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Subtypes of Rumination Associated with
White Matter Integrity in Women with Depression

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Abstract

Recent studies have begun to examine white matter connectivity aberrations in psychiatric populations, such as major depressive disorder. Several studies have found reduced white matter integrity (WMI) in depressed samples, though the location of this reduction is not clear.

Incorporating symptom measures of depression severity and rumination may allow for increased identification and localization of aberrant WMI in this heterogeneous disorder. This study examined WMI, specifically fractional anisotropy (FA), using diffusion tensor imaging in a sample of depressed adult women ($N=45$). The relationship between depression severity and subscales of rumination with fractional anisotropy in six tracts were analyzed, including the bilateral superior longitudinal fasciculus, bilateral uncinate fasciculus, and bilateral cingulum bundle. Increased reflective rumination was associated with increased FA in the right cingulum bundle and left uncinate fasciculus. Additionally, post-hoc analyses considered other measures of WMI in those two tracts. Results found that depression rumination and brooding rumination were associated with aberrant WMI in the left uncinate fasciculus. Findings from this study offer a unique understanding of how white matter integrity in prefrontal, temporal, and limbic regions may be associated with different forms of rumination in women diagnosed with major depression.

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Introduction

White matter (WM), myelination of the axons of neurons, is essential for effective conduction of neural signals. Recent studies have begun to examine WM in psychiatric populations and found that it is damaged in major depressive disorder, especially in the prefrontal cortex (PFC), at the animal (Liu et al., 2012; Makinodan, Rosen, Ito, & Corfas, 2012), genetic, and post-mortem levels (Sokolov, 2007; Tham, Woon, Sum, Lee, & Sim, 2011). The most common measure of white matter integrity (WMI) is fractional anisotropy (FA), which is measured through diffusion tensor imaging (DTI). Diffusion tensor imaging involved applying magnetic gradients at different angles to measure the diffusion of water molecules in 3D space in axons of the brain. Fractional anisotropy is a measure of the proportion of water molecule movement parallel to an axon fiber (axial diffusivity) compared with movement perpendicular to the fiber (radial diffusivity). Thus, FA is a composite measure of integrity of white matter tracts and most studies examining WMI in depression analyze this measure. Only a few studies have examined other measures of WMI in depression such as axial diffusivity (AD), mean diffusivity (MD), and radial diffusivity (RD) (Hayakawa et al., 2014; Ota et al., 2015; Poletti et al., 2018; Zhang et al., 2012). Reduced FA is a measure of reduced ineffective communication between certain brain regions, whereas increased FA may represent increased focus on specific stimuli (Alba-Ferrara & de Erausquin, 2013). White matter integrity changes with age, although the rate and age of peak maturation differ by tract and by measure of integrity (Abe et al., 2010; Giorgio et al., 2010; Hsu et al., 2008; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Rathee, Rallabandi, & Roy, 2016; Yoon, Shim, Lee, Shon, & Yang, 2008). White matter hyperintensities are more common in older adults and are associated with cognitive impairments and an increased

risk of dementia, stroke, Alzheimer's disease, and late-onset depression (Herrmann, Le Masurier, & Ebmeier, 2008; Kandel et al., 2016; Wardlaw, Valdes Hernandez, & Munoz-Maniega, 2015). Environmental factors that can affect WMI in animals and humans are physical exercise, a rich social environment, motor training, and cognitive training (Fields, 2010; Wang & Young, 2014).

Recent studies indicate that regional FA measures offer an index that improves the diagnostic accuracy of major depressive disorder (MDD), even taking into account the clinical heterogeneity of depression (Schnyer, Clasen, Gonzalez, & Beevers, 2017). Several larger-scale studies find reduced FA in depressed samples, though the location of reduced FA is inconsistent (Kieseppa et al., 2010; Liao et al., 2013; Olvet et al., 2016; Shen et al., 2017). Discrepancies in the literature and lack of localization of regions may be due to symptom variability in depressed participants. Accounting for individual differences in depressive symptom presentation may clarify how WMI relates to psychological processes associated with depression (Keedwell et al., 2012; Olvet et al., 2016; Walther et al., 2012; Zuo et al., 2012).

Meta-analytic studies and studies with large sample sizes that examined DTI structural integrity have found mixed results in depressed populations (Liao et al., 2013; Murphy & Frodl, 2011; Olvet et al., 2016; Shen et al., 2017). Two meta-analyses and one brain bank study of WMI comparing depressed with healthy participants found that depressed individuals had reduced FA in widespread cortical and subcortical regions, without consensus on localization (Liao et al., 2013; Murphy & Frodl, 2011; Shen et al., 2017). However, a recent multi-site study of participants found no significant differences when implementing multiple methods of WMI analyses between healthy and depressed individuals (Olvet et al., 2016). Differences were found between healthy and depressed participants in this study when including clinical variables, such

as depression severity and age of onset, as covariates in analyses of WMI (Olvet et al., 2016). Moreover, increased FA has been found in a few studies of adolescents with high levels of anhedonia, adults with early-onset MDD, and adults with MDD and high anxiety (Blood et al., 2010; Cheng et al., 2014; Henderson et al., 2013). Using a dimensional approach, such as incorporating symptom measures of depression severity and specific symptoms, may allow for identification and localization of decreased WMI in this heterogeneous disorder.

Individuals diagnosed with depression vary by many factors such as age of onset, severity, recurrence, and symptom profile of the nine core symptoms. Factor analysis and principal component analysis techniques have been used to examine symptom, person, and time dimensions that group together, although there are no agreed upon distinct groups of individuals with depression in the literature (Goldberg, 2011; Monden, Wardenaar, Stegeman, Conradi, & de Jonge, 2015). For example, in research studies, an individual who was diagnosed at 60 with their first depressive episode related to a cancer diagnosis is treated the same as an individual who was diagnosed as an adolescent and has recurrent depression with several courses of medication and psychotherapy treatment. Symptom-specific analysis techniques have been applied to examine the symptom of psychomotor retardation correlated with reduced WMI in the motor cortex (Bracht et al., 2012; Walther et al., 2012). Also, in samples diagnosed with either a mood or anxiety disorder, depressive symptoms have been correlated with reduced WMI in regions of several tracts: the uncinate fasciculus, the cingulum bundle, the superior longitudinal fasciculus, and the corpus callosum (Charlton et al., 2014; Cole et al., 2012; Dalby et al., 2010; de Diego-Adelino et al., 2014; Jenkins et al., 2016). Accordingly, incorporating symptom-specific

measures will allow for more specificity in localization of compromised WMI and a functional understanding of these differences.

Women, who experience depression at two times the rate as men, have inherent structural and functional brain differences (Substance Abuse and Mental Health Services Administration, 2017; Zagni, Simoni, & Colombo, 2016). Specifically, women exhibit differing WMI compared with men, such as increased FA in the corpus callosum and decreased FA in the cerebellum (Chou, Cheng, Chen, Lin, & Chu, 2011; Dunst, Benedek, Koschutnig, Jauk, & Neubauer, 2014; Kanaan et al., 2014; Lorenzetti, Allen, Fornito, & Yucel, 2009; Takao, Hayashi, & Ohtomo, 2014; van Hemmen et al., 2017). However, regional differences in FA between men and women differ depending on age (Abe et al., 2010; Hsu et al., 2008; Rathee et al., 2016). Most studies to date include both sexes when examining white matter differences in depression. One study found no white matter differences in a sample of healthy men and women with varying levels of depressive symptoms. But, when men and women were considered separately, a significant correlation between WMI in cingulate tracts and depression severity emerged only for women (Hayakawa et al., 2014). Moreover, using a sample of only women, and a symptom-specific measure (anhedonia), WMI was associated with reduced WMI in cingulate tracts (Keedwell et al., 2012). Therefore, examining WMI in a sample of only women, as well as incorporating measures of depressive symptomatology, will be advantageous in elucidating the unique brain connectivity associated with depression in women.

