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Altered fimbria-fornix white matter integrity in anorexia nervosa predicts harm avoidance

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ABSTRACT

The eating disorder anorexia nervosa (AN) is associated with high anxiety. The brain mechanisms that drive those behaviors are unknown. In this study we wanted to test whether brain white matter (WM) integrity is altered in AN, and related to heightened anxiety. Sixteen adult women with AN (mean age 24 ± 7 years) and 17 healthy control women (CW, mean age 25 ± 4 years) underwent diffusion tensor imaging (DTI) of the brain. The DTI brain images were used to calculate the fractional anisotropy (FA) of WM tracts, which is a measure for WM integrity. AN individuals compared to CW showed clusters of significantly reduced FA ($p<0.05$, corrected) in the bilateral fimbria-fornix and the fronto-occipital fasciculus, as well as the posterior cingulum WM. In the AN group, Harm Avoidance was predicted by FA in the left and right fimbria-fornix. Those findings were not due to WM volume deficits in AN. This study indicates that WM integrity is abnormal in AN in limbic and association pathways, which could contribute to disturbed feeding, emotion processing and body perception in AN. The prediction of Harm Avoidance in AN by fimbria-fornix WM integrity suggests that this pathway may be mechanistically involved in high anxiety in AN.

1. Introduction

The eating disorder (ED) anorexia nervosa (AN) is a severe psychiatric disorder associated with self-driven food refusal and emaciation, altered body perception and preoccupations with weight and shape (American Psychiatric Association, 2000). Heightened anxiety, such as high Harm Avoidance and Trait Anxiety, is common in AN, and has been associated with prolonged illness (Bulik et al., 2000; Klump et al., 2004).

The underlying pathophysiology of AN core behaviors or high anxiety is largely unknown. Brain imaging studies in the past identified grey (GM) and white matter (WM) volume abnormalities in youth and adults ill with AN (Katzman and Colangelo, 1996; Swayze et al., 2003), and a recent study in adult AN showed specifically decreased GM in the anterior cingulate cortex, frontal operculum, temporo-parietal cortex and the precuneus (Joos et al., 2010). That study furthermore suggested that parietal cortex GM volume could be related to drive for thinness in AN. AN has also been associated with abnormal neurotransmitter availability (Kaye et al., 2009), but the relationship between neurobiology and illness behavior remains incompletely understood. While we are just beginning to identify functionally related brain structures that are important for AN, the visual presentation of anxiety-provoking food items has consistently activated multiple brain regions in AN more than in controls, including frontal, parietal, temporal and occipital cortex (Nozoe et al., 1995; Ellison et al., 1998; Naruo et al., 2000; Gordon et al., 2001; Seeger et al., 2002; Uher et al., 2004), suggesting those regions to be a correlate for heightened vigilance and fear response. The presentation of tasks that tested the response of AN subjects to their own or schematic body images showed a more complex picture, with increased activation of frontal, parietal and occipital brain regions in one study (Wagner et al., 2003), but reduced parietal activation in AN subjects when viewing their own compared with someone else's body (Sachdev et al., 2008), and reduced brain response in the parietal cortex in response to body shape drawings. The insula, which processes taste as well as other sensory input, showed increased activation in AN subjects to "thin" stimuli, but reduced activation to "fat" valence in an emotional Stroop task, as well as reduced activation in recovered AN to sucrose solution compared to

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controls (Uher et al., 2005; Santel et al., 2006; Wagner et al., 2007, 2008; Redgrave et al., 2008; Sachdev et al., 2008). Altogether, there are various brain networks that are activated in AN depending on the task used. An important aspect here is that the cognitive bias in AN toward body shape and food most likely drives the brain activation patterns, and it is often complicated to disentangle underlying biological alterations from activations that are driven by cognitive-emotional features.

Complex human behaviors are believed to be mediated by the interaction of functionally connected brain regions (Dehaene and Changeux, 2000). Brain WM axons physically connect cortical and subcortical brain structures and thus could have critical impact on cognitive and emotional processing. A relatively novel area of brain research that targets WM function is the magnetic resonance imaging (MRI) technique diffusion tensor imaging (DTI) (Filler, 2009). One of the DTI measures, the fractional anisotropy (FA) value, measures water diffusion along the WM tracts. Higher FA is thought to reflect better axonal coherence, density and myelination (Le Bihan, 2003; Cohen et al., 2009). Another measure, the apparent diffusion coefficient (ADC), provides information about the average diffusion-freedom water molecules have in each voxel, and correlates with local cell breakdown (Jiang et al., 2006).

While DTI has been previously applied in other psychiatric disorders (White et al., 2008), it has not been used in AN research. Importantly, one DTI study found that WM pathway integrity is inversely related to Trait Anxiety (Kim and Whalen, 2009), a potentially important finding for AN research, in light of the high anxiety associated with AN. Thus, pathological anxiety in AN could be directly related to altered brain structure and function (Dehaene and Changeux, 2000), and WM functionality could help identify networks of associated brain structures that drive AN-related behaviors.

We hypothesized that WM integrity would be reduced in AN, suggesting a disruption of brain connectivity in AN compared to matched controls. We further wanted to test whether such altered WM function would be directly related to Harm Avoidance and Trait Anxiety in AN (Kim and Whalen, 2009), providing a possible mechanism for abnormal anxiety in this disorder.

