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UNCINATE FASCICULUS FRACTIONAL ANISOTROPY CORRELATES WITH TYPICAL USE OF REAPPRAISAL IN WOMEN BUT NOT MEN

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Abstract

Emotion regulation refers to strategies through which individuals influence their experience and expression of emotions. Two typical strategies are reappraisal, a cognitive strategy for reframing the context of an emotional experience, and suppression, a behavioral strategy for inhibiting emotional responses. Functional neuroimaging studies have revealed that regions of the prefrontal cortex modulate amygdala reactivity during both strategies, but relatively greater down-regulation of the amygdala occurs during reappraisal. Moreover, these studies demonstrated that engagement of this modulatory circuitry varies as a function of gender. The uncinate fasciculus is a major structural pathway connecting regions of the anterior temporal lobe, including the amygdala, to inferior frontal regions, especially the orbitofrontal cortex. The objective of the current study was to map variability in the structural integrity of the uncinate fasciculus onto individual differences in self-reported typical use of reappraisal and suppression. Diffusion tensor imaging was used in 194 young adults to derive regional fractional anisotropy values for the right and left uncinate fasciculus. All participants also completed the Emotion Regulation Questionnaire. In women but not men, self-reported typical reappraisal use was positively correlated with fractional anisotropy values in a region of the left uncinate fasciculus within the orbitofrontal cortex. In contrast, typical use of suppression was not significantly correlated with fractional anisotropy in any region of the uncinate fasciculus in either men or women. Our data suggest that in women typical reappraisal use is specifically related to the integrity of white matter pathways linking the amygdala and prefrontal cortex.

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Disclosure

None of the authors have any conflicts of interest to disclose.

Keywords

emotional regulation; uncinate fasciculus; amygdala; orbitofrontal cortex; fractional anisotropy

Introduction

Emotion regulation (ER) refers to the processes through which individuals influence their experience and expression of emotions, and includes attenuation, amplification and continuation of emotions. Individuals differ significantly in the frequency and ability of applying such ER strategies (Davidson, Putnam, & Larson, 2000; Gross & John, 2003), and dysregulation of emotion is a hallmark of mood and anxiety disorders (S. F. Taylor & Liberzon, 2007). Two common ER strategies are reappraisal (REAP), which is a cognitive strategy for reframing the context of an emotional experience, and suppression (SUP), which is a behavioral strategy to reduce emotional responses (Quirk & Beer, 2006; Vrticka, Sander, & Vuilleumier, 2011). REAP is an antecedent-focused strategy, because it immediately influences the emotional response, while SUP is a response-focused strategy, as it tries to suppress the emotional response after it has arisen (Goldin, McRae, Ramel, & Gross, 2008; Gross, 1998). Critically, individuals differ significantly in the use of these strategies (Gross & John, 2003).

Functional neuroimaging studies (Drabant, McRae, Manuck, Hariri, & Gross, 2009; S. H. Kim & Hamann, 2007; Levesque et al., 2003; Levesque et al., 2004; Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner et al., 2004; Ohira et al., 2006; Phan et al., 2005; Urry et al., 2006) have revealed that increasing or decreasing positive and negative emotions during active ER is associated with increased activity in multiple subregions of the prefrontal cortex (PFC), including the orbitofrontal cortex (OFC). In contrast, amygdala reactivity is increased specifically when subjects are instructed to either maintain or enhance their emotional response, and decreased when they are instructed to decrease their emotional response (S. H. Kim & Hamann, 2007; Ochsner et al., 2004; Schaefer et al., 2002). Furthermore, the strength of functional coupling between the PFC and amygdala is related to successful down regulation of negative affect (Banks et al., 2007; Urry et al., 2006).