Rumination is currently conceptualized as a complex cognitive construct and may incorporate both adaptive and maladaptive components. One group of researchers, Martin et al., hypothesize that rumination is a strategy for thinking about the pursuit of goals, Goal Progress

Theory (Martin, 1996). They argue that rumination about a goal can either lead to future problem-focused, or emotion-focused coping. Problem-focused coping, an adaptive strategy, can in turn help an individual change their behavior to effectively attain a goal; conversely, emotion-focused coping, a maladaptive strategy, causes passive thoughts about a goal without a change in behavior. Overall, this theory emphasizes the adaptive aspects of rumination that lead to goal accomplishment. A second theory, Self-Regulatory Executive Function (S-REF) developed by Matthews and Wells describes rumination as focused on self-discrepancies (Wells & Matthews, 1996). This theory proposes that positive meta-cognitions about rumination lead to an increased reliance on this coping strategy to reduce self-discrepancies. Rumination is conceptualized as maladaptive, as it interferes with more adaptive coping strategies. The most prominent theory proposed by Nolen-Hoeksema and her colleagues conceptualizes rumination from response style theory (RST) as critical, self-focused, and related to negative affective states. This is the most widely accepted and narrowly defined definition of rumination. This theory has been criticized in the literature for its overlap with depression, worry, and reflection assessments. However, factor analyses have been used to examine this measure and have found distinct components within the broad construct of rumination (Smith & Alloy, 2009).

Rumination is a cognitive process characterized by recurrent and persistent thoughts about the self with the goal of alleviating current distress (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Although individuals implement rumination as a coping strategy to alleviate low mood (Nolen-Hoeksema et al., 2008), in fact, rumination leads to an increased bias towards negative information, decreased problem-solving ability, and sustained negative mood states (Lyubomirsky, Caldwell, & Nolen-Hoeksema, 1998; Lyubomirsky & Nolen-Hoeksema,

1995). Moreover, rumination induction is related to difficulties with inhibition (Philippot & Brutoux, 2008; Whitmer & Gotlib, 2012), attention switching (Philippot & Brutoux, 2008), and autobiographical memory (Raes et al., 2006; Raes, Schoofs, Griffith, & Hermans, 2012; Watkins & Teasdale, 2001). Frequent rumination is associated with increased duration and severity of depressive episodes (Abela & Hankin, 2011), as well as an increased risk of developing future depressive episodes, especially in women (Abela & Hankin, 2011; Burwell & Shirk, 2007; Nolen-Hoeksema, 2000, 2001).

Among depressed samples, rumination, conceptualized by the RST, has been found to have three distinct components (Nolen-Hoeksema et al., 2008; Treynor, 2003). It is commonly measured by self-report, specifically using the Ruminative Response Scale (RRS). The RRS is a 22-item self-report questionnaire that assessed the frequency of ruminative thinking and behavior during periods of depressed mood (Treynor, 2003). Twelve items of this scale were found to be redundant with items from the Beck Depression Inventory, termed depression rumination. The other ten items were subjected to a principal component analysis and found to separate into two distinct factors: brooding (eigenvalue = 3.41) and reflective (eigenvalue = 1.64) that were distinct from items assessing depression severity (Treynor, 2003). Self-report measures can exhibit reconstruction biases and are dependent on an individual's awareness of their own cognitive processes (Luminet, 2004). As individuals with depression demonstrate attention and memory biases for negative stimuli, other types of assessment for rumination, such as performance or physiological measures, could be considered in future studies. Some studies employ a rumination induction task that involves a negative mood induction and an internal focus period where individuals are instructed to think about what and why they are currently

feeling a certain way. Participants who engage in the rumination induction task report higher levels of depressed mood and higher levels of self-reported rumination (Nolen-Hoeksema & Morrow, 1993; Watkins & Brown, 2002; Watkins & Teasdale, 2001).

Brooding rumination, involving self-critical judgments, has been uniquely associated with a bias towards negative stimuli (Joormann, Dkane, & Gotlib, 2006), difficulty disengaging from a negative stimulus (De Lissnyder, Koster, Derakshan, & De Raedt, 2010), and negative coping styles (Koster, De Lissnyder, Derakshan, & De Raedt, 2011; Lo, Ho, & Hollon, 2008). Also, in adolescents, brooding rumination is predictive of future depressive episodes, especially in girls (Abela & Hankin, 2011; Burwell & Shirk, 2007; Raes & Hermans, 2008). Although, brooding rumination is found to be a distinct construct from depression severity, when it is considered along with other personality factors, such as neuroticism, it explains between 40%-60% of the variability in depression severity (Hong et al., 2010; Koval, Kuppens, Allen, & Sheeber, 2012; Kuyken, Watkins, Holden, & Cook, 2006). These results highlight the importance of examining brooding rumination, specifically, in depression in women, as it is a core feature associated with depression severity and cognitive biases.

Functional connectivity (FC) between grey matter regions has been found to correlate with WMI in corresponding tracts, such as between nodes of the default mode network (de Kwaasteniet et al., 2013; Greicius, Supekar, Menon, & Dougherty, 2009; Steffens, Taylor, Denny, Bergman, & Wang, 2011). Some studies have found analogous differences in structural and functional connectivity in the default mode network in depressed participants (Greicius et al., 2009; Yin et al., 2016). Functional brain connectivity has also been associated specifically with rumination, specifically brooding rumination (Berman et al., 2011; Vanderhasselt et al.,

2013; Vanderhasselt, Kuhn, & De Raedt, 2011; Whiteman & Mangels, 2016). Regions associated with emotion processing (amygdala), cognitive control (prefrontal), and coordination of bottom-up and top-down signals (cingulate) are implicated in this maladaptive form of rumination (Berman et al., 2011; Cooney, Joormann, Eugene, Dennis, & Gotlib, 2010; Hamilton, Farmer, Fogelman, & Gotlib, 2015). However, only one previous study has correlated rumination and WMI in depressed participants. In this study, depressed participants had decreased FA in a left frontal region that correlated with self-reported rumination (Zuo et al., 2012). Thus, the results from the FC literature and the single WMI study provide a strong basis for examining the regions of WMI that are associated with rumination in a sample of women.

The current study examined WMI associated with depression severity and dimensions of rumination in women with depression. Our first aim was to assess the association between and depression severity and WMI in six tracts of interest. We hypothesized that depressed participants would show an inverse correlation between depressive severity and WMI in these tracts. Our next aim was to assess the association between three dimensions of rumination—depression, brooding, and reflection—and WMI in six tracts of interest. We hypothesized that depression and brooding rumination would have a negative correlation with WMI in these same tracts. Conversely, we hypothesized that reflection rumination would not be correlated, or would have a positive correlation, with WMI in these tracts. The six tracts of interest are the bilateral *uncinate fasciculus*, which connects orbitofrontal, temporal, and limbic regions; the bilateral *superior longitudinal fasciculus*, which connects the frontal, temporal, parietal, and limbic regions; and the bilateral *cingulum bundle*, which connects anterior and posterior components of the cingulate in our sample of depressed women (Cole et al., 2012; Dalby et al., 2010; de Diego-

Adelino et al., 2014; Olvet et al., 2016). We also base our tract of interest on the integrated ‘impaired disengagement’ model of the biological, neural, and cognitive processes that underlie depression proposed by De Raedt and Koster 2010. This model draws a connection between the maintenance of a stress response and increased vulnerability to depressive states with rumination that is maintained by aberrant, reciprocal prefrontal, cingulate, and amygdala activity, but does not draw from studies examining structural connectivity between these regions (i.e. WMI) (De Raedt & Koster, 2010). Decreased WMI in these tracts would suggest decreased speed of connection between prefrontal to limbic regions associated with emotion dysregulation. Increased WMI in these tracts would suggest increased speed and usage of prefrontal to limbic connectivity associated with increased focus on emotional stimuli. Attention to rumination, a hallmark feature of depression, not just diagnostic status, will advance the study of WMI in depression. Indeed, the National Institutes of Health recommend the study of rumination on a continuum within the negative valence system to characterize individuals suffering from emotional disorders (National Institutes of Health, 2011). Furthermore, incorporating depression severity or rumination measures into analyses of FA in depression will allow for a more mechanistic and localized understanding of the neural correlates of cognitive and affective symptoms in this disorder that then may be generalized to other clinical populations. We then chose to examine other measures of WMI (AD, RD, and MD) in the tracts with significant results to more fully elucidate the microstructural changes that may underlie the relationship between rumination and FA. The field has been limited by studies using the coarse measure of diagnostic status to examine white matter differences in depression. This work will use a narrow symptom-based lens to skirt the issue of clinical heterogeneity in depression while analyzing

differences in tracts of interest that have previously been found to be aberrant in depressed samples.

