkins et al., 2016), the particular mechanism underlying a relationship between the white matter microstructure of these tracts and emotional recovery requires further study. Additionally, given that results for the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus and superior longitudinal fasciculus were the result of post-hoc analyses employing false discovery rate correction, a relatively liberal method, these findings should be interpreted cautiously. Future research should employ longitudinal designs and/or manipulations aimed at altering affective functioning – such as emotion regulation training – to better understand the relationship between the microstructure of these tracts and emotional recovery. We hope to do so in future waves of the MIDUS project.



Our results implicate the uncinate fasciculus in the recovery of emotional responses to negative provocation. This finding is consistent with work suggesting that this tract carries fibers involved in regulating affective processing (d'Arbeloff et al., 2018; Delgado et al., 2008; Zuurbier et al., 2013), and suggests that this tract may participate in implicit emotion regulation processes. White matter microstructure of the uncinate fasciculus may be an important neural correlate of individual differences in affective functioning. Our results also suggest that the inferior longitudinal, inferior fronto-occipital and superior longitudinal fasciculi support emotional recovery following negative stimuli. This finding suggests a potential mechanism for the involvement of these tracts in mood and anxiety disorders (Jenkins et al., 2016). While we found no evidence for a relationship between the microstructure of any of these tracts and self-reported anxiety and depression symptomatology in the current sample, future work should continue to investigate the role that these tracts may play in emotional processes contributing to vulnerability to psychopathology in addition to well-being.

### **Funding**

The MIDUS Refresher study was funded by the National Institute on Aging (P01-AG020166, U19-AG051426). The MIDUS Neuroscience Project data collection was supported in part by a core grant to the Waisman Center from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (U54 HD090256). WSP was supported by the National Institute of Mental Health (T32MH018931) and the National Center for Complementary and Integrative Health (1F32AT010101-01). DCD was supported by the National Institute of Mental Health (4 R00 MH110596 03). NA was supported in part by grants from the following: The BRAIN Initiative (R01-EB022883), the Waisman Intellectual and Developmental Disabilities Research Center (U54-HD090256), the Center for Predictive and

Computational Phenotyping (CPCP; U54-AI117924), and the Alzheimer's Disease Connectome Project (ADCP; UF1-AG051216, R56-AG037639, R01-AG037639, and RF1-AG059312).

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Sex	
Female	54.6%
Male	45.4%
Race	
White	64.8%
Black or African American	28.7%
Native American or Alaskan	1.9%
Native	
Asian	0.9%
Other	3.7%
Education	
High school or less	22.2%
Some college, no degree	21.3%
Graduated college	38%
Advanced degree	18.5%
Marital Status	
Married	56.5%
Never Married	22.2%
Divorced or Windowed	21.3%
Depression (past 12 months)	13.9%
Anxiety disorder (past 12 months)	3.7%

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Table 1. Demographics and Psychiatric Disorders. This table includes participants used in our primary analysis (i.e. those whose corrugator and DTI data passed quality assurance, N=108).

Scale	Minimum	Maximum	Mean	<i>SD</i>
Trait Negative Affect	1	3.5	1.485	.486
Trait Anxiety	1.05	3.15	1.722	.478
Suppression	1	7	3.507	1.278
Reappraisal	2.33	7	5.24	.956
Anxiety Symptoms	14	34.5	18.834	4.008
MASQ General Distress - Anxious Symptoms	11	43	16.629	4.991
MASQ Anxious Arousal	17	36	21.038	4.076
Depression Symptoms	10	32	15.232	4.251
MASQ General Distress – Depressive Symptoms	12	37	18.411	5.603
MASQ Loss of Interest	8	27	12.053	3.279

Table 2. Descriptive statistics for self-report scales. Trait anxiety scores used in analyses were mean scores for the STAI-X2, while mean scores for the negative affect subscale of the PANAS-General were used as trait negative affect scores. Sums for the Anxious Arousal and General Distress – Anxiety subscales of the MASQ were computed and averaged to obtain an estimate of anxiety symptoms. Similarly sums for the Loss of Interest and General Distress – Depression subscales of the MASQ computed and averaged to produce an estimate of depression symptoms. Mean scores from the ERQ expressive suppression and cognitive reappraisal subscales were used as measures of the two emotion regulation styles.

