White Matter Integrity is Reduced in Bulimia Nervosa

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ABSTRACT

Objective: To investigate brain white matter (WM) functionality in bulimia nervosa (BN) in relation to anxiety.

Method: Twenty-one control women (CW, mean age 27 ± 7 years) and 20 BN women (mean age 25 ± 5 years) underwent brain diffusion tensor imaging to measure fractional anisotropy (FA; an indication of WM axon integrity) and the apparent diffusion coefficient (ADC; reflecting WM cell damage).

Results: FA was decreased in BN in the bilateral corona radiata extending into the posterior limb of the internal capsule, the corpus callosum, the right sub-insular WM, and right fornix. In CW but not BN, trait anxiety correlated negatively with fornix, corpus callosum, and left corona radiata FA. ADC was increased in BN compared with CW in the bilateral corona radiata, corpus callosum, inferior fronto-occipital, and uncinate fasciculus. Alterations in BN WM functionality were not due to structural brain alterations.

Discussion: WM integrity is disturbed in BN, especially in the corona radiata, which has been associated with taste and brain reward processing. Whether this is a premorbid condition or an effect from the illness is yet uncertain. The relationships between WM FA and trait anxiety in CW but not BN may suggest that altered WM functionality contributes to high anxious traits in BN. © 2013 by Wiley Periodicals, Inc.

Keywords: bulimia nervosa; white matter integrity; diffusion tensor imaging; fractional anisotropy

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Introduction

The eating disorder (ED) bulimia nervosa (BN) is most distinctively characterized by episodic binge eating, followed by purging behaviors,[1] although individuals with BN also frequently restrict food intake in between binges. BN is associated with anxious traits[2] and comorbid anxiety disorders,[3] as well as depression,[1] but also altered taste perception[4,5] and brain reward response.[6–8] The neurobiologic underpinnings of increased anxiety in BN are still unknown, although brain serotonin 1A, 2A, and dopamine D2/3 receptors have been associated with anxious traits in the past.[9–12]

Recently, we showed that brain white matter (WM) in AN was related to anxiety.[13] In that study, we used diffusion tensor imaging (DTI) and found that patients with AN had reduced WM integrity in the bilateral fimbria fornix, an outflux tract of the medial temporal cortex and hippocampus, as well as in the inferior and superior fronto-occipital fasciculus and cingulum. Importantly, fornix WM integrity, expressed as the so-called fractional anisotropy (FA), predicted inversely harm avoidance and trait anxiety in the AN individuals. That finding raised the question whether BN would have similar WM alterations that would predict high trait anxiety in the disorder.

For a long time, it has been known that WM lesions in the brain may lead to disconnection syndromes, and studies over the past 10 years now have increasingly implicated more subtle WM tract functionality in neuropsychiatric disorders.[14] WM functionality can be studied using DTI, a relatively

new tool in psychiatric research that uses magnetic resonance imaging (MRI) to assess WM functionality. DTI maps WM pathways by measuring water diffusivity along axons expressed as FA.[15] FA is, therefore, a measure of the integrity of axons, their myelination, and density. A second measure is the apparent diffusion coefficient (ADC), which measures water diffusivity at the voxel level and is thought to be an indicator of the health of the axonal cells. A higher ADC indicates dispersed water diffusion reflecting disruption of these cells.[15] Studies have investigated WM functionality in, for instance, mood and psychotic disorders,[16] most commonly reporting reduced FA values across many brain regions, but increased WM FA has also been reported.[17] The functionality of WM has not been studied previously in BN. Psychiatric disorders including BN are characterized by a complex interplay of cognitive and emotional behavior and rely heavily on the connections between brain regions.[18] Thus, functional WM alterations in BN could be an important aspect of the pathophysiology of this disorder.