However, while subjective emotional experiences decrease during both ER strategies, there is typically a larger decrease during REAP than SUP (Davidson et al., 2000; Vrticka et al., 2011). This pattern is mirrored in greater down-regulation of amygdala reactivity during REAP than SUP (Goldin et al., 2008; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). Furthermore, individuals who frequently use REAP experience more positive emotions and less negative emotions, and show higher levels of psychological well-being than SUP users (Gross & John, 2003). Individuals who use REAP more often in daily life also exhibit relatively decreased amygdala and increased PFC responses to threat-related facial expressions (Drabant et al., 2009)

Importantly, there are gender differences in the use of ER strategies with women reporting greater use (Nolen-Hoeksema, 2012). Such differences may contribute to the emergence of gender differences in mood and anxiety disorders (Gater et al., 1998). Accordingly, there is evidence for gender differences in the engagement of prefrontal circuitry during ER (Domes

et al., 2010; McRae, Ochsner, Mauss, Gabrieli, & Gross, 2008). However, the directionality of these differences has not been consistent with one study reporting relatively increased (McRae et al., 2008) and another decreased (Domes et al., 2010) prefrontal activity in women compared with men.

The above neuroimaging studies indicate that ER is dependent on a circuitry involving the amygdala and PFC, and that the magnitude of responsiveness in these two regions maps onto variability in ER use and success in what appears to be a gender-specific manner. White matter pathways linking these regions in part determine the functional dynamics between the amygdala and PFC. Prominent amongst these pathways is the uncinate fasciculus (Catani, Howard, Pajevic, & Jones, 2002; Ebeling & von Cramon, 1992; Ghashghaei, Hilgetag, & Barbas, 2007; Schmahmann & Pandya, 2006). Lower fractional anisotropy (FA) values in the UF have been reported in several mood and anxiety disorders including Major Depressive Disorder, Bipolar Disorder and Social Phobia, as well as correlated with trait anxiety (Baur et al., 2011; Baur, Hanggi, & Jancke, 2012; Kawashima et al., 2009; M. J. Kim & Whalen, 2009; McIntosh et al., 2008; Phan et al., 2009; Price et al., 2008; S. F. Taylor & Liberzon, 2007; A. Zhang et al., 2011). Thus, much like the functional response of the amygdala and PFC, the structural integrity of the uncinate fasciculus (UF) may also be related to ER.

Here, we examine the relationship between variability in the structural integrity of the UF and individual differences in typical ER use in 200 young adult volunteers. Diffusion tensor imaging (DTI), which provides a voxelwise measure of water diffusion (anisotropy), was used to determine the degree of anisotropy (i.e., fractional anisotropy) in the right and left UF. Fractional anisotropy (FA) values depend on myelination, coherence in orientation, and density of fibers. Higher FA values reflect greater structural integrity and, in turn, capacity for functional communication between connected brain regions (Thomason & Thompson, 2011). Typical use of REAP and SUP was determined by self-report using the Emotion Regulation Questionnaire (Gross & John, 2003). The previously observed greater decrease of amygdala activity during REAP than SUP suggests that the functional pathway between the amygdala and PFC may be more involved in the former process. Thus, we hypothesized that higher FA values in the UF would be associated with greater use of REAP specifically. Given the significant gender differences in typical ER use and the neural correlates of ER, we also explored the moderating effect of gender on this relationship.

Materials and Methods

Participants

A total of 200 participants (117 women; mean age 19.65 ± 1.30 years) were investigated from an ongoing parent protocol, the Duke Neurogenetics Study (DNS), which assesses a wide range of behavioral and biological traits among non-patient, young adult, student volunteers. Six participants were excluded due to DTI artifacts, frontal distortions or abnormal anatomical structure (Supplementary Figure 1). Therefore, 194 subjects (113 women; mean age 19.66 ± 1.30 years) were included in analyses. For one participant, data from only one DTI scan was available due to a time constraint. For all others, however, two DTI scans were used in analyses. All participants provided informed consent in accord with