Tracts	MD			RD			AD		
	$\beta$	$t$	$p$	$\beta$	$t$	$p$	$\beta$	$t$	$p$
Uncinate Fasciculus	.29	2.19	.062	.46	3.23	<b>.003</b>	-.03	-.31	1
Cingulum (Cingulate Portion)	-.03	-.19	.942	.15	.81	.579	-.18	-1.67	.672
Cingulum (Hippocampal Portion)	.15	1.04	.603	.2	1.5	.275	-.07	-.6	.887
Corticospinal Tract	<.01	<.01	.997	.15	.99	.486	-.17	-1.36	.672
Forceps Major	.45	3.14	<b>.025</b>	.45	3.23	<b>.01</b>	.03	.28	.887
Forceps Minor	.29	2.17	.115	.32	2.38	.058	.03	.27	.887
Fornix	.24	2.36	.09	.24	2.38	.058	.15	1.55	.672
Inferior Fronto-Occipital Fasciculus	.48	3.06	<b>.025</b>	.63	3.79	<b>.005</b>	.07	.47	.887
Inferior Longitudinal Fasciculus	.45	2.68	.051	.6	3.59	<b>.005</b>	-.04	-.3	.887
Superior Longitudinal Fasciculus	.34	1.68	.288	.48	2.43	.058	-.14	-.84	.756

Table 3. Effect of mean diffusion (MD), radial diffusion (RD), and axial diffusion (AD) on late recovery corrugator activity following negative images by ROI, while controlling for global white matter for a given diffusion measure. Significant p-values are in bold (see *Statistical Analysis* for correction for multiple comparison scheme).

Tract	Zero-Order			Controlling Age, Sex and Race			Controlling Global FA		
	$\beta$	$t$	$p$	$\beta$	$t$	$p$	$\beta$	$t$	$p$
Uncinate Fasciculus	-.35	-3.89	<b>&lt;.001</b>	-.27	-2.55	<b>.024</b>	-.45	-3.35	<b>.002</b>
Cingulum (Cingulate Portion)	-.21	-2.18	.063	-.15	-1.52	.257	-.13	-.92	.499
Cingulum (Hippocampal Portion)	-.23	-2.4	<b>.047</b>	-.18	-1.89	.139	-.17	-1.58	.291
Corticospinal Tract	-.22	-2.33	<b>.049</b>	-.23	-2.44	.06	-.16	-1.37	.346
Forceps Major	-.27	-2.94	<b>.018</b>	-.24	-2.45	.06	-.26	-2.03	.16
Forceps Minor	-.25	-2.67	<b>.032</b>	-.14	-1.22	.366	-.23	-1.64	.291
Fornix	-.19	-1.97	.088	-.1	-.94	.526	-.13	-1.24	.394
Inferior Fronto-Occipital Fasciculus	-.35	-3.85	<b>.002</b>	-.28	-2.66	.06	-.62	-3.76	<b>.002</b>
Inferior Longitudinal Fasciculus	-.37	-4.07	<b>.002</b>	-.32	-3.19	<b>.034</b>	-.56	-3.85	<b>.002</b>
Superior Longitudinal Fasciculus	-.32	-3.53	<b>.004</b>	-.26	-2.45	.06	-.51	-3.13	<b>.014</b>

Table 4. Effect of mean fractional anisotropy (FA) on late recovery corrugator activity following negative images by ROI. While all tracts except for the cingulate portion of the cingulum and fornix exhibited a zero-order relation between mean FA and late corrugator activity following negative images, only the uncinate, fronto-occipital, inferior longitudinal, and superior longitudinal fasciculi exhibited this relationship when controlling for global white matter FA. Significant p-values are in bold (see *Statistical Analysis* for correction for multiple comparison scheme).

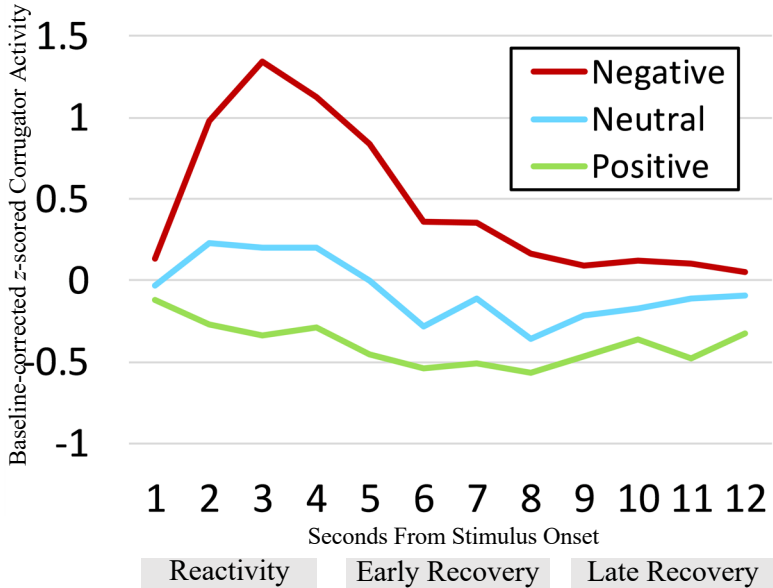


Figure 1. Time-course for baseline-corrected z-scored corrugator activity by image valence condition. For each time-window (reactivity, early recovery, and late recovery), mean corrugator activity was larger for negative than neutral and larger for neutral than positive.