Only few brain-imaging studies have investigated brain structure such as gray matter (GM) or WM in BN. Early studies analyzed total GM or WM and cerebrospinal fluid volumes. The first structural studies have shown potential brain atrophy[19,20] or widening of the sulci and enlargement of the ventricles despite normal body weight.[21–23] With advancement in technology using "voxel-based morphology" (VBM), that is, a whole brain analysis of structural brain images that are normalized to a standard space and compared across groups, studies now can in much more detail investigate localized volume alterations that could be related to a specific brain disorder. One recent study found normal GM volumes in BN but "drive for thinness" was positively related to parietal cortex GM volume.[24] Another study found increased orbitofrontal cortex and ventral striatal GM volume compared with controls.[25] In that study, purging frequency and body mass index (BMI, weight in kg/height in m^2) were directly related to the volume of those regions. One study in recovered BN indicated normal WM volume.[26] Most studies did not take comorbid depression or medication use into account, factors that have been shown to affect brain volumes. This and the differing analysis techniques most likely account for the conflicting results and more definite studies are still needed. Various neurotransmitter alterations were also found in BN, such as reduced serotonin (5HT) transporter binding in thalamus and hypothalamus.[27] After recovery, BN showed reduced midbrain but increased cingulate cortex 5HT transporter

availability,[28] reduced orbitofrontal 5HT2A,[29] and increased 5HT1A receptor binding,[10] most prominently in prefrontal, cingulate, and parietal cortex regions. Altogether, those studies indicate brain alterations in BN in ill and recovered states, which may be related to altered food intake, mood states, and anxiety, but their relationship to WM function is unclear.

In this study, we wanted to investigate whether we would find altered WM functionality in BN similar to results we previously reported in AN.[13] Following on our AN results, we hypothesized that we would find reduced FA values in BN in the fornix area, fronto-occipital fasciculus, and the cingulum, and those findings would not be due to WM volume alterations. We further hypothesized that lower FA would predict higher harm avoidance and trait anxiety. If BN were to have similar WM disturbances as the AN individuals, this might indicate a common vulnerability across ED groups. Furthermore, we wanted to test whether BN specific behaviors such as binge/purge frequency would predict WM functionality, as it did predict brain reward response in BN in the past.[8]

Method

Participants

A total of 41 right-handed women were recruited, 20 with BN, and 21 healthy control women (CW). Thirteen BN women took psychoactive medications: eight were on serotonin reuptake inhibitors (fluoxetine, citalopram, escitalopram, or sertraline), four were on novel anti-psychotics (aripiprazole, ziprasidone, or quetiapine), three were on a non-SSRI antidepressant (bupropion), and two were on selective serotonin/norepinephrine reuptake inhibitors (cymbalta or effexor). Twelve of the CW and five of the BN women were on oral contraceptives.

Screening and Study Inclusion

Participants with BN were recruited through the Eating Disorders Program at the Children's Hospital Colorado and the Eating Disorder Center of Denver, which included patients in inpatient ($n = 3$) or day-hospital treatment ($n = 17$) 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. Study participants met individually with the study investigator (G.K.W.F.) to assess medical and psychiatric history. In addition, all participants were assessed with the Structured Clinical

Interview for DSM-IV Axis I Disorders[30] 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 BN met current DSM-IV-TR[1] criteria for BN. BN individuals completed all study procedures within 1–2 weeks after admission into the treatment program. This time period is needed for consent procedures and study set up as well as also gets participants back on a normalized eating routine, reducing the effects of acute malnutrition. BN individuals did not have electrolyte or blood count 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,[31] (2) Harm Avoidance and Novelty Seeking from the Temperament and Character Inventory-3,[32] (3) State and Trait Anxiety from the Spielberger State and Trait Anxiety Inventory,[33] and (4) Depression from the Beck Depression Inventory.[34]

Brain Imaging Procedures

Study participants arrived at the University of Colorado Denver brain imaging facility on the morning of the study. That facility is equipped with a GE 3 T whole-body MRI scanner, maximum gradient amplitude of 40 mT/m, and maximum slew rate of 150 T/m/s. An eight-channel phased-array head coil was used. All CW had a standardized breakfast. BN individuals ate breakfast according to their meal plan. Breakfast calories were similar across groups on the morning of the study (p ns). Brain imaging procedures were 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 (T_1, SPGR field of view 22 cm, flip angle $10°$, slice thickness 1.2 mm, scan matrix 256×256, TR 10, TE 3, voxel size 1.2 mm^3).