Duke University guidelines, and were in good general health. The participants were free of the following study exclusions: (1) medical diagnoses of cancer, stroke, head injury with loss of consciousness, untreated migraine headaches, diabetes requiring insulin treatment, chronic kidney or liver disease, or lifetime history of psychotic symptoms; (2) use of psychotropic, glucocorticoid, or hypolipidemic medication; and (3) conditions affecting cerebral blood flow and metabolism (e.g., hypertension). Diagnosis of any past or current DSM-IV Axis I disorder, as assessed by the clinical interview using the electronic Mini-International Neuropsychiatric Interview (eMINI), was not a criteria for exclusion as the DNS seeks to establish broad variability in multiple behavioral phenotypes related to psychopathology (e.g., impulsivity). Of the 194 participants included in the data analyses, 34 received clinical diagnoses according to *DSM-IV* (Supplementary Table 1). However, as stated above no subjects were taking psychotropic medication at the time of or at least 10 days prior to study participation. See supplementary material for information regarding observed distribution of psychopathology in the current sample (Supplementary Table 1).

Behavioral assessment

The ERQ (Gross & John, 2003) was used to measure everyday use of REAP and SUP. Six items for REAP (e.g., When I want to feel more positive emotion, I change the way I'm thinking about the situation) and four items for suppression (e.g., I control my emotions by not expressing them) were used. Subjects rated each item on a scale from 1 (strongly disagree) to 7 (strongly agree). The summed scores for each subscale were used as index of typical REAP and SUP use respectively. IQ was determined using the Wechsler Abbreviated Scale of Intelligence (WAIS-IV). In addition, relative social standing was determined using the 'social ladder' (Adler, Epel, Castellazzo, & Ickovics, 2000), which asks participants to rank themselves to other people in the United States on a scale from 0–10, with the people who are best off at the top (10) and the people who are the worst off at the bottom (0). Lower social status is related to greater use of SUP as ER strategy (Gross & John, 2003).

To further establish the specificity of any observed relationships between FA values in the UF and typical use of adaptive ER strategies (i.e., REAP but not SUP), we conducted secondary analyses comparing men and women and examining correlations between UF FA values and a measure of trait rumination/worry, which represents a maladaptive form of processing emotions. Our composite measure of trait rumination/worry was derived using specific items (see Supplementary material for details) from the State Trait Anxiety Inventory – Trait Version (STAI-T; (Spielberger, 1983)) and the NEO-PI-R (Costa, 1992).

DTI acquisition and analysis

Each participant was scanned using a research-dedicated GE MR750 3T scanner at the Duke-UNC Brain Imaging and Analysis Center (BIAC). This scanner is equipped with high-power, high-duty-cycle 50-mT/m gradients at 200 T/m/s slew rate, and an eight-channel head coil for parallel imaging at high bandwidth up to 1MHz. Following an ASSET calibration scan, two 2 minutes 50 seconds high angular resolution diffusion imaging (HARDI) acquisitions were collected, providing full brain coverage with 2 mm isotropic resolution and 15 diffusion weighted directions (repetition time (TR) 10 sec; echo time (TE)

84.9 ms; b value 1000 s/mm²; FOV 240 mm; flip angle 90°; acquisition matrix 128 × 128; slice thickness 2 mm).

DTI analyses were completed using SPM8 implemented in Matlab v7.11.0 (R2010b). All diffusion weighted scans were realigned to the first scan with a b value of 0 to correct for head movement. The two DTI sequences were used in the tensor model to calculate eigenvector, eigenvalues and FA values for each voxel and non-brain tissue was removed. Each image was normalized to the Montreal Neurological Institute (MNI) space by affine registration to the FMRIB58_FA template, taken from FMRIB's Software Library (FSL) (Smith et al., 2004). After normalization each image was smoothed using 4 mm full-width at half maximum Gaussian kernel.

Voxelwise regression analysis was performed on the individual FA images with typical REAP and SUP scores as the dependent variable. Gender was included in the model as a moderator. IQ, age, race/ethnicity, and social standing were entered as covariates because each has been found to correlate with FA values or typical use of REAP and SUP (Gross & John, 2003; Salat et al., 2005; Szeszko et al., 2003; Tang et al., 2010). Following our *a priori* hypothesis, the left and right UF were taken separately as region of interests (ROIs) defined using the probabilistic fiber maps of the Laboratory of Brain Anatomical MRI (Y. Zhang et al., 2010). Within these ROIs (Figure 1) the voxelwise significance threshold was set at $p < 0.05$, FWE corrected for multiple comparisons. The relationship between our composite rumination/worry score and the FA values from the UF region identified by our primary analysis of REAP was also examined.