Methods

Participants

Participants were English-speaking women (age range: 17–65 years) who were recruited from the Chicago area using online and posted flyers. Interested women, with and without depression, were asked to participate in a study approved by the Institutional Review Board (IRB) at Northwestern University Feinberg School of Medicine in the Department of Psychiatry and Behavioral Sciences. All women were initially screened via telephone interviews. Those who were eligible were invited to the Northwestern University Medical School campus in Chicago, IL. During their first visit, eligible participants provided written informed consent, completed clinician-administered interviews, self-reported questionnaires, and two computer-based tasks assessing affect and attention processing. Within a week, participants returned for a second visit to complete functional and anatomical neuroimaging scans. Participants were compensated for their involvement.

Inclusion and Exclusion Criteria

Included participants were English-speaking, right-handed, females with normal or corrected-to-normal vision. Depressed participants met criteria for current and primary MDD as diagnosed by the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID) (First, Spitzer, Gibbon, & Williams, 2002b) and by a score of at least 24 on the Inventory of Depressive Symptomatology—Clinician Rated (IDS-C) (moderate depression severity) (Rush, Carmody, & Reimnitz, 2000). Women who were diagnosed with a co-morbid anxiety disorder were included

only if MDD was the primary diagnosis. Healthy controls did not meet criteria for any lifetime or current DSM-IV diagnosis and scored less than 11 on the IDS-C (no depression).

Participants were excluded if they met criteria for current or history of another DSM-IV Axis I disorder (bipolar I and II, schizophrenia or delusional disorder, post traumatic stress disorder, obsessive-compulsive disorder, or substance dependence/abuse) or any Axis II disorder (American Psychiatric Association, 2000). Depressed participants were excluded if they reported current treatment or psychotropic medication use in the past two weeks for MDD symptoms or current suicide risk. Other exclusion criteria were tobacco use (>1 pack/week), catecholaminergic antihypertensive medication use, vasovagal syncope, and a history of head trauma or a neurological disorder. For scanning safety purposes, participants were also excluded if they had metal implants, were claustrophobic, or were currently pregnant or planning on becoming pregnant. Finally, participants were excluded for unusable neuroimaging data: no resting-state scan, excessive motion during (>2 mm), equipment failure, and irregular brain findings.

A final sample of participants ($N=45$) was included in the analyses. The self-reported rumination measure was added to the study after running several participants through the protocol. Thus, a subset of this sample who completed the behavioral rumination measure ($N=36$) was included in subsequent analyses.

Measures

Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID). The SCID is a semi-structured clinician-administered interview that assesses for lifetime and current American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders—4th edition (DSM-IV)

diagnoses (First, Spitzer, Gibbon, & Williams, 2002a). The SCID is an established clinical interview and has moderate to strong inter-rater reliability ($K=0.70-1.00$) (First et al., 1995). Research assistants who were graduate students in clinical psychology at Northwestern University were trained in administration of the SCID by reviewing training videos and supervised practice administration. Fleiss kappa was calculated and the inter-rater reliability was found to be strong ($\kappa =0.82-0.88$) (Fleiss, 1971; Fleiss & Cohen, 1973; Randolph, 2016). The SCID was used to diagnose current primary major depressive disorder for depressed participants and lack of diagnoses for healthy controls.

Inventory of Depressive Symptomatology—Clinician Rated (IDS-C). The Inventory of Depressive Symptomatology—Clinician Rated (IDS-C) is a 30-item clinician-rated questionnaire that assess symptoms associated with major depressive disorder as detailed by the DSM-IV (Association, 1994; Rush et al., 2000). Clinicians scored participant's responses using a 0 – 3 point scale. Then 28 out of 30 questions were summed, with higher scores indicating more severe and frequent depressive symptoms during the past week. High convergent validity was found between the IDS-C and Beck Depression Inventory and Hamilton Rating Scale for Depression (all r 's > 0.85) (Rush, Gullion, Basco, Jarrett, & Trivedi, 1996). MDD participants were required to score greater than or equal to 24 (moderate depression), while healthy controls scored less than 11 (no depression) on the IDS-C.

Ruminative Response Scale (RRS). The Ruminative Response Scale is a 22-item self-report questionnaire that assesses frequency of ruminative thoughts and behaviors in response to sad or depressed mood (Treynor, 2003). Individuals record their responses on a 1–4 point scale, with higher scores indicating generally more frequent ruminative thoughts and behaviors. Items

are summed to create subscales for divergent types of rumination: depression (12 items), brooding (5 items), and reflection (5 items). The RRS has been found to be a valid and reliable measure of rumination in healthy and depressed individuals (Luminet, 2004). Only brooding rumination is distinct when comparing depressed individuals with individuals with other mental disorders and individuals that are healthy (Joormann et al., 2006; Siegle, Moore, & Thase, 2004). Rumination is fairly stable across the lifespan, except for reduced rumination in older age (Sutterlin, Paap, Babic, Kubler, & Vogele, 2012). Within participants, self-focused rumination (“I think, Why do I react this way?”), compared with symptom-focused rumination (“Think about how hard it is to concentrate.” (Treynor, 2003)) is relatively stable over time in depressed populations (Bagby, Rector, Bacchiochi, & McBride, 2004). However, symptom-focused rumination varies with changes in depressive symptoms.

Statistical Analyses

Demographic and clinical frequencies of participants were examined using Statistical Package for the Social Sciences (SPSS, Version 25). Pearson’s bivariate correlations were implemented to examine the relationship between the IDS-C and the subscales of the RRS.

Imaging Protocol and Preprocessing. Anatomical and diffusion tensor neuroimaging data were acquired using a 3-Tesla Tim Trio scanner (Siemens) with a 32-channel head coil. Foam inserts and earplugs were implemented to reduce head movement and to decrease scanner noise. Whole-brain data was obtained along the anterior-posterior commissure. High-resolution T1-weighted magnetization-prepared rapid acquisition gradient echo (MP-RAGE) anatomical images were acquired during a 9 minute 50 second scan sequence (repetition time (TR)=2200 ms, echo time (TE)=2.91 ms, flip angle=9°, field of view (FOV)=256 x 256 mms, voxel

dimension=1 mm isotropic). Diffusion weighting was applied along 64 non-collinear directions and a single volume was collected with no diffusion gradients applied ($b_0 = 0 \text{ s/mm}^2$ TR=9700 ms, TE=90 ms, flip angle=90°, FOV=1179 x 1170 mms, voxel resolution=1.97 x 1.97 x 2.00 mms).

DTI Data Processing. Preprocessing of anatomical and diffusion tensor images was conducted using a pipeline on the Northwestern University Neuroimaging Data Archive (NUNDA) (Alpert, Kogan, Parrish, Marcus, & Wang, 2016). Initially, diffusion tensor images were imported and diffusion-encoding b-value and b-vector files were generated. Next, diffusion images were denoised using a principal component analysis approach to reduce Rician noise and improve the signal-to-noise ratio. A B0 reference image was then created for each participant by calculating the mean of the non-diffusion weighted scans and the T1 structural image was skull-stripped and warped to MNI space using nonlinear warping. A pseudo-T2 image in subject space is created from the T1 image by inverting the contrast. The image is rigidly aligned to the B0 reference image and the B0 reference image is warped to the pseudo-T2 image and a distortion field is calculated. Subsequently, eddy current correction was performed to account for potential distortions associated with the fast switching of gradient coils. A nonlinear weighted positive definite tensor-fitting algorithm (NLA) was implemented to create the tensors (Cook et al., 2006). Tensors at each voxel in the brain were estimated in order to obtain measures of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) for each participant. Finally, the FA, MD, AD, and RD masks were warped to an MNI template. A detailed description of the processing steps in this pipeline is outlined elsewhere (Kurani & Parish, 2018).

DTI Group Level Processing. Participant's FA maps, were concatenated into a single file to prepare for group analyses. Region-specific analyses were carried out implementing six white-matter tract masks from the John's Hopkins University ICBM-DTI-81 atlas: left and right uncinate fasciculus, left and right superior longitudinal fasciculus, and left and right cingulum bundle (Hua et al., 2008; Mori, Wakana, van Zijl, & Nagae-Poetscher, 2005; Wakana et al., 2007). Each participant's FA image was masked and an average FA value for each of the six tracts was calculated. Then multiple linear regression analyses were implemented with age as a covariate in four different general linear models: (1) including IDS-C as a covariate, (2) including RRS depression as a covariate, (3) including RRS brooding as a covariate, and (4) including RRS reflective as a covariate. Age was incorporated as a covariate, as FA has previously been found to decrease linearly with age (after around 20 years) in women (Abe et al., 2010; Giorgio et al., 2010; Hsu et al., 2008; Lebel et al., 2008; Rathee et al., 2016; Yoon et al., 2008).