Then, for each participant, 26 diffusion-weighted images (DWIs) were acquired for DTI mapping, which included 25 DWI diffusion gradient images and one b_0 (baseline) image. Each DWI included 29 slices acquired in axial anterior-posterior commissure orientation and in a 128×128 matrix, TR = 8,500 ms, field of view = 28 cm, and slice thickness = 3.5 mm with 0.5 mm gap.

Brain Imaging Analysis

The DTI datasets were processed using the NordicICE version 2.3.12 MRI toolbox (http://www.nordicneurolab.com). NordicICE performs fiber tracking using the algorithm referred to as Fiber Assignment by Continuous Tacking, which is able to achieve 3D tracking of axonal projections.[35] Fibers are tracked continuously based on water diffusion from the center of a voxel and proceeding according to the vector direction. Where the tract leaves the voxel and enters the next, the direction is changed to that of the neighboring voxel. An exhaustive search tracking method was implemented and a principal eigenvector angle stopping threshold of $41°$ was used. The minimum fiber length was 5 mm and only FA values greater than 0.2 were included.[35,36]

The whole brain FA and ADC maps for each participant were further analyzed using statistical parametric mapping (SPM5, http://www.fil.ion.ucl.ac.uk/spm/soft ware/spm5) software. The FA and ADC images for each participant were co-registered[37] with that person's SPGR image. Then, each SPGR image was normalized to the SPM/MNI152 template image, and those participant-specific parameters were used to normalize each individual's FA and ADC image. Next, 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 WM mask. A two-sample t-test was then used to compare study groups. Thresholds of $p < .005$ uncorrected and 25 voxel contiguity were used to create the result maps. For the resulting clusters, mean FA values based on the whole cluster were then extracted using the SPM marsbar toolbox in order to test whether WM integrity was related to behavioral indices.

The WM bundles identified as significantly different across groups were then identified by visual inspection and using the "Atlas of Brain Function"[38] and "Dissecting the White Matter Tracts: Interactive Diffusion Tensor Imaging Teaching Atlas" by Hutchins et al., an online atlas (http://www.asnr2.org/neurographics).

The structural SPGR images were compared across groups using SPM5 software and VBM, which allowed analysis of GM and WM density probability across the entire brain. Preprocessing of T_1-weighted images was performed in SPM5 using the VBM toolbox (VBM5.1 version 1.19; http://dbm.neuro.uni-jena.de/vbm/vbm5-for-spm5/). All original images were manually aligned on the anterior-posterior commissure line. Images were then normalized to MNI space and segmented into GM, WM, and cerebrospinal fluid using unified segmentation.[39] Nonlinear modulated data were used for the analyses and images were smoothed to a 6-mm full-width at half maximum Gaussian kernel. Between group contrasts were then assessed using independent t-tests and a significance threshold of $p < .005$ uncorrected and 25 voxel cluster threshold.

Statistical Analyses

All behavioral data and regression analyses were performed using the PASW19 software package (SPSS,

Chicago IL, 2009). Two-sided independent sample *t*-tests were used for group comparisons. Adjusted degrees of freedom were reported for comparisons with unequal variances based on Levene's test for equality of variances. Pearson correlation analyses tested relationships between the FA, ADC data, and behavioral/demographic variables. A statistical threshold of $p < .05$ was set to reject the null hypothesis

Results

Demographic Data

Groups were matched for age and BMI; however, BMI variance was significantly greater in the BN group (BMI range in CW 19.8–24.4, in BN 17.8–40.9; **Table 1**). BN had been ill for 74.2 ± 63.7 months and had a binge eating/purging frequency of 23 ±

TABLE 1. Demographic variables for control (CW) and bulimia nervosa women (BN)

	CW (n = 21)		BN (n = 20)			
	Mean	S.D.	Mean	S.D.	df	p
Age (Years)	27.5	6.6	25.2	5.3	39.00	.222
Body mass index (BMI)	21.55	1.19	22.59	5.69	20.57	.432
Harm avoidance	9.24	3.52	22.95	5.76	39.00	.001
Novelty seeking	18.38	5.32	22.10	6.74	39.00	.057
Reward dependence	17.05	3.97	15.95	4.73	39.00	.425
Depression (BDI)	1.10	0.995	24.45	11.35	19.28	.001
Drive for thinness (EDI-3)	2.52	3.56	23.10	4.54	36.64	.001
Body dissatisfaction (EDI-3)	1.48	2.27	19.45	6.53	23.34	.001
State anxiety	31.29	11.62	47.80	12.77	38.21	.001
Trait anxiety	32.05	10.45	55.95	10.88	38.68	.001