2. Methods

2.1. Participants

A total of 33 right-handed adult Caucasian females were recruited, 16 patients with AN, and 17 healthy control women (CW). Six AN individuals were of the binge eating/purging subtype, 10 of the restricting subtype. Eight AN individuals took psychoactive medication: two individuals took novel antipsychotics (ziprasidone and risperidone), and six took serotonin reuptake inhibitors (escitalopram, fluoxetine [2], venlafaxine, sertraline, fluvoxamine). No subject had a psychotic or alcohol/substance use disorder. Eight of the CW and two of the AN individuals were on an oral contraceptive. No study participant was a smoker.

2.2. Screening and study inclusion

Participants with AN were recruited through the Eating Disorders Program at The Children's Hospital in Aurora, Colorado and the Eating Disorder Center of Denver, both of which included patients in inpatient or day-hospital treatment levels of care. CW were recruited through local advertisements in the Denver/Metro area. After complete description of study procedures, written informed consent was obtained from each participant. All research procedures were approved by the Colorado Multiple Institutional Review Board. All study participants met individually with the study investigator (GKWF) to assess medical and psychological history. In addition, all subjects were assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1996) by a doctoral level interviewer. CW had a lifetime history of healthy body weight (between 90% and 110% of ideal body weight since menarche), did not endorse symptomatic eating or weight concerns, and were free from any lifetime major medical or psychiatric illness. Participants with AN met current DSM-IV-TR (American Psychiatric Association, 2000) criteria for AN, either restricting or binge/purging subtype. AN individuals completed all study procedures within 1 to 2 weeks after admission. AN individuals did not have any gross electrolyte or CBC abnormalities (exclusion criteria), and all ate and drank according to a supervised meal plan.

All study participants completed a battery of self-report questionnaires (1. Drive for Thinness, Bulimia, and Body Dissatisfaction from the Eating Disorder Inventory-3 (Garner, 2004), 2. Harm Avoidance from the Temperament and Character Inventory-3 (Cloninger et al., 1994); 3. Trait Anxiety from the Spielberger State and Trait Anxiety Inventory (Spielberger, 1983); 4. Depression from the Beck Depression Inventory (Beck et al., 1961)).

2.3. Brain imaging procedures

Study participants were admitted to the University of Colorado Denver brain imaging facility on the morning of the study. That facility is equipped with a GE 3 Tesla whole-body MRI scanner, maximum gradient amplitude of 40 mT/m and maximum slew rate of 150 T/m/s; we used an eight-channel phased-array head coil. All control women had a standardized breakfast. AN individuals ate breakfast according to their meal plan. Breakfast calories were similar across groups on the morning of the study ($p>0.1$). Brain imaging was performed between 8 and 9 AM.

First, a structural spoiled gradient recalled (SPGR) MRI was acquired on each individual for delineation of individual brain anatomy and registration to the template image. Then, for each subject, 26 diffusion-weighted images (DWIs) were acquired for DTI mapping, which included 25 DWI diffusion gradient images and one b0 (baseline) image. Each DWI included 29 slices acquired in axial anterior-posterior commissure orientation and in a 128×128 matrix, TR = 8500 ms, field of view = 28 cm, and slice thickness = 3.5 mm with 0.5 mm gap.

2.4. Brain imaging analysis

DTI data were pre-processed and analyzed with DTI Studio software (DtiStudio; https://www.mristudio.org/). DTI Studio estimates fiber tracts based on the Fiber Assignment by Continuous Tracking (FACT) algorithm and a brute-force reconstruction approach (Jiang et al., 2006). Affine body co-registration was used to register all brain images to remove small bulk motions that occurred during the scans (AIR 5; http://bishopw.loni.ucla.edu/AIR5/). Every scan was visually inspected for quality. Corrupted images were discarded from further analysis. The gradient table was reconstructed based on the total number of directions, b0, and the calculated trace image. Then, tensor calculations were performed to obtain FA maps (providing information about the orientation of the underlying structure of the fiber tracts in the brain based on direction of water diffusivity). An FA threshold of >0.2 and a turning angle of 41° were used to obtain more accurate WM fibers. The z-component box was also checked to change the sign of this component and thus flip the eigenvector (Jiang and Mori, 2005). Apparent Diffusion Coefficient (ADC) maps were also obtained, by averaging all gradient orientations per voxel.

The whole brain FA and ADC maps for each subject were further analyzed using statistical parametric mapping (SPM5, http://www.fil.ion.ucl.ac.uk/spm/software/spm5) software. The FA and ADC images for each subject were co-registered (Collignon et al., 1995) with that person's SPGR image. Then each SPGR image was normalized to the SPM/MNI template image, and those subject-specific parameters were

used to normalize each individual's FA and ADC image. Then each normalized FA and ADC map was carefully visually inspected for quality of normalization. All FA and ADC images were smoothed with a 6-mm FWHM filter and masked with a white matter mask. A two-sample *t*-test was used to compare study groups. Thresholds of $p<0.005$ and 100 voxel contiguity were used to create the result maps. For the resulting significant clusters, mean FA values based on the whole cluster were then extracted using mricron software (www.mricron.com) in order to test whether WM integrity was related to anxiety or BMI.

In order to visualize particular WM fiber tracts, circular-shaped regions of interest (ROIs) based on group comparison results were placed in MRI Studio on single slices of the axial view by one author who was blind to diagnosis (DK). This operation produced WM projection bundles. The particular resultant WM bundles were identified by comparison with established anatomical WM structures using visual inspection and the 'MRI Atlas of Human White Matter' by Mori et al. (2005).