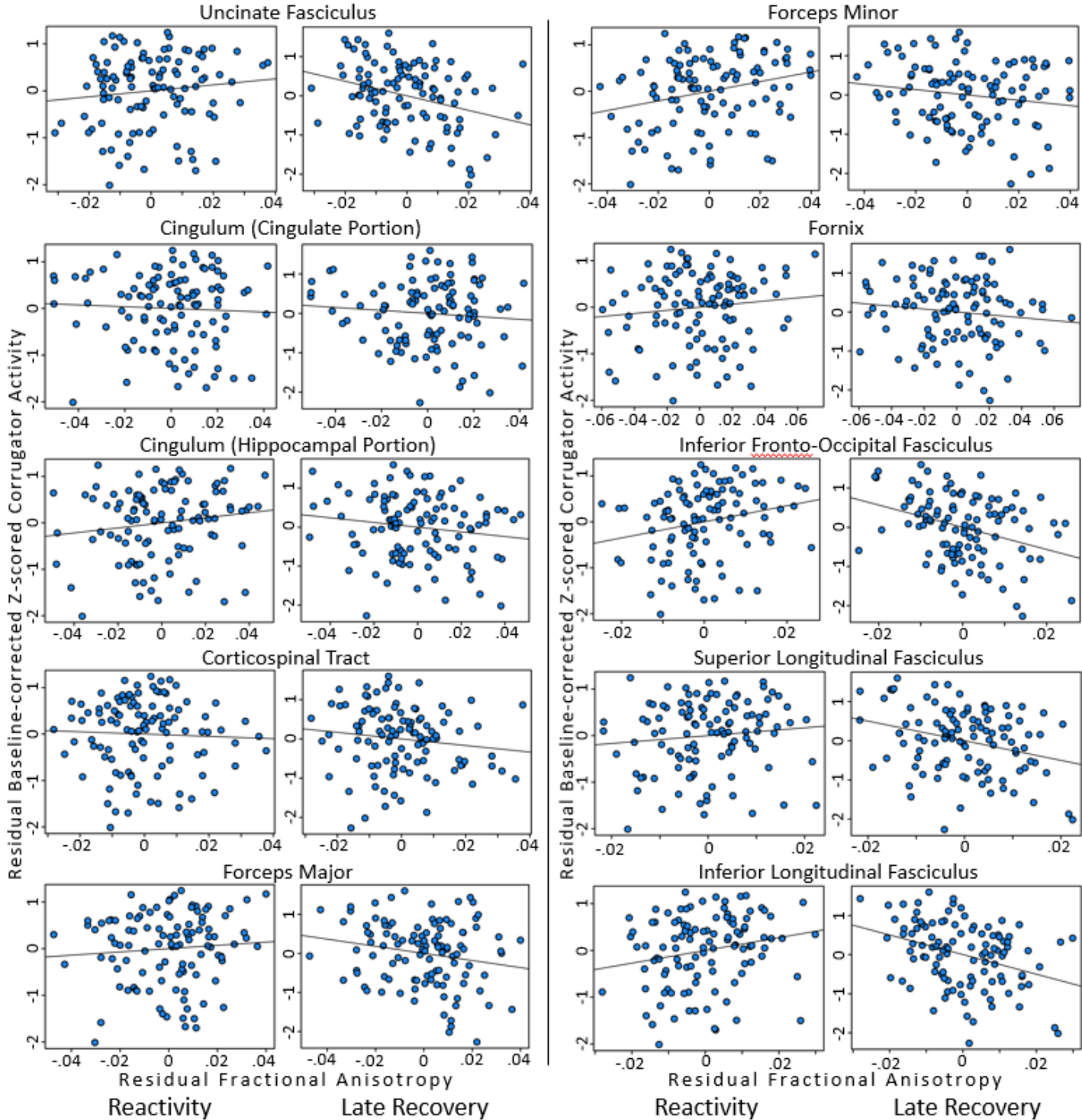


Figure 2. Partial plots depicting relationship between fractional anisotropy (FA) and mean baseline-corrected z-scored corrugator activity in response to negative images for reactivity (left), and late recovery (right) time windows while controlling for global FA. Late corrugator activity was significantly related to FA in the uncinate, inferior longitudinal, inferior fronto-occipital, and superior longitudinal fasciculi. Mean FA was not related to corrugator reactivity for any tract.