17 episodes per week. BN individuals scored higher on Harm Avoidance, Depression (BDI), Drive for Thinness (EDI-3), Body Dissatisfaction (EDI-3), and State and Trait Anxiety. One BN individual had Bipolar II Disorder—currently depressed, seven had Major Depressive Disorder, and 12 had one or more anxiety disorder (five social phobia, three PTSD, and six generalized anxiety disorder) (**Table 1**).

Structural VBM Analysis

The acquired SPRG image analysis did not show clusters of differences between groups in GM or WM volume.

FA Group Analysis

To account for comorbidity and medication use as well as high variance in BMI in the BN group, we included as covariates "use of antidepressant," "use of antipsychotic," "mood disorder," "anxiety disorder," as well as "BMI" in the group analysis. That analysis indicated five regions of group difference (CW > BN) in the bilateral corona radiata extending into the posterior limb of the internal capsule, in the corpus callosum, as well as right subinsular WM, and right fornix, three of which were significant at the cluster level after false discovery rate (FDR) multiple comparison correction (**Table 2**, **Figure 1**).

BN women did not show significant correlations between the extracted FA values and behavior including binge/purge frequency, demographic values, or duration of illness. In CW, trait anxiety correlated negatively with FA values in the right fornix ($x = 38$, $y = −18$, $z = −14$; $r = −.599$,

TABLE 2. Regions of significant FA and ADC differences

Pathway/Region	Cluster Level		MNI Coordinates			
	Cluster Size	$p_{FDR\ corrected}$	x	y	z	Z
FA						
Corona radiata, posterior limb of internal capsule, L	160	.036	−26	−10	18	3.73
Corona radiata, posterior limb of internal capsule, R	174	.036	22	−14	12	3.52
Corpus callosum, L, R	193	.036	8	14	24	3.38
Subinsular white matter, R	45	.527	48	2	10	3.34
Fornix, R	42	.527	38	−18	−14	3.23
ADC						
Corona radiata, R	896	<.001	−18	6	60	4.78
Corona radiata, L	682	<.001	12	−8	62	4.69
Corona radiata, anterior limb of internal capsule, L	586	<.001	−36	36	2	4.09
Corpus callosum, L, R	440	<.001	−14	30	20	3.94
Corona radiata, anterior limb of internal capsule, R	379	<.001	38	46	4	3.92
Posterior corona radiata, R	57	.286	30	−28	28	3.80
Inferior fronto-occipital fasciculus, uncinate fasciculus, external capsule, L	361	<.001	−34	12	2	3.65
Inferior fronto-occipital fasciculus, uncinate fasciculus, external capsule, R	65	.285	28	12	0	3.39
Anterior corona radiata, L	134	.07	−40	24	16	3.29

The a priori threshold was set at $p < .005$ and 25 voxel cluster threshold.