The SPGR images were also used for a structural analysis of white matter across the AN and CW groups to determine whether DTI differences between groups were related to structural/volume aberrations using voxel-based morphometry (VBM) and the SPM5 VBM5.1 toolbox (http://dbm.neuro.uni-jena.de/vbm/). Tissue segmentation, bias correction, and spatial normalization were conducted in a unified model (Ashburner and Friston, 2005). Hidden Markov Random Fields (HMRF) were applied to improve accuracy of tissue segmentation. White matter maps were smoothed with an 8-mm FWHM kernel. Data were evaluated using a two-sample *t*-test in SPM5. Similarly to the FA analysis, results maps were thresholded at $p<0.005$ and 100 voxel contiguity.

2.5. Statistical analyses

All behavioral data and regression analyses were performed using the PASW 17 software package (SPSS, Chicago IL, 2009). Two-sided independent sample *t*-tests were used for group comparisons. Adjusted degrees of freedom (d.f.) were reported for comparisons with unequal variances. Regression analyses tested relationships between the FA data and behavioral/demographic variables. A statistical threshold of $p<0.05$ was set to reject the null hypothesis.

3. Results

3.1. Demographic data (Table 1)

Both groups were matched for age, but AN individuals had lower body mass index (BMI) and scored higher on Body Dissatisfaction, Drive for Thinness, Harm Avoidance, Trait Anxiety, and Depression. Eight AN Individuals had current major depressive disorder (MDD), eight AN individuals had one or more current anxiety disorders (two social phobia, four obsessive-compulsive disorder, and two post-traumatic stress disorder) (Table 1).

Table 1
Demographic variables for both study groups, control (CW) and anorexia nervosa women (AN); Eating Disorders Inventory-3, EDI-3; Temperament and Character Inventory, TCI; State and Trait Anxiety Inventory, STAI; Beck Depression Inventory, BDI.

	CW ($n=17$)		AN ($n=16$)		d.f.	*p*
	Mean	S.D.	Mean	S.D.		
Age (years)	25.1	4	23.9	7	22.6	0.5
Body mass index (BMI)	21.5	1	16.5	1	31	<0.001
Duration of illness (years)	–	–	7.5	8	–	–
Drive for thinness (EDI-3)	3.1	4	19.3	6	25.3	<0.001
Body dissatisfaction (EDI-3)	5.5	5	22.4	10	20.5	<0.001
Harm avoidance (TCI)	9.1	4	22.9	7	22.2	<0.001
Trait anxiety (STAI)	27.4	5	55.7	9	31	<0.001
Depression (BDI)	1.1	1	24.6	9	15.3	<0.001

3.2. FA group analysis

The FA group comparison result map yielded six significant (voxel and cluster level) areas of difference: in the bilateral fimbria-fornix region, the fronto-occipital fiber bundles, and the posterior cingulum (Table 2, Fig. 1). There was no area of greater FA in AN compared to CW. The extracted FA values per ROI yielded the following mean ± standard deviation results and group differences: Inferior fronto-occipital fasciculus, left, CW 0.25 ± 0.03, AN 0.19 ± 0.02, d.f. = 22, $p<0.001$; superior fronto-occipital fasciculus, right, CW 0.32 ± 0.06, AN 0.24 ± 0.04, d.f. = 31, $p<0.001$; fimbria-fornix left, CW 0.39 ± 0.03, AN 0.34 ± 0.03, d.f. = 31, $p<0.001$; fimbria-fornix right, CW 0.4 ± 0.03, AN 0.34 ± 0.02, d.f. = 28, $p<0.001$; posterior cingulum, left CW 0.22 ± 0.03, AN 0.17 ± 0.01, d.f. = 31, $p<0.001$; posterior cingulum right CW 0.38 ± 0.03, AN 0.33 ± 0.03, d.f. = 31, $p<0.001$.

The whole brain group comparison was repeated with the unmedicated subset of AN versus the CW sample. This comparison, at a lower threshold of $p<0.01$, showed virtually identical qualitative results, including bilateral reduced fimbria-fornix FA in the AN group, as well as FA reductions in cingulum, prefrontal and occipital WM.

We assessed whether AN subtype or comorbidity affected the study results. There was no difference between the restricting versus binge eating AN subtypes. There was also no significant difference between AN with ($n=8$) and without ($n=8$) current MDD, and AN without MDD had reduced (results maps threshold $p<0.005$, 100 voxel contiguity) right ($x=24$, $y=-28$, $z=-4$, $p<0.05$ corrected cluster level) and left ($x=-34$, $y=-30$, $z=0$, $p<0.001$ corrected cluster level) fimbria-fornix FA compared to CW. Similarly, AN with and without anxiety disorder (results maps threshold $p<0.005$, 100 voxel contiguity) did not show significant differences, and the eight individuals without anxiety disorder had reduced fimbria-fornix FA right ($x=26$, $y=-30$, $z=-4$, cluster size 147 voxels, $p<0.002$ uncorrected) and left ($x=-30$, $y=-26$, $z=-6$, cluster size 76, $p<0.015$ uncorrected). Lastly, five AN individuals had neither MDD nor an anxiety disorder. Those compared to controls showed right ($x=26$, $y=-32$, $z=-2$, cluster size 108, $p<0.004$ uncorrected), and left ($x=-30$, $y=-3$, $z=-4$, cluster size 48, $p<0.04$ uncorrected) fimbria-fornix reductions in AN compared to CW.