F-statistics and *p*-values for the regression model as well as *T*-statistics and *p*-values for significant predictors are reported. Additionally, standardized beta (β) and R^2 values are displayed to help understand the effect size of the results. Finally, post-hoc multiple linear regression models were analyzed incorporating other measures of DTI integrity (RD, MD, and AD) to more fully examine the tracts with significant results from the initial analyses.

Results

Demographic and Clinical

The final sample consisted of 45 depressed women who were assessed for depression severity (IDS-C), with a subset ($n=36$) who also completed the self-reported rumination measure

(RRS). The mean age of the whole sample was found to be 34.02 years (range: 17–59 years). Sixty-four percent of the sample was Caucasian, 27% African American, 4% Asian or Alaska Native/American Indian, and 4% not reported. The majority of the sample identified as non-Hispanic white (76%), with 22% identifying as Hispanic, and 2% not reported. Forty percent of the sample has a partial college education, 24% were found to have a college degree, 24% have a high school degree or less, and 11% have a graduate degree. Half of the sample reported that the current depressive episode was their first; the rest of the sample had recurrent MDD (range: two episodes to too many to count). The mean age of onset for MDD for the sample was 27.74 (range: 11-57). Depression severity in the sample ranged from moderate to very severe with 60% with moderate depression, 31% with severe depression, and 9% with very severe depression. On the RRS ($N=36$), the mean scores for the subscales was as follows, brooding $M=13.42$ ($SD=3.08$), reflection $M=13.31$ ($SD=2.76$), and depression $M = 33.44$ ($SD=6.03$). There were no significant differences found on the IDS-C or on the three RRS subscales between the MDD and comorbid MDD and anxiety groups (all $p's > .05$) (see Table 1 and 2).

Pearson's bivariate correlations were calculated to determine the association between the IDS-C and the three subscales of the RRS. No significant relationship was found between the IDS-C and the brooding and reflection subscales ($p's > .05$). However, a significant positive correlation emerged between the IDS-C score and depression subscale of the RRS ($r=.375$, $p=.024$). Among the subscales of the RRS, there was a significant positive correlation between the depression and the brooding as well as the depression and reflection subscales ($r=.465$, $p=.004$; $r=.368$, $p=.027$). Brooding and reflection subscales were not correlated ($p > .05$) (see Table 2).

Quality Assurance

The IDS-C total score and the two subscales of the RRS (reflective and depression) were found to be normally distributed, with non-significant Kolomogorov-Smirnov tests (all p 's > .05) however the brooding subscale was significantly non-normal ($D=.165$, $p=.015$) (Field, 2009). Thus, the \log_{10} of the brooding subscale (logBrooding) was taken and was found to be normally distributed ($p>.05$). Five of the six DTI integrity measures did not significantly deviate from normal, with non-significant Kolomogorov-Smirnov tests (p 's > .05); however FA in the left SLF was significantly non-normal ($D=.177$, $p=.001$). In order to account for this non-normality, the left SLF values were trimmed for values +/- 1.5 standard deviations ($N=2$) (Field, 2009; Ramsey, 2007). Then the remaining values ($N=43$) were reverse-scored (1-n) and then the square root was taken. The subsequent calculated values (sqrtRevLSLF) did not significantly deviate from normal. For the subsequent analyses the logBrooding and sqrtRevLSLF variables were implemented.

Fractional Anisotropy

Multiple linear regression models were implemented to examine the association between (1) depression severity (IDS-C) and FA in six tracts, (2) depression rumination (RRS depression) and FA in six tracts, (3) brooding rumination (RRS brooding) and FA in six tracts, and (4) reflective rumination (RRS reflective) and FA in six tracts. As this was an exploratory study, there were a large number of hypotheses tested, and the hypotheses were highly related, we did not implement a Bonferroni multiple comparisons correction (Chen, Feng, & Yi, 2017). Age was included as a covariate in the first step of each model in order to account for any potential age-

related effects. No significant results were obtained when including depression severity, depression rumination, or brooding rumination in the analyses (all p 's > .05). Conversely, reflective rumination was found to be a significant predictor of FA in the right cingulum bundle (rCB) and left uncinate fasciculus (IUF). As age did not significantly add to the model, the regression analyses were re-run only including reflective rumination as an independent variable. Reflective rumination significantly predicted FA in the rCB ($b=.336$, $t(35)=2.084$, $p=.045$) and explained a significant proportion of variation in the FA rCB values with a medium effect size ($R^2=.113$, $F(1, 34)=4.341$, $p=.045$). Also, reflective rumination significantly predicted FA in the IUF ($b=.384$, $t(35)=2.422$, $p=.021$) and explained a significant proportion of variation in the FA IUF values with a medium effect size ($R^2=.147$, $F(1, 34)=5.868$, $p=.021$). For both of these tracts, there was a positive relationship between reflective rumination and FA, higher reflective rumination was associated with higher FA (see Table 3 and Figures 1 and 2). When we compared the significant results of the MDD only and comorbid MDD groups, no significant differences were found.

Post-Hoc Analyses

In order to more comprehensively understand the results of the FA analyses, we chose to examine other white matter integrity measures (AD, RD, and MD) in the tracts with significant results, left uncinate fasciculus and right cingulum bundle. Although FA is the most commonly implemented metric, it is a summary value and thus does not allow for interpretation of the specific changes in white matter. The mean diffusivity (MD) is the average movement of the water in each of the directions and has been found to be aberrant with edema and neoplasia.

Axial diffusivity (AD), the rate of water flow parallel to the tract, has been associated with axonal degeneration; radial diffusivity (RD), the rate of water flow perpendicular to the tract, has been associated with changes in myelin (Alexander, Lee, Lazar, & Field, 2007). As the values of three measures are very small, each value was multiplied by 10^9 to allow for easier interpretation. These three other WMI measures, MD, AD, and RD, in the rCB and IUF were found to be normally distributed, with non-significant Kolomogorov-Smirnov tests (all p 's>.05)

No significant results were obtained for the right cingulum bundle or when including depression severity and reflective rumination in the analyses (all p 's>.05). But, we did examine the other measures of white matter integrity associated with reflective rumination in the rCB and IUF (See Figures 3 and 4). Depression rumination significantly predicted MD ($b=-.365$, $t(35)=-2.285$, $p=.029$) and AD ($b=-.363$, $t(35)=-2.273$, $p=.029$) in the IUF and explained a significant proportion of variation with medium effect sizes in MD ($R^2=.133$, $F(1, 34)= 5.220$, $p=.029$) and AD ($R^2=.132$, $F(1, 34)=5.167$, $p=.029$) (see Table 4 and Figure 5). As MD is a composite of AD and RD, the significant result for depression rumination and MD is driven by the significant inverse relationship between depression rumination and AD. Additionally, brooding rumination significantly predicted MD ($b=-.476$, $t(35)=-3.157$, $p=.003$) and RD ($b=-.485$, $t(35)=-3.235$, $p=.003$) in the IUF and explained a significant proportion of variation with large effect sizes in MD ($R^2=.227$, $F(1, 34)=9.967$, $p=.003$) and RD ($R^2=.235$, $F(1, 34)=10.463$, $p=.003$) (see Table 4 and Figure 6). As MD is a composite of AD and RD values, the significant result for brooding rumination and MD is, in fact, driven by the significant inverse relationship between brooding rumination and RD. Depression and brooding rumination were negatively associated with MD, RD, and AD in the IUF.