FIGURE 1. Reduced WM FA in BN compared to CW. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
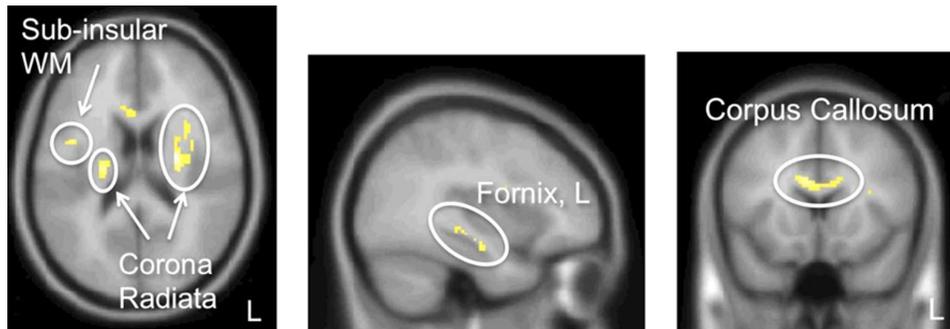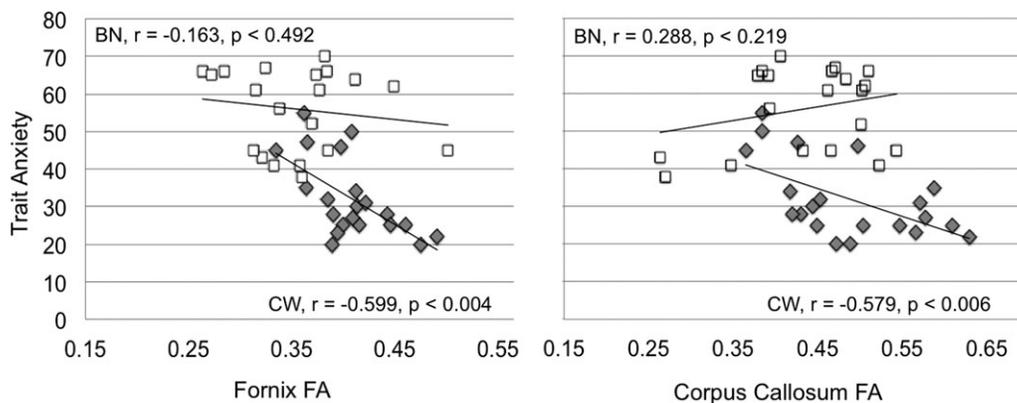

FIGURE 2. Correlation graphs for WM FA and trait anxiety in CW (full diamonds) and BN (open squares).

$p < .004$), corpus callosum ($x = 8$, $y = 14$, $z = 24$; $r = -.579$, $p < .006$), and left corona radiata ($x = -26$, $x = -10$, $z = 18$; $r = -.480$, $p < .028$).

ADC

Similarly to the FA analysis, we included medication, comorbidity, and BMI as covariates and whole brain group comparison indicated nine clusters (bilateral corona radiata, corpus callosum, inferior fronto-occipital, and uncinate fasciculus) that contrasted BN from CW (BN > CW), six of which were significant at the cluster level after FDR correction (**Table 2**, **Figure 2**).

In BN, there was no correlation between behavior or demographics and ADC values; however, in CW, trait anxiety correlated significantly positively with ADC in the right external capsule/inferior fronto-occipital, uncinate fasciculus ($x = 28$, $y = 12$, $z = 0$; $r = .502$, $p < .020$), and left anterior corona radiata ($x = -40$, $y = 24$, $z = 16$; $r = .510$, $p < .018$).

Discussion

This is the first study that indicates that WM integrity is altered in BN. Decreased FA indicated reduced WM axon integrity in BN in the bilateral corona radiata extending into the internal capsule, corpus callosum, the right sub-insular WM, and right fornix. In CW but not BN, trait anxiety correlated negatively with left fornix, corpus callosum, and left corona radiata FA. Increased ADC values in BN compared with CW suggested WM cell disruption in BN in the bilateral corona radiata, corpus callosum, as well as the bilateral inferior fronto-occipital and uncinate fasciculus extending into the external capsule. Trait anxiety was positively correlated with corona radiata and right inferior fronto-occipital and uncinate fasciculus ADC.

These results indicate that BN is associated with reduced WM functionality and this could be related to altered trait anxiety in this disorder.

DTI FA Results

The corona radiata is a collection of fiber bundles that radiate from the internal capsule to the wide