3.3. FA relationships with behavior, demographic variables

Regression analysis revealed that FA values in the bilateral fimbria-fornix predicted negatively Harm Avoidance in the AN group (Fig. 2). Similarly, in AN, lower right fibria-fornix FA predicted higher Trait Anxiety, but no other behavioral variables ($R^2=0.3$, Beta = −0.5, $p<0.04$; Table 3). Recently, Trait Anxiety has been inversely associated with FA in healthy controls (Kim and Whalen, 2009). That study used

Table 2
Significantly reduced fractional anisotropy (FA) regions in anorexia nervosa (AN) compared to control women (CW). There were no regions where AN had greater FA compared to CW. The a priori statistical threshold was set at $p<0.005$ and 100 voxel contiguity. This resulted in six significant clusters. Within those clusters, the peak voxel was significant, FDR corrected <0.05; the *x*, *y*, *z* coordinates of the peak voxel are based on the Montreal Neurological Institute (MNI) template.

Pathway/region	Cluster level		MNI coordinates			*Z*
	Cluster size	$P_{corrected}$	*x*	*y*	*z*	
Inferior fronto-occipital fasciculus, left	247	<0.001	−26	−64	−14	4.62
Superior fronto-occipital fasciculus, right	154	<0.02	18	−18	22	4.33
Fimbria-fornix left	200	<0.003	−26	−26	−8	3.78
Fimbria-fornix right	241	<0.001	24	−26	−4	4.29
Posterior cingulum, left	270	<0.001	−10	−56	4	4.08
Posterior cingulum right	122	<0.05	14	−54	26	3.97

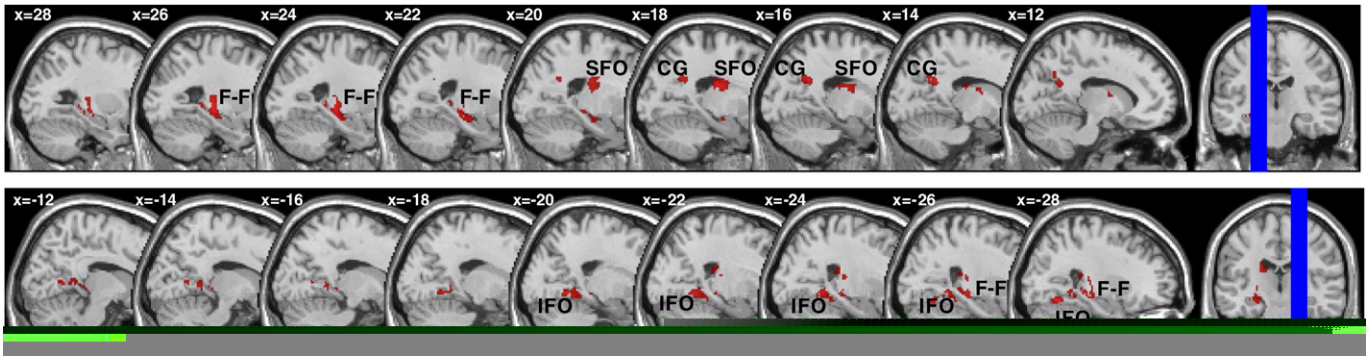

Fig. 1. Brain maps showing significantly greater brain white matter (WM) fractional anisotropy (FA) in control women (CW) compared to anorexia nervosa women (AN). The top row indicates right, and bottom row indicates left sided group difference results (red) overlaid on the Montreal Neurological Institute (MNI) template image in sagittal view; the blue bars to the right indicate range of planes shown in coronal view; fimbria-fornix, FF; Inferior fronto-occipital fasciculus, IFO; Superior fronto-occipital fasciculus, SFO; cingulumWM, CG.

a different analysis path, performing whole brain regression analysis of FA and Trait Anxiety, and found that amygdala-related WM integrity predicted Trait Anxiety. We wanted to explore in the CW group whether we would find similar results using similar analysis methods (Kim and Whalen, 2009). That would support the previous research and underlying concept of FA relating to WM tract functionality. Comparable with that study, we found, using whole brain regression analysis and Trait Anxiety that within the CW group there were two significant clusters that related to left ($x=-40, y=0, z=-20$, 202 voxel cluster size, $p<0.008$ corrected) and right ($x=24, y=4, z=-12$, 347 voxel cluster size, $p<0.001$ corrected) amygdala-related WM tracts, including the uncinate fasciculus.

In AN, higher BMI predicted higher right fimbria-fornix FA ($R^2=0.3$, beta = 0.5, $p<0.05$). In the CW group there were no significant correlations between fimbria-fornix FA and behavior or BMI. BMI predicted neither Harm Avoidance ($R^2=-0.07$, $p<0.8$) nor Trait Anxiety ($R^2=-0.07$, $p<0.99$) in AN.

Using regression analysis, the other regional WM FA group differences did not predict Anxiety or eating disorder specific behaviors ($p>0.3$) in ANs, nor did BMI or duration of illness predict FA in those regions ($p>0.3$).