Discussion

This study examined the connection between depression severity and subscales of rumination with white matter integrity in depressed women. White matter integrity was measured using DTI and assessed multiple measures including FA, RD, AD, and MD. Six tracts of interest that have previously been implicated in depression were examined: bilateral uncinate fasciculus, bilateral superior longitudinal fasciculus, and bilateral cingulum bundle. Age was also incorporated as a covariate in these analyses as white matter integrity has been found relate to age. Initially, white-matter integrity measured by FA was examined. When including depression severity, depression rumination, or brooding rumination in the analyses, no significant results were found in any of the six tracts of interest. However, reflective rumination was found to be a significant predictor of FA in two tracts: the right cingulum bundle (rCB) and left uncinate fasciculus (IUF). In these two analyses, age did not significantly add to the model, but there was a significant positive relationship between reflective rumination and FA in both tracts. Post-hoc analyses examined the other measures of white matter integrity, specifically the AD, RD, and MD, in these two tracts with significant results. There were no significant results found for the right cingulum bundle (rCB). Also, no significant results were obtained for when including depression severity or reflective rumination in the analyses of the left uncinate fasciculus (IUF). Nonetheless, depressive rumination was a significant predictor of MD and AD in the IUF. Additionally, brooding rumination was a significant predictor of MD and RD in the IUF.

Many studies focus on areas of decreased FA, as this is proposed to be related to decreased speed of communication and thus debilitating symptoms of many neurocognitive and psychiatric disorders (Liao et al., 2013). However, increased FA has been found in several

studies of early-onset MDD, older participants with MDD who do not remit, adolescents with high levels of anhedonia, and in cortico-spinal and reward tracts in MDD with high anxiety (Blood et al., 2010; Cheng et al., 2014; Henderson et al., 2013; Sacchet et al., 2014; Taylor et al., 2008). When examined as a group, depressed participants had decreased FA compared with healthy controls, however, when broken down into early onset (ages 18-29 years) and late onset (ages 30-45 years) groups, only early onset participants had areas of increased FA (Cheng et al., 2014). Some studies suggest that individuals with early onset depression have increased prevalence of personality disorders, neuroticism, and maladaptive maternal relationships, but there is a lack of consistent results when examining studies using a meta-analytic techniques (Brodaty et al., 2001; Bukh, Bock, Vinberg, Gether, & Kessing, 2011; Grayson & Thomas, 2013). Volumetric subcortical brain differences, such as a smaller hippocampus, have been associated with an earlier age of onset (Schmaal et al., 2016). Early-onset MDD, however, is normally correlated with an higher number of depressive episodes, thus, it is hard to tease apart if differences are associated with the age of onset or the cumulative burden of depressive episodes (Schmaal et al., 2016; Wilson, Hicks, Foster, McGue, & Iacono, 2015). In our sample 68.89% of could be characterized as early-onset MDD, age of onset prior to 30 years. More research is needed examining structural connectivity differences between early-onset and late-onset MDD, accounting for the cumulative burden of recurrent depressive episodes.

Increased FA in MDD participants has also been found in adolescents and older adults (Henderson et al., 2013; Taylor et al., 2008). As previously stated, white matter tracts have different maturational trajectories and many do not fully reach peak maturation until 20-30 years of age. Adolescents and early adults, ages 13-20 years, with increasing anhedonia had increased

FA in a region in the posterior cingulate cortex (Henderson et al., 2013). Older adults, ages greater than 60 years, with MDD who were treated with sertraline and did not remit had higher FA in superior frontal gyrus and anterior cingulate cortex (Taylor et al., 2008). It is likely that there is a complicated relationship between age, age of onset, number of episodes, and symptom presentation and white matter integrity differences. In our sample we recruited a broad age range of women with MDD in order to generalize the results to women across the lifespan, however future studies should consider examining subgroups of women at different ages with first episode and recurrent depression.

Increased FA has also been reported in adults with MDD and a high level of anxiety (Blood et al., 2010). The proposed neural underpinnings of this increase in FA are related to increased stress response effects on microstructural architecture. Increased attention to threat and a history of early life trauma in healthy adults have also been associated with increased FA (Carlson, Cha, & Mujica-Parodi, 2013; Frodl et al., 2012). Comorbid psychiatric conditions may relate to aberrant white matter integrity. In our study we limited comorbidities by only allowing individuals diagnosed with a comorbid anxiety disorder to participate. We had about one third of the sample diagnosed with a comorbid anxiety disorder. However, no group differences in the significant results were found when comparing the MDD-only and MDD + anxiety disorder groups. In schizophrenia, autism, and obsessive-compulsive disorder increased FA in some tracts has been reported (Alba-Ferrara & de Erausquin, 2013; Billeci, Calderoni, Tosetti, Catani, & Muratori, 2012; Lochner et al., 2012). Increased FA in schizophrenia in certain tracts is associated with increased positive symptoms and thought to reflect “excessive salience and or focus on irrelevant stimuli as in the case of hallucinations” (Alba-Ferrara & de Erausquin, 2013).

These studies finding increased FA in depression and other psychiatric conditions can lend support to the interpretation of increased FA in the current study.

The cingulum bundle (CB) is a collection of tracts that crosses the cingulate and connects to cortical regions in the frontal, parietal, and medial temporal regions of the brain. Although the function of the CB is still being examined, it is most likely linked with the roles of cingulate gyrus: emotion (including social interactions), motivation, attention, pain, and memory (Bubb, Metzler-Baddeley, & Aggleton, 2018). The uncinate fasciculus (UF) connects orbital-frontal to temporal regions to the amygdala. This fiber tract is also proposed to have many functions. One recent paper suggested that this tract incorporates different information to allow individuals to make choices and act, integrating social, emotional, memory, and language information. Thus, the function is proposed to be helping individuals learn, and respond to, socially rewarding stimuli based on memory and language, especially in the left UF (Von Der Heide, Skipper, Klobusicky, & Olson, 2013). Thus, both the UF and CB have been associated with limbic functioning and likely help an individual relay and access emotional information stored in memory. Additionally, they both are tracts that reach peak maturation later in life, which may lead them to be more significantly altered by life experiences, such as depressive episodes.

The relationship between FA in the cingulum bundle and depression diagnosis in adults is inconclusive. Some studies have found decreased FA in the CB in currently depressed adults compared with healthy controls (de Diego-Adelino et al., 2014; Ouyang et al., 2011; Seok et al., 2013). However, others studies have found no difference in FA in the CB between depressed and healthy adults (Carballedo et al., 2012; Zhang et al., 2012). In a sample of participants assessed before and after remission from depression, younger participants had increased FA in the right

CB but older participants had decreased FA in this same tract (Bracht, Jones, Muller, Wiest, & Walther, 2015). Also, one study found a reduced FA of the bilateral CB with anhedonia and a family history of depression in a sample of healthy women (Keedwell et al., 2012). So FA in this tract appears to change based on depression status and age. In this study, as we only examined FA in a sample of depressed women, we cannot directly compare our results with studies comparing depressed and healthy participants. No studies to date have found increased FA in the CB associated with increased symptoms of depression. The literature examining FA in schizophrenia proposes that increased FA is related to persistent attention on stimuli. The increased FA associated with increased reflective rumination in the cingulum bundle found in this study may relate to the persistent attention on emotional content from memory that is associated with ruminative thinking.

On the other hand, there is a more consistent relationship between FA in the UF and depression. Several studies have found decreased FA in the UF in depressed versus healthy adults, suggesting atypical connection in a mood regulating circuit (Bhatia, Henderson, Hsu, & Yim, 2018; Carballo et al., 2012; de Kwaasteniet et al., 2013; Murphy et al., 2012; Zhang et al., 2012). In adolescents, however, depressed participants had increased FA (increased AD, decreased RD, and preserved MD) compared with healthy participants (Aghajani et al., 2014). Additionally, increased FA in the UF has been associated with increased attention to threat and a history of early life trauma in healthy adults (Carlson et al., 2013; Frodl et al., 2012). However, increased reliance on adaptive emotion regulation strategies, such as cognitive reappraisal and mindfulness, is also related to increased FA in the UF in healthy adults (Holzel et al., 2016; Zuurbier, Nikolova, Ahs, & Hariri, 2013). As the IUF is hypothesized to allow individuals to

learn, and respond to, socially rewarding stimuli based on memory and language, its connection to rumination can be hypothesized. Ruminative thinking involves persistent self-focus about current distress and is associated with increased negative cognitive biases in depression. Additionally, rumination is associated with impaired memory for autobiographical and emotional material, impaired reward-learning, and impaired social problem solving (Joormann, Levens, & Gotlib, 2011; Raes et al., 2006; Raes et al., 2012; Watkins & Baracaia, 2002; Watkins & Teasdale, 2001; Whitmer, Frank, & Gotlib, 2011). The abstract and verbal focus on negative qualities of the self in rumination is linked with these autobiographical memories difficulties (Raes, Watkins, Williams, & Hermans, 2008). Functional connectivity studies link amygdala—ventromedial prefrontal cortex (vmPFC) connectivity with structural connectivity of the uncinate fasciculus (Steffens et al., 2011; Von Der Heide et al., 2013). Increased verbal worry has been associated with increased functional connectivity between the amygdala and prefrontal regions and amygdala and temporal regions in participants with generalized anxiety disorder (Makovac et al., 2018). Interestingly, in this study, increased verbal worry was also associated with increased depressive symptoms and rumination. Moreover, increased functional connectivity between the amygdala and vmPFC mediated the relationship between rumination and depressive symptoms in adolescent girls (Fowler, Miernicki, Rudolph, & Telzer, 2017). Thus the increased FA associated with increased rumination found in our study may be associated with the persistent nature of rumination, increased focus on current distress. Also, increased FA in the IUF could be linked with the passive coping style and verbal processing of emotional information from memory that is found in rumination.