spread cerebral cortex.[40] These fiber bundles include the auditory and optic radiation, and the anterior, superior, inferior, and posterior thalamic radiations. Thus, the corona radiata connects the cortex of the brain with the basal ganglia and spinal cord. The anterior limb of the internal capsule includes cortico-pontine, thalamo-cortical, and cortico-thalamic fibers, whereas the posterior limb of the internal capsule encompasses the cortico-spinal tract as well as more thalamo-cortical and corticothalamic fibers. The thalamo-cortical projections in the internal capsule transmit peripheral sensory information including taste, which could be relevant for BN pathophysiology.[4,5] The internal capsule also connects taste related brain pathways from the midbrain and pons to the cortex.[41] Lesions to the corona radiata and internal capsule have been found in central taste disorders,[42] and deep brain stimulation in the internal capsule leads to altered taste and smell perception, as well as anxiety, panic, and mood alterations.[43] Another region of FA alteration, the corpus callosum, connects the brain hemispheres and facilitates communication between left and right-sided brain structures. Interestingly, an increasing number of studies in humans and non-humans implicate the corpus callosum in taste processing.[44–46] The insula contains the primary taste cortex but is also important for sensory integration, body perception, and pain. Thus, all those regions with reduced FA in BN are associated with central taste pathways and could contribute to altered taste processing in BN.[4,5,47]

Deficient WM tract functionality could also contribute to altered brain reward function in BN.[6–8] Reduced corona radiata WM integrity has been associated with substance use and possibly predicting relapse,[48] and both reduced corona radiata and corpus callosum WM integrity have been found in young binge drinking individuals.[49] WM FA in the uncinate fasciculus, inferior fronto-occipital fasciculus, corticospinal tract, and corpus callosum predicted brain reward response in a sample of healthy youth,[50] and internal capsule WM fibers have been associated with brain reward and self-stimulation.[51,52] Furthermore, the fornix fiber tracts that originate from the hippocampus,[53] and project to the hypothalamus, thalamus, and cingulate cortex, as well as the bilateral nucleus accumbens,[54] are part of the brain network that is involved in reward processing.[55] The fornix also responds to food restriction or administration of the feeding inhibiting hormone leptin,[56] and lesions of the fornix resulted in altered feeding and drinking patterns[57] and resistance to behavior extinction.[58] Thus, the identified WM structures with low FA in

BN could be involved in altered reward function in the disorder. This will need to be explored further. The compulsive nature of binge episodes and comorbidity with substance use disorders was thought to be possible evidence that BN could at least in part share vulnerabilities and pathophysiology seen in substance use disorders.[59] The association of altered corona radiata WM functionality in substance using youth may further point to possible commonalities between BN and substance use disorders.

In our previous study in AN, we found reduced FA compared with CW in the bilateral fornix, the superior and inferior fronto-occipital fasciculus, as well as the cingulum WM.[13] That study's results in the fornix were most interesting because lower fornix FA predicted higher trait anxiety and harm avoidance in AN. In this current study, FA was reduced in BN in the fornix, but even more so in the corona radiata, corpus callosum, and sub-insular WM. FA in this BN group was not correlated with anxiety, but rather CW trait anxiety was most strongly and negatively related to fornix FA, followed by corpus callosum and corona radiata FA. Two samples of healthy individuals linked trait-based anxiety measures to cortico-limbic WM in the past,[60,61] and our results in the CW group are in line with those studies. However, high-trait anxiety in both AN and BN does not seem to be simply predicted by lower WM FA. In healthy participants, higher trait anxiety and harm avoidance are related to lower FA values. It could be that the fornix WM integrity is particular important in relationship to trait anxiety in AN and BN; however, the weight status[62] may affect the different relationships between low FA in that region with trait anxiety and harm avoidance. It could be that low weight in AN adds to or magnifies this relationship, whereas normal weight or a tendency toward higher weight in BN might attenuate such a direct correlation. The possible mechanism for such a connection has yet to be determined; however, brain cortisol and its interaction with BMI effects could be involved. That is, brain cortisol, which differs between AN and BN, has been associated with stress and anxiety but also reduced brain volume, whereas both under- and over-weight also tend to impair brain structure and subsequently WM functionality.[63–65] The combination of those factors could contribute together to WM functionality and trait-based anxiety modulation in EDs. This is speculative and needs empirical study.

ADC Results

FA and ADC are commonly inversely related, where regions that have low fiber tract integrity

indicated by low FA show increased ADC values as an expression of WM cell damage. This was the case in our study for the corpus callosum and the corona radiata. In addition, the inferior fronto-occipital and uncinate fasciculus showed increased ADC values, indicating WM lesions at the cellular level.