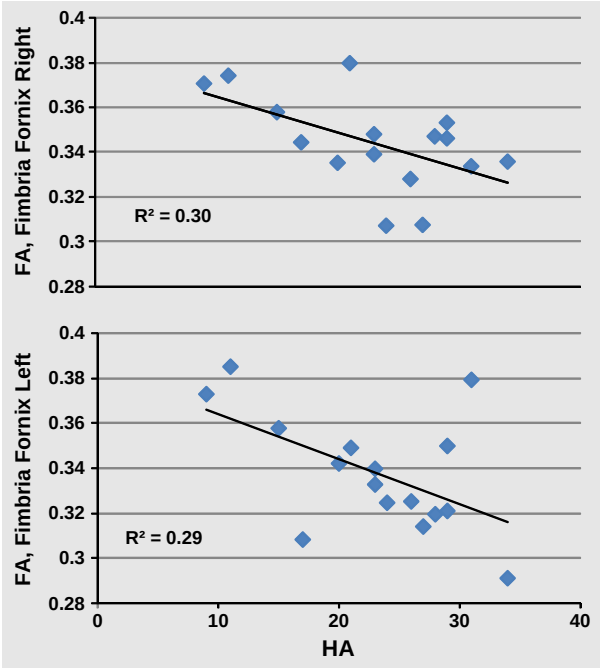

Fig. 2. Significant regression results between right ($F=6.0$, Beta = −0.55, $p<0.03$) and left ($F=5.8$, Beta = −0.54, $p<0.03$) fimbria-fornix fractional anisotropy (FA), a measure for white matter (WM) integrity, and Harm Avoidance (HA) in the anorexia nervosa (AN) group.

3.4. FA fiber tracking, ADC and VBM analysis

We used the bilateral fimbria-fornix regions as identified by the group comparison to identify the associated fiber tracts in each subject. For that we placed a 4-mm circular ROI on each individual's FA map in DTIStudio for fiber tracking. This identified in each subject the fornix in its path anterior-superiorly and converging to the midline. Fig. 3 shows an example image for a CW. The extraction of FA data on the un-standardized FA maps is difficult since there are no easy to apply templates for parts of white matter tracts for such images. Still on an exploratory basis, we exacted FA values for the fimbria-fornix from each study subject's raw FA image, that is, within its original space, unwarped. We used the following landmarks for ROI center point delineation, guided by the SPM group results: transaxially the height of the ventral striatum, sagitally one of the last slices laterally of the putamen and including the trigone of the lateral ventricle, and coronally about ¾ of the distance of the amygdala posteriorly and superiorly along the length of the hippocampus, clearly showing the dentate gyrus; we then placed an ROI on the coronal image since that image shows bilaterally the circular fimbria-fornix structure. If at all possible we identified the ROI bilaterally on the same slice, but since the unwarped images are frequently tilted, we often had to identify the ROI on different slices for the left or right fimbria-fornix. Most fimbria-fornix regions on the coronal slice were covered by a circular ROI with between 30 and 40 voxels, mean voxel numbers for right side was for CW 36 ± 6, for AN 38 ± 5, d.f. = 31, $p<0.3$, and left side CW 37 ± 7, AN 36 ± 6, d.f. = 31, $p<0.5$. For the right fimbria-fornix FA values, right sided means were for CW

Table 3
Regression analysis in the AN group for 1. demographic variables age, body mass index (BMI) and duration of illness predicting fornix fractional anisotropy (FA), and 2. Fornix FA predicting behavioral variables Harm Avoidance (HA), Trait Anxiety, eating disorder behavior (EDI-3) and depression (Beck Depression Inventory, BDI).

	Fornix left		Fornix right	
	Beta	p	Beta	p
Age	0.35	0.19	0.08	0.78
BMI	−0.06	0.83	0.52	0.04
Duration of illness	0.32	0.23	0.06	0.82
HA	−0.54	0.03	−0.55	0.03
Trait anxiety	−0.37	0.16	−0.53	0.04
Drive for thinness	−0.04	0.88	0.07	0.80
Body dissatisfaction	−0.3	0.26	−0.20	0.47
BDI	−0.17	0.54	−0.13	0.63