Although many studies solely examine FA in regards to WMI in depression, examining other DTI measures as well may generate a better understanding of the microstructural changes that underlie the differences in FA (Alexander et al., 2007). Fractional anisotropy incorporates measures of the flow of water parallel (axial diffusivity) and perpendicular (radial diffusivity) to the tract. Thus, the specific damage associated with FA changes can further be understood by incorporating these other measures. Mean diffusivity can also give a sense of the overall rate of flow of water molecules. Axial diffusivity is associated with axonal damage, whereas radial diffusivity is associated with demyelination, although these measures both are impacted by crossing fibers in the brain (Winklewski et al., 2018). One study that examined these four measures found decreased FA, increased MD, and increased RD in the right anterior cingulate and IUF associated with depressive symptoms in a healthy population (Hayakawa et al., 2014). Another study that compared MDD and HC found decreased FA and increased MD in depressed participants (Ota et al., 2015). Also, decreased FA and increased RD in right UF was reported when comparing MDD and HC (Zhang et al., 2012). A recent study found decreased FA, increased RD, and decreased AD in several tracts, including the uncinate fasciculus, in MDD (Poletti et al., 2018). However, MDD and HC groups were not matched for age or ratio of male to female participants, so results should be interpreted with caution. Furthermore in this study, in the depressed group only, increased early-life stress was associated with decreased MD and AD. In a sample of treatment-naïve adolescents with MDD compared with HC, increased FA values in the uncinate fasciculus (UF), coupled with increased AD, decreased RD, and preserved MD were found (Aghajani et al 2014). Since our study only examined the white matter integrity in a sample of depressed women, the results from these previous studies cannot be directly compared.

There are consistent results of increased FA with decreased MD in many studies, however, the results for AD and RD appear to be less clear.

In our study, the significant results for reflective rumination associated with FA in the rCB and IUF guided further analysis of the other three measures of WMI (see Figures 3 and 4). The significant results of increased reflective rumination associated with increased FA appears to be driven by a positive relationship with AD and negative relationship with RD. Hence, increased reflective rumination is associated with increased AD and decreased RD in these tracts. Healthy aging in females is associated with increases in both AD and RD, proposed to reflect deterioration in axons and myelination with age (Kumar, Chavez, Macey, Woo, & Harper, 2013). Accordingly, the increased reflective rumination associated with increased FA in these tracts may be associated with axonal differences. These results should be interpreted with caution, as the results for RD and AD associated with reflective rumination were not significant.

Also in the IUF, increased depression rumination was associated with decreased MD, driven by decreased AD (see Figure 5). Additionally, increased brooding rumination was associated with decreased MD, driven by decreased RD (see Figure 6). Thus, depression rumination may be more related to axonal differences, while brooding rumination may be more related to myelination differences. Previous studies find increased RD and decreased or no relationship with AD in MDD participants (Hayakawa et al., 2014; Ota et al., 2015; Poletti et al., 2018; Zhang et al., 2012). Interestingly, these post-hoc results show a different pattern of the multiple measures of WMI (decreased AD with decreased RD) compared with the findings for reflective rumination (increased AD with decreased RD) within the same tract.

There are some limitations of the current study including incorporating masks of whole tracts, potential association of depression symptom measures, and the broad age range. This study implemented white matter tract masks from the John's Hopkins University ICBM-DTI-81 atlas: left and right uncinate fasciculus (UF), left and right superior longitudinal fasciculus (SLD), and left and right cingulum bundle (CB) (Hua et al., 2008; Mori et al., 2005; Wakana et al., 2007). Then, the mean measure of white matter integrity from the entire tract is calculated. However, each of these three tracts can be further broken down into subdivisions based on the putative function of the WM in this region (Makris et al., 2005; Von Der Heide et al., 2013; Wu, Sun, Wang, Wang, & Ou, 2016). Moreover, a recent study found aberrant FA in only portions of the cingulum bundle and uncinate fasciculus in individuals with depression (Bhatia et al., 2018). Implementing this course measure of WMI cannot identify differences associated with depression symptoms to more localized regions that may be associated with rumination, such as the subgenual anterior cingulate cortex. Another limitation is considering the intertwined measures of age of onset, number of depressive episodes, depression severity, and rumination. Rumination is associated with increased duration and severity of depressive episodes in women (Abela & Hankin, 2011; Burwell & Shirk, 2007; Nolen-Hoeksema, 2000, 2001). Additionally, number of depressive episodes is associated with brain connectivity differences (Marchetti, Koster, Sonuga-Barke, & De Raedt, 2012; Meng et al., 2014). One study found that individuals with early onset MDD had increased FA in several tracts, however those with late onset MDD had decreased FA in different tracts (Cheng et al., 2014). Thus, the association between rumination and these other depression measures cannot be completely disentangled. In our study, however, only depression rumination was significantly correlated with depression severity.

White-matter integrity of tracts changes as a function of age, although these changes follow different maturational trajectories for individual tracts (Abe et al., 2010; Giorgio et al., 2010; Hsu et al., 2008; Lebel et al., 2008; Rathee et al., 2016; Yoon et al., 2008). Although we did not find any significant linear association of age and white-matter integrity in this study, age may still be an important factor. The broad age range in this sample allows the results to be generalized to a broader population of women with depression, however it does not fully elucidate the impact of age.

Future studies should consider a larger sample size of women across the lifespan and potentially split the sample into group to further understand the impact of age on WMI. Also, it would be important to consider the cumulative effect of recurrent depression as well as the age of onset when testing WM brain connectivity differences associated with rumination. Studies should continue to employ multiple measures of WMI in order to more fully understand axonal or myelination differences associated with rumination in depression. Also, in the future, researchers should consider using tract based spatial statistics within the tracts with significant results—cingulum bundle and uncinate fasciculus—to localize aberrant WMI in individuals with depression. If localized differences are found in rumination in women with depression then other clinical groups should be employed to understand if connectivity associated with rumination cuts across diagnosis. Finally, studies may consider a longitudinal design to examine changes in subtypes of rumination associated with changes in multiple measures of WMI in currently and remitted depressed participants.

This study contributes to the research about white matter brain connectivity associated with subtypes of rumination in depressed women. We did not find support for significant

decreased FA in our tracts of interest, as hypothesized. However, we did find increased FA in the right cingulum bundle and left uncinate fasciculus associated with reflective rumination.

Additionally, aberrant WMI in the left uncinate fasciculus was associated with depression and brooding rumination. This study is the first study to examine multiple measures of white matter integrity associated with subtypes of rumination in a sample of women with depression. The findings in the left uncinate fasciculus may point to atypical communication between prefrontal, temporal, and limbic regions associated with the persistent past-focused attention on emotional stimuli in ruminative processing.