Results

There was good reliability and internal consistency for both measures of REAP ($M = 5.2$, $SD = 0.8$, Cronbach's $\alpha = 0.84$) and SUP ($M = 3.7$, $SD = 1.0$, Cronbach's $\alpha = 0.74$). REAP and SUP were not significantly correlated ($r = -0.097$, $p = 0.18$). Neither REAP nor SUP were correlated with age ($r = 0.001$, $p = 0.99$; $r = -0.043$, $p = 0.55$), IQ ($r = 0.11$, $p = 0.12$; $r = -0.058$, $p = 0.42$), or race/ethnicity ($r = -0.029$, $p = 0.69$; $r = -0.007$, $p = 0.92$, respectively). Gender (dummy coded: male = 0, female = 1) and social status did not correlate with typical REAP ($r = -0.007$, $p = 0.93$; $r = 0.11$, $p = 0.12$), but were marginally related to typical SUP ($r = 0.12$, $p = 0.095$; $r = -0.14$, $p = 0.055$, respectively). Thus, IQ, age, gender, race/ethnicity and social standing were used as covariates in subsequent regression analyses examining relationships between FA values in the UF and typical ER use.

There was a significant positive correlation ($\beta = 33.87$, $t(193) = 4.28$, $p < 0.001$, FWE corrected) between typical REAP use and FA values in a left UF cluster (48 mm³) within the OFC (Figure 1). FA values in this cluster accounted for 8.7% of the inter-individual variability in typical REAP use. This correlation survived correction for covariates ($\beta = 34.48$, $t(193) = 4.31$, $p < 0.001$, FWE corrected, R^2 change = 0.022). There was a significant gender-by-FA interaction predicting REAP ($\beta = 34.06$, $t(193) = 2.16$, $p < 0.05$, $R^2 = 0.11$; adjusted for covariates: $\beta = 34.99$, $t(193) = 2.22$, $p < 0.05$, R^2 change = 0.023) such that only women ($\beta = 49.88$, $t(112) = 4.61$, $p < 0.001$, $R^2 = 0.16$; adjusted for covariates: $\beta = 50.73$, $t(112) = 4.60$, $p < 0.001$, R^2 change = 0.09) but not men ($\beta = 15.83$, $t(80) = 1.39$, $p = 0.17$;

adjusted for covariates: $\beta = 15.43$, $t(80) = 1.35$, $p = 0.18$) showed a significant correlation between REAP and FA in the left UF (Figure 2). There were no negative correlations between FA values in the UF ROIs and typical REAP use. There were neither positive nor negative correlations between FA values in the UF ROIs and typical SUP use ($\beta = 1.61$, $t(193) = 0.23$, $p = 0.82$; adjusted for covariates ($\beta = 0.099$, $t(193) = 0.014$, $p = 0.99$).

Typical use of REAP ($r = -0.18$, $p < 0.05$) and SUP ($r = 0.22$, $p < 0.01$) were both correlated with our trait measure of rumination/worry in the predicted directions. However, rumination/worry scores were not correlated with the FA values in the left UF cluster ($\beta = 9.46$, $t(193) = 1.42$, $p = 0.16$; adjusted for covariates: $\beta = 10.56$, $t(193) = 1.63$, $p = 0.10$) and did not show a gender-by-FA interaction ($\beta = 12.55$, $t(193) = 0.95$, $p = 0.35$).