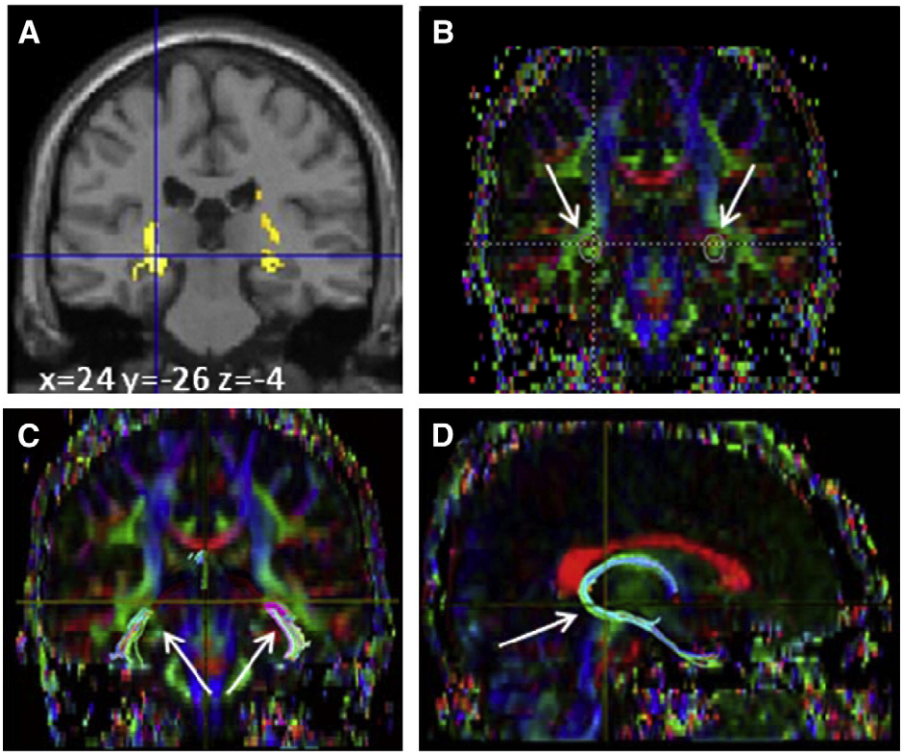

Fig. 3. Example fornix reconstruction based on the bilateral fimbria-fornix group difference (yellow) overlaid on the normalized structural MR image (A), and then using a 4 mm circular region of interest (ROI) on the diffusion tensor color image to tract related fiber bundles (here in a control woman, B). This procedure was done for all study individuals and showed similar qualitative identification of the fornix pathway (coronal view, C; sagittal view, D).

0.51 ± 0.08, and for AN 0.41 ± 0.07, d.f. $= 31$, $p < 0.001$; left sided means were for CW 0.49 ± 0.06, AN 0.45 ± 0.09, d.f. $= 31$, $p < 0.1$.

The ADC maps, applying thresholds of $p < 0.005$, 100 voxel contiguity, yielded three areas of significant difference with AN greater than CW (all cluster size corrected $p < 0.001$); the regions and mean $\pm$ standard deviation, including p for t-test result, per group were 1. the fronto-parietal WM, $x = -45$, $y = -36$, $z = 54$, cluster size 134, CW 0.86 ± 0.06, AN 1.06 ± 0.09, d.f. $= 31$, $p < 0.001$; 2. $x = 9$, $y = -21$, $z = 51$, cluster size 129, CW 0.82 ± 0.03, AN 0.95 ± 0.09, d.f. $= 20$, $p < 0.001$; and 3. in the parieto-occipital WM, -51, -75, 24, cluster size 200, CW 0.90 ± 0.03, AN 1.05 ± 0.05, d.f. $= 24$, $p < 0.001$. BMI did not predict significantly ADC results (p for all regression analyses ≥ 0.3, $R^2 < 0.1$). ADC and FA results are frequently inversely correlated and we explored whether we would find ADC results that would overlay with the FA result map at a lower threshold. In fact at $p < 0.009$, 100 voxel contiguity we found significant clusters (all cluster size $p < 0.001$ corrected, p indicates t-test result for extracted mean ADC values) that included the right fimbria-fornix region ($x = 15$, $y = -36$, $z = 3$, cluster size 359 voxels, cluster size; CW 1.00 ± 0.08, AN 1.19 ± 0.14, d.f. $= 31$, $p < 0.001$), and left fimbria-fornix region ($x = -15$, $y = 3$, $z = 9$, cluster size 287 voxels; CW 1.09 ± 0.13, AN 1.30, d.f. $= 31$, $p < 0.001$) as well as in the parietal lobe ($x = -45$, $y = -36$, $z = 54$, cluster size 1324; CW 0.90 ± 0.03, AN 1.06 ± 0.05, d.f. $= 23$, $p < 0.001$), frontal lobe ($x = 9$, $y = -21$, $z = 51$, cluster size 413; CW 0.84 ± 0.05, AN 0.97 ± 0.07, d.f. $= 31$, $p < 0.001$), occipital lobe ($x = 33$, -75, -15, cluster size 241; CW 0.99 ± 0.05, AN 1.17 ± 0.08, d.f. $= 31$, $p < 0.001$), and temporal lobe ($x = -45$, $y = -51$, $z = -18$, cluster size 309, CW 0.91 ± 0.04, AN 1.06 ± 0.07, d.f. $= 31$, $p < 0.001$). The right fimbria-fornix ADC value predicted Harm Avoidance in the AN group ($R^2 = 0.2$, $p < 0.05$, Beta 0.5), the other regions did not predict Harm Avoidance ($p > 0.3$), nor did BMI significantly predict ADC in the AN or CW group ($p > 0.2$ for all regression analyses).

VBM WM analysis identified four significant or near significant clusters for CW greater than AN: 1. $x = -34$, $y = -50$, $z = -4$, cluster size 293 voxels, $p < 0.05$ corrected (temporal lobe, paraventricular WM); 2. $x = 6$, $y = 56$, $z = 28$, cluster size 265 (frontal lobe, anterior prefrontal WM), $p < 0.07$; 3. $x = 52$, $y = -6$, $z = 26$, cluster size 386 voxels, $p < 0.01$ corrected (right sensorimotor area WM); 4. $x = -12$, $y = 48$, $z = -24$, cluster size 247 voxels, $p < 0.09$ (left orbitofrontal cortex WM). The analysis did not reveal group differences in WM volume in regions with reduced FA in the DTI analysis. Thus, VBM WM volume changes should have only minimal effect on normalization of the regions of interest in the FA, ADC maps. No regions of greater WM volume in AN relative to CW were observed.