Table 1

Demographic frequencies of the full sample (N=45) and subset with the rumination measure (N=36)

		N=45	N=36
		N(%)	N(%)
Education	High School or Less	11 (24.4)	9 (25.0)
	Partial College	18 (40.0)	13 (36.1)
	College Graduate	11 (24.4)	10 (27.8)
	Graduate or professional	5 (11.1)	4 (11.1)
Marital Status	Never married	31 (68.9)	24 (66.7)
	Married	6 (13.3)	4 (11.1)
	Separated	2 (4.4)	2 (5.6)
	Divorced	6 (13.3)	6 (16.7)
Race	American Indian/ Alaska Native/ Asian	2 (4.4)	2 (5.6)
	White	29 (64.4)	22 (61.1)
	African American	12 (26.7)	10 (27.8)
	Not reported	2 (4.4)	2 (5.6)
Ethnicity	Not Hispanic or Latino	34 (75.6)	26 (72.2)
	Hispanic or Latino	10 (22.2)	9 (25.0)
	Not reported	1 (2.2)	1 (2.8)

Table 2

Demographic and clinical frequencies of the full sample (N=45) and subset with the rumination measure (N=36)

		N=45	N=36			
		N(%)	N(%)			
Diagnosis ^a	MDD Only	31 (68.9)	24 (66.7)			
	Comorbid MDD	14 (31.1)	12 (33.3)			
Number of MDE ^b	1	23 (51.1)	18 (50)			
	> 1	22 (48.9)	18 (50)			
Depression Severity	Moderate	27 (60.0)	20 (55.6)			
	Severe	14 (31.1)	12 (33.3)			
	Very Severe	4 (8.9)	4 (11.1)			
		Mean (Range)	Mean (Range)	Correlation with IDS-C (r)	Correlation with Brooding (r)	Correlation with Reflective (r)
Age		34.02 (17-59)	34.69 (17-59)			
Age of Onset of MDD		27.74 (11-57)	28.24 (11-57)			
IDS-C		35.42 (24-57)	36.36 (24-57)			
RRS Brooding			13.42 (7-19)	.263		
RRS Reflective			13.31 (7-18)	.025	.203	
RRS Depression			33.44 (20-47)	.375*	.465*	.368*

Note. Inventory of Depressive Symptomatology—Clinician Rated (IDS-C) (Rush et al., 2000), Ruminative Response Scale (RRS) (Treyner, 2003)

^aNo differences in clinical variables between the MDD Only and Comorbid MDD groups (all p 's >.05)

^bMajor Depressive Episodes (MDE)

*Significant at $p < .05$

Table 3

Significant results of reflective rumination associated with FA

Tract	<i>F</i>	<i>df</i>	<i>p</i>	<i>R</i>²	Standardized <i>β</i>	<i>t</i>	<i>p</i>
Right Cingulum Bundle	4.341	1, 34	.045	.113	.336	2.084	.045
Left Uncinate Fasciculus	5.868	1, 34	.021	.147	.384	2.422	.021

Note. Fractional Anisotropy (FA)

Table 4

Significant results for multiple measures of white matter integrity within the left uncinate fasciculus

DTI Measure	Symptom Measure	<i>F</i>	<i>df</i>	<i>p</i>	<i>R</i>²	Standardized β	<i>t</i>	<i>p</i>
MD	Depression	5.220	1, 34	.029	.133	-.365	-2.285	.029
	Brooding	9.967	1, 34	.003	.227	-.476	-3.157	.003
AD	Depression	5.167	1, 34	.029	.132	-.363	-2.273	.029
RD	Brooding	10.463	1, 34	.003	.235	-.485	-3.235	.003

Note. Mean Diffusivity (MD), Axial Diffusivity (AD), Radial Diffusivity (RD)

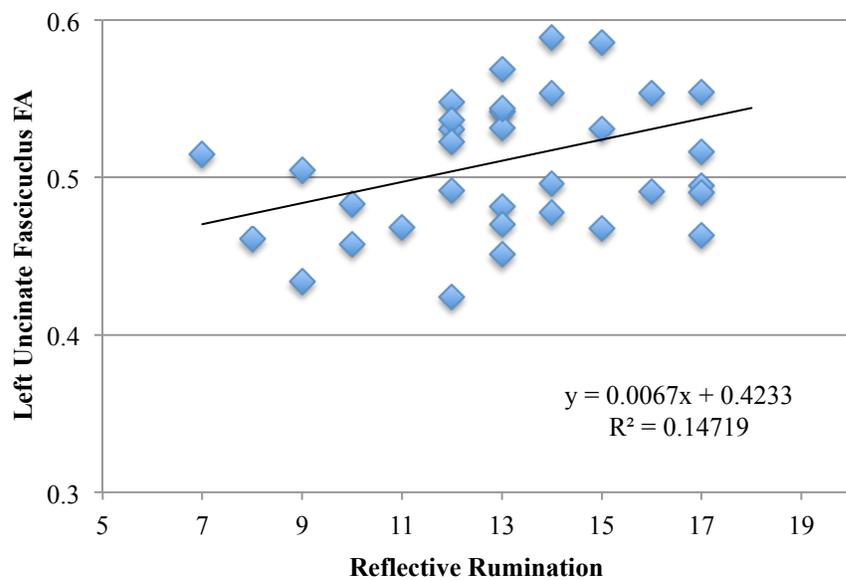


Figure 1. Reflective rumination associated with fractional anisotropy in the left uncinate fasciculus.

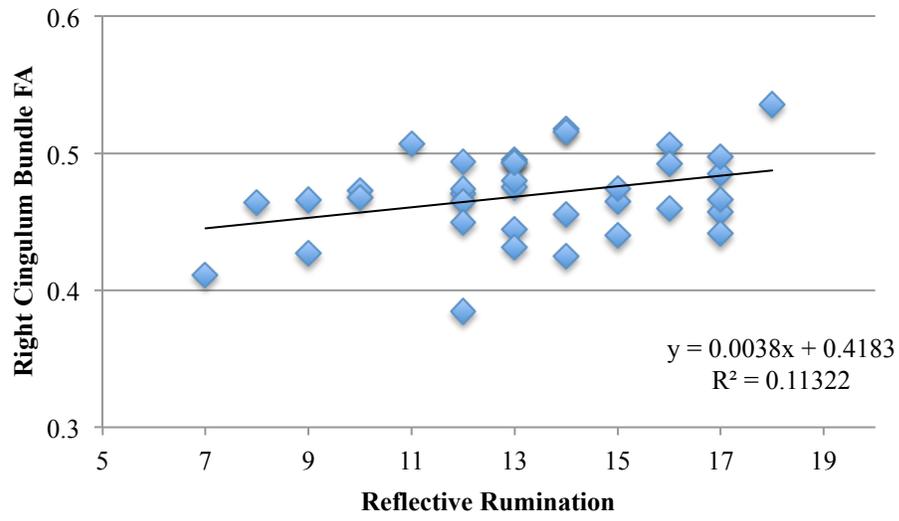


Figure 2. Reflective rumination associated with fractional anisotropy in the right cingulum bundle.

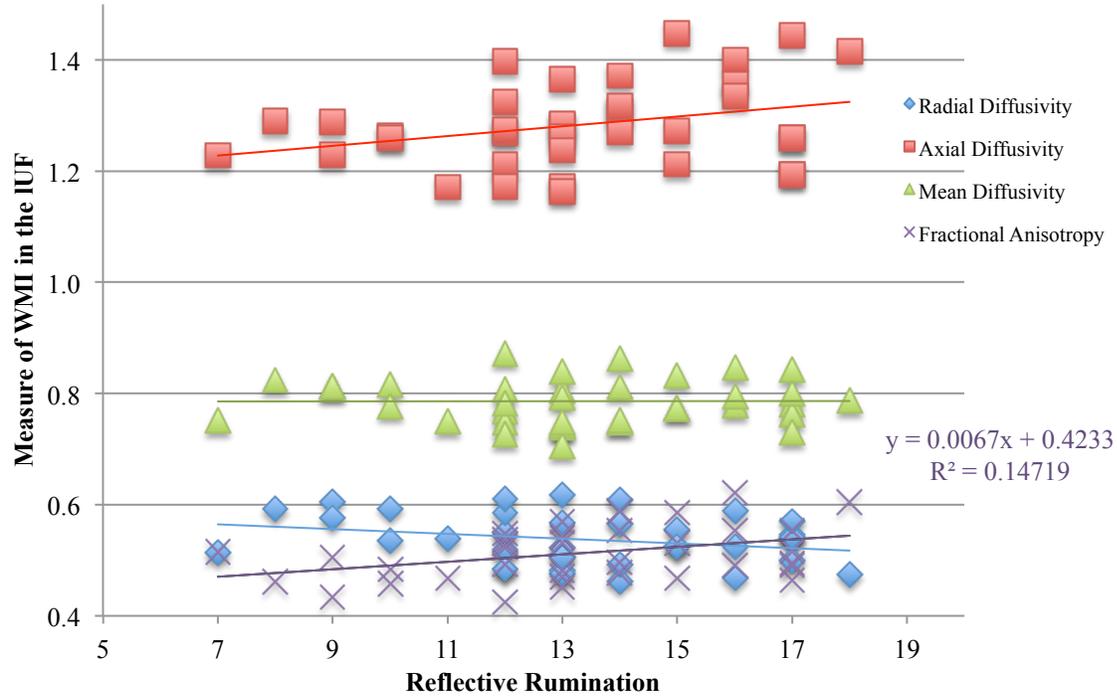


Figure 3. Multiple measures of white matter integrity in the left uncinus fasciculus (IUF) associated with reflective rumination. Fractional anisotropy is significantly associated with reflective rumination.