Discussion

Consistent with our hypothesis, our results indicate that typical use of REAP, but not SUP or trait rumination/worry, maps onto the structural integrity of the uncinate fasciculus. Specifically, FA values from a small cluster in the left UF within the OFC was positively correlated with self-reported typical use of REAP in women. The strength of functional connectivity between the amygdala and prefrontal cortex in the left hemisphere is related to successful down regulation of negative affect during REAP (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Urry et al., 2006). The positive correlation between REAP use and FA values in the left UF is consistent with these functional MRI findings. Increased FA values in the UF likely represent stronger structural connectivity between these areas and possibly account for increased information processing within this circuit. Multiple psychological processes are likely reflected by the structural integrity of the UF. To rule out the possibility that higher structural integrity of the UF may be associated with maladaptive emotion regulation strategies other than suppression, we examined the relationship between a trait measure of rumination/worry and the UF FA values revealed by our primary analysis of reappraisal. This trait measure was not correlated with these FA values, suggesting that the identified UF cluster is specifically associated with adaptive forms of emotion regulation. A validated worry questionnaire is needed to confirm this finding.

Consistent with findings from fMRI studies (Eippert et al., 2007; Garavan, Ross, & Stein, 1999; Goldin et al., 2008; Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007; Konishi et al., 1999; Ochsner et al., 2002; Vrticka et al., 2011), typical REAP use correlated with FA values in the UF of the left but not right hemisphere. This left-right asymmetry may be consistent with the dependency of REAP on a cognitive, verbal strategy for reframing the context of an emotional experience. Previous studies have reported that the left hemisphere is related to positive motivation and experience and the right hemisphere to negative motivation and experience (Harmon-Jones & Allen, 1998). Also, left-lateralized PFC activation is associated with increased positive affect and attenuated negative emotions (Tomarken, Davidson, Wheeler, & Doss, 1992) and early-onset depression was associated with a structural deficit in the UF in the left hemisphere (W. D. Taylor, MacFall, Gerig, & Krishnan, 2007). Accordingly, individuals who use REAP more often experience more positive emotions (Gross & John, 2003). Increased FA values in the left UF within the OFC

could represent a structural basis for these functional neural and behavioral differences associated with REAP.

The association between FA in the left UF and REAP use was only seen in women. Gender differences have been found during cognitive REAP (Domes et al., 2010; McRae et al., 2008), in OFC volume (Welborn et al., 2009) and lower FA values in the left UF have been found in women compared to men (W. D. Taylor et al., 2007). While more research is needed to confirm the gender effects reported herein, our results are also consistent with studies reporting gender differences in emotionality and the prevalence of mood disorder (Kring & Gordon, 1998; Weissman et al., 1996) and may thus contribute to the mechanistic understanding of these commonly observed differences between men and women.

An important limitation of this study is the reliance on self-reported typical REAP and SUP use. We used the ERQ, because it is a well-validated and widely utilized probe of these two common ER strategies (Davidson et al., 2000; Drabant et al., 2009; Eippert et al., 2007; Garavan et al., 1999; Giuliani, Drabant, & Gross, 2011; Goldin et al., 2008; Gross & John, 2003; Konishi et al., 1999; Vrticka et al., 2011; Wager et al., 2008). However, future studies confirming our results using a lab-based emotion regulation paradigm would lend further support to our findings. In addition, the size of the UF cluster we found to be correlated with REAP use is quite small. While we applied statistical correction for multiple comparisons with our UF ROIs to minimize Type I error, replication of this relationship would further confidence. Establishing an association between FA values in this region and neural circuit function during REAP would allow for a more direct evaluation of the predictive links suggested by our data through mapping of variability in the structural integrity of the UF, the response dynamics of the amygdala and PFC, and individual differences in the ability to successfully regulate emotions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Overlay of the left and right uncinate fasciculus ROIs (red) and the significant positive correlation between FA values and REAP (yellow) in the left uncinate fasciculus located within the orbitofrontal cortex ($x = -18$, $y = -26$, $z = -18$; $T = 4.31$, $p < 0.001$; 48 mm^3 ; corrected for covariates).

Figure 2.

Plot of single-subject FA values from cluster in Figure 1 and typical REAP use scores for men ($T = 1.37$, $p = 0.17$, adjusted for covariates $T = 1.35$, $p = 0.18$) and women ($T = 4.63$, $p < 0.001$, adjusted for covariates $T = 4.70$, $p < 0.001$) separately.