4. Discussion

This study is, to our knowledge, the first to investigate WM integrity in AN. Our results indicate that: (1) WM integrity in AN is reduced in the bilateral fimbria-fornix, fronto-occiptal, as well as cingulum WM association fiber tracts; and (2) anxiety, as measured by Harm Avoidance and Trait Anxiety scores in AN, is predicted by fimbria-fornix WM integrity. Thus, reduced WM integrity in AN could provide a mechanism for heightened anxiety in this disorder.

The fornix is an important fiber tract that originates from the hippocampus as the fimbria-fornix (Saunders and Aggleton, 2007) and projects superior-anteriorly toward the midline, forming the body of the fornix. The fornix then winds around and between the two lateral ventricles and projects inferiorly to the anterior commissure, from which it then projects to the hypothalamus and mammillary bodies, the thalamus and cingulate cortex, as well as the septal nuclei and bilateral nucleus accumbens (Sudheimer et al., online atlas). The fornix is part of the larger Papez Circuit which is an important structure in the limbic system, and involved in the regulation of emotions by higher order frontal cortical brain regions (Dalgleish, 2004). Lesions of the fornix or fimbria-fornix in rodents result in altered feeding and drinking patterns (Osborne and Dodek, 1986) and resistance to behavior extinction (Osborne et al., 1987). The fornix is part of a brain network that is involved in reward processing (Salinas and White, 1998) and responds to food restriction or administration of the feeding inhibiting hormone

leptin (Fulton et al., 2000). Thus, abnormal integrity of the fornix fiber path could lead to altered feedback between limbic and higher order brain structures including hippocampus, amygdala, cingulate cortex, ventral striatum and orbitofrontal cortex (LeDoux, 2003). Altogether, those studies suggest that fornix alterations in AN could be involved in the characteristic food restriction, disrupted meal patterns and altered food reward processing (Keating, 2010) seen in AN (American Psychiatric Association, 2000), as their well as difficulties to make behavior changes (Holliday et al., 2005).

Other areas of reduced WM FA included the cingulum and fronto-occipital WM pathways. The fronto-occipital WM association fibers connect frontal with occipital and posterior parietal and temporal lobes, including the uncinate fasciculus. They integrate auditory and visual association cortices, and may have a role in the experience of hallucinations (Hutchins et al., online atlas), spatial awareness and neglect, as well as emotion recognition and expression (Philippi et al., 2009). The limbic association fibers of the cingulum WM connect frontal lobe regions with more posterior structures including temporal lobe and hippocampus, and are part of a network that integrates behaviors necessary for executive function and emotion recognition (Hutchins et al., online atlas). Altered body perception in AN, which is reminiscent of disturbed reality testing, could thus be related to fronto-occipital WM abnormality. Furthermore, AN has been associated with abnormal recognition of emotions in others (faces) and emotion regulation within themselves (Harrison et al., 2010). The fronto-occipital WM is involved in vision processing and attention (Schmahmann et al., 2007), while the cingulum and the fimbria-fornix are part of the limbic system including the Papez Circuit; these structures are important in recognizing, regulating and responding to emotions. Alterations in those structures could be related to altered emotion identification and processing in AN.

Our findings point to the possibility that altered fimbria-fornix function could be directly related to elevated Harm Avoidance and Trait Anxiety in AN. The fimbria-fornix WM integrity in AN inversely predicted Harm Avoidance and Trait Anxiety, and thus reduced WM function could directly affect over-anxious, avoidant behaviors in AN. Such a potential mechanism regulating human behavior could have important implications if future studies can identify treatments capable of promoting WM protection and subsequently reduce pathologic anxiety. Harm Avoidance is a measure derived from the Temperament and Character Inventory (Cloninger et al., 1994), and it measures the proposed heritable tendency to respond to aversive stimuli by behavior inhibition in order to avoid punishment, novelty and frustrating non-reward. Harm Avoidance is a familial trait that is consistently elevated in AN, and more so when ill compared to after recovery (Jacobs et al., 2009). Trait Anxiety measures anxiety proneness, a person's disposition to experience stressful situations as threatening and anxiety provoking (Spielberger, 1983). Previously, AN Harm Avoidance scores were found to relate to frontal, parietal, temporal and subcortical serotonin and dopamine neurotransmitter receptor availability (Kaye et al., 2009). Most recently, one study found that reduced WM integrity in amygdala-frontal cortex fiber tracts was associated with increased Trait Anxiety in healthy individuals (Kim and Whalen, 2009). We tested whether we could replicate this relationship in the control group, and in fact found comparable results which validated the overall approach. Taken together, our results are consistent with previous research and indicate that WM integrity could be an important factor in the modulation of anxiety in AN. The mechanisms by which altered WM function could affect anxiety are unknown. For instance, it might be possible that reduced fimbria-fornix FA leads to altered connectivity between emotion activated limbic and more cognitive prefrontal brain regions, and subsequently to heightened anxiety because of the lack of frontal regulation.

BMI as a measure of disorder severity was significantly positively related to the right fimbria-fornix integrity in the AN group, indicating a state-related phenomenon. Underweight patients with AN usually experience great difficulties engaging in treatment programs and are able to truly benefit from psychotherapy only when they are at least partially re-fed. Whether general malnutrition, low sex hormones or the lack of fat for instance during starvation may contribute to this finding is unknown. It will be important to subsequently study recovered AN individuals in order to disentangle relationships between WM FA, Anxiety and BMI. One recent study found that BMI in obese individuals was inversely related to brain WM FA (Marks et al., 2010) which raises the question whether both under- and overweight status may cause WM abnormalities.