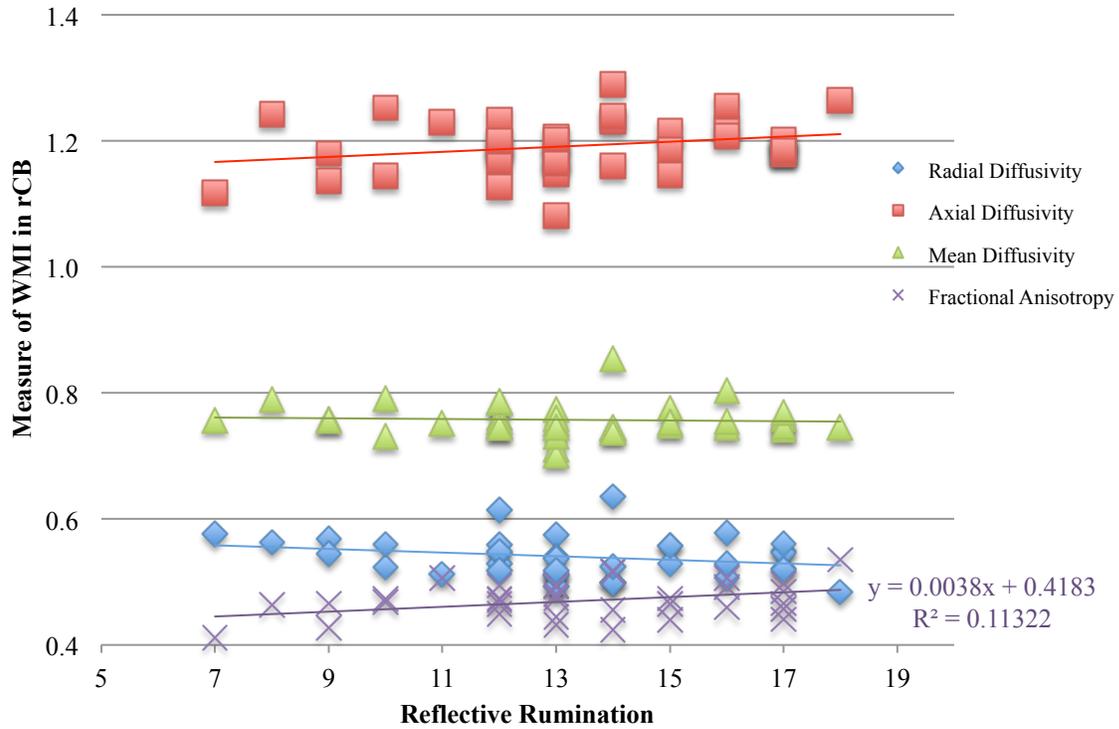


Figure 4. Multiple measures of white matter integrity in the right cingulum bundle (rCB) associated with reflective rumination. Fractional anisotropy is significantly associated with reflective rumination.

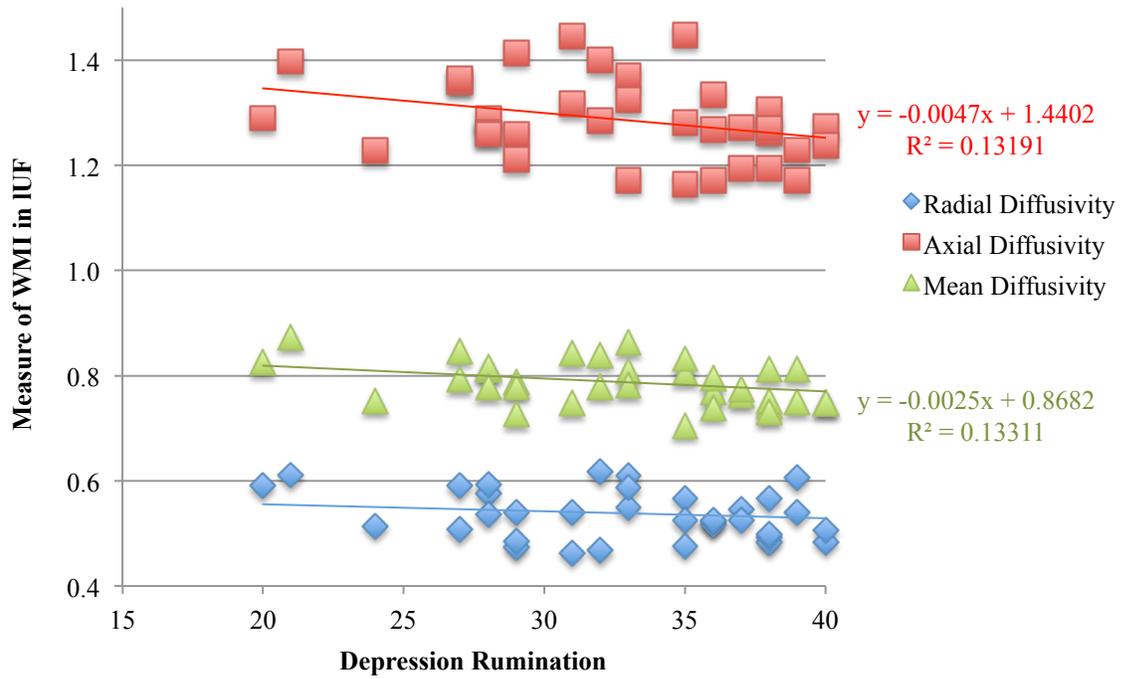


Figure 5. Multiple measures of white matter integrity in the left uncinate fasciculus (IUF) associated with depression rumination. Axial diffusivity and mean diffusivity are significantly associated with depression rumination.

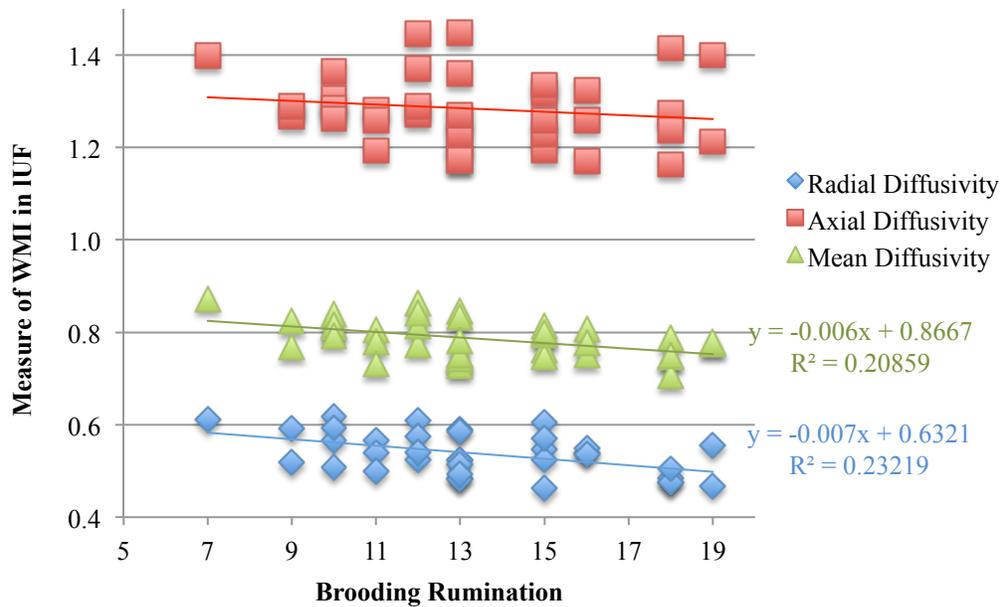


Figure 6. Multiple measures of white matter integrity in the left uncinete fasciculus (IUF) associated with brooding rumination. Radial diffusivity and mean diffusivity are significantly associated with brooding rumination.

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