The ADC maps, measuring water diffusivity per voxel, suggest increased diffusivity or WM damage on the voxel level. The initial results at the threshold set as for the FA comparison did not overlap with the fiber tract integrity results. However, when using a slightly more liberal threshold, we found that there were in fact several brain regions with increased ADC values in the AN group compared to CW, and two of those regions were overlapping with the fimbria-fornix areas identified in the FA comparison. Only the fimbria-fornix region ADC correlated significantly and positively with Harm Avoidance. FA and ADC values are often inversely correlated and the results suggest that AN is associated not only with WM tract integrity alterations as measured by FA (Le Bihan, 2003; Cohen et al., 2009), but also with cell breakdown suggested by increased ADC in the AN group (Jiang et al., 2006). This is important since it indicates a particular damage to the brain from starvation in AN and it is unclear whether such cells regenerate. GM and WM volumes tend to normalize with long-term recovery from AN, although there are reports that suggest abnormalities in the recovered state (Wagner et al., 2006; Muhlau et al., 2007; Castro-Fornieles et al., 2009), and future studies will need to determine whether this is also the case for WM FA and ADC-related WM function.

A variety of studies have previously investigated FA using the DTI technology in psychiatric disorders (White et al., 2008). For the most part, reduced FA was found in a multitude of regions across mood, psychotic, anxiety and substance use disorders. These findings suggest that reduced FA is not an AN-specific abnormality. The identification of the fornix as a primary abnormality is less common, although various studies in mild and severe dementias have found reduced FA across various brain regions, including the fornix, and lower FA was associated with impaired cognitive performance such as set shifting (Perry et al., 2009) in the past. Set shifting deficits are often observed in adult AN (Roberts et al., 2007), and altered WM functionality could have a direct impact on cognition in this disorder as well. In summary, studies suggest that various psychiatric disorders are associated with WM abnormalities, but findings are very heterogeneous with respect to brain region and behavior-relationships at this point.

4.1. Limitations

The sample size of this study was not large due to the low prevalence of the disorder, and this study needs to be replicated. Still, the effect size for the right fimbria-fornix difference was large, with partial eta squared = 0.5. Various factors could influence the DTI measure, such as age, gender, and genotype (Chiang et al., 2011), BMI and exercise (Marks et al., 2010). Those factors contribute to regionally different white matter densities suggesting that individual brain regions show different susceptibilities. In this study we recruited one gender only, and individuals were age-matched adults. We certainly cannot exclude genetic effects, but those would most likely be difficult to identify in light of the sample size and the commonly relatively small genetic effects. Our a priori hypothesis was that DTI would predict Harm Avoidance and may be related to BMI. Both of those hypotheses were correct, although since that was only true for the fimbria-fornix regions but not for other brain regions, the resulting p values would not withstand a conservative Bonferroni

multiple comparison correction. However, since fimbria-fornix FA predicted Harm Avoidance bilaterally and that region has been repeatedly associated with anxiety modulation (Degroot and Treit, 2004; Duarte et al., 2010), we believe that this finding is not simply by chance. Another potentially confounding factor is medication use. Our subset of AN individuals without current psychoactive medication showed reduced WM FA in similar areas as did the full sample, but it is possible that past medication treatment could have contributed to the finding. The retrospective assessment of medication use for AN, a disorder that has no approved medication regimen, is in our experience very unreliable, and this is a potential confound in this investigation. It is uncertain whether the abnormalities found in this study are a state or trait phenomenon. Since it is difficult to identify AN prior to illness onset, investigators have studied AN individuals after recovery. The downside of that approach is the uncertainty of whether the abnormalities found are really trait-related or a remnant from the underweight state. Abnormal biologic findings in the underweight state that relate to behavior could point to a mechanism that is important for acute psychopathology, and specific interventions that treat that biologic disturbance could help with faster recovery, regardless of whether it is a trait phenomenon or not. DTI FA is based on water diffusivity. As such, malnutrition or dehydration could theoretically influence the outcome. We tried to address this potential problem by studying AN individuals in highly structured treatment programs with supervised food and fluid intake, as well as monitoring of hydration, electrolyte, and CBC status. Nevertheless, DTI studies have not been conducted in non-AN starvation states, and even with the listed physiologic parameters intact, WM integrity and DTI results could be affected by protracted malnutrition. Another potential limitation involves the question of how much DTI FA abnormalities truly reflect altered white matter fiber pathways. A recent combined DTI and histopathologic study that used DTI imaging in epilepsy patients prior to brain surgery where fimbria-fornix tissue was removed suggested that DTI FA results are directly related to fiber histology (Concha et al., 2010), although axon density and myelination could all also contribute to the DTI signal (Cohen et al., 2009). The meaning of altered FA diffusivity values on the cellular level, such as neuronal firing, is unknown.

In conclusion, our study is the first one to assess FA in AN. Our results suggest that AN is associated with reduced WM integrity in brain regions that integrate reward, emotion and cognitive behaviors. Furthermore, our study indicates that reduced fimbria-fornix WM integrity could be directly related to elevated Harm Avoidance and Trait Anxiety in AN, suggesting a mechanism for pathologic anxiety in this disorder.

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