The fronto-occipital WM association fibers connect frontal with occipital and posterior parietal and temporal lobes. They integrate auditory and visual association cortices and may have a role in the experience of hallucinations, spatial awareness and neglect, as well as emotion recognition and expression.[66] The uncinate fibers especially connect hippocampus and amygdala with the orbitofrontal cortex. Alterations in the uncinate fasciculus have been associated with anxiety, depression, and psychotic disorders.[67] Altered WM cell functionality in those regions could have various implications for BN. For one, it has long been recognized that BN has body image distortions comparable with AN,[68] and alterations in fronto-occipital WM pathways could be related to abnormal body self-perception. Depression and anxiety in BN could be related to fronto-occipital and uncinate fasciculus ADC. Furthermore, the uncinate fasciculus is one of the brain WM tracts that takes the longest in the developmental maturation process.[69] BN most commonly starts during middle to late adolescence,[1] which is a prime time for brain development,[70] and altered maturation in the uncinate fasciculus followed by altered emotional development and processing could directly contribute to disturbed mood and anxiety in BN.

Consistent with lower FA being related to higher trait anxiety in the CW, here higher ADC values were associated with higher trait anxiety in the right inferior fronto-occipital and uncinate fasciculus, as well as the left corona radiata, further suggesting a role of WM integrity in anxiety regulation. So far, the relationship between trait related anxiety and WM functionalities seems primarily established for healthy individuals,[61] whereas the anxiety literature is mixed with increased or decreased WM functionality in anxiety disorders[71] and as stated above there may be a complex interplay of BMI, stress, and cortisol response and probably other neurotransmitters that together drive anxious traits in BN. The exact mechanisms in this anxiety regulating network need further exploration.

Limitations

The DTI methodology has been used for many years now; however, due to resolution of the brain images, there can be inaccuracies in the resulting fiber paths identified where small fiber paths are close together.[72] We have carefully explored the fiber paths involved in this study and report only large pathways that are relatively easy identifiable.

Various studies investigated WM integrity using the DTI technology in psychiatric disorders other than EDs or anxiety disorders.[16] For the most part, reduced FA was found in a multitude of regions across mood, psychotic, and substance use disorders. These findings suggest that reduced WM functionality per se is not a BN-specific abnormality and the results are not always homogeneous limiting the ability to relate alterations to specific pathologic behaviors. Most of the BN individuals had comorbid anxiety or depression, and many were on psychoactive medication. To address this, we used depression and anxiety diagnoses as well as medication as covariates in the whole brain analysis. Despite the modest sample size and the various covariates, we found large areas of group differences, suggesting that those factors were not solely responsible for the results found. However, effects of depression, anxiety, or medication treatment cannot be excluded. Further, the BN group showed greatly higher BMI variability and while we included BMI also as a covariate in the group analysis, we cannot exclude significant effects of this variable on study results. Several of the regions found in our study have been implicated in studies of anxiety, depression, reward circuitry, and OCD.[16,73–75] Thus, it is difficult to disentangle what alterations in this study are specific to BN versus depression or anxiety. Studying unmedicated BN without comorbidity would be best, but about 80% of BN have a history of depression and 40% a history of comorbid anxiety,[1] and there is probably an interplay between BN specific effects and effects of comorbid psychopathology that shape the BN phenotype. Ideally, we will have a combined depressed/anxious group for comparison in future studies.

Medication effects may also play an important confounding role. Relatively, little is known about the exact effects of medication on WM structure and functionality. However, recent studies indicate that medication has either no effect or in fact normalizes brain structure.[76,77] Thus, we do not believe that medication effects caused Type 1 errors for reduced WM functionality in BN in this study.

Aside form the potential effects of comorbid conditions and medication, the question remains what factors underlie WM functionality alterations across the various brain pathologies. WM FA impairment is related to hypoxia and hypoglycemia

and increased cellular stress or inflammatory factors.[78] Reduced WM functionality has also been found in young adults who were born preterm.[79] Thus, whether altered WM functionality is rather an injury from environmental factors before or after birth and whether there are genetic vulnerability factors involved is yet unclear. All in all, WM seems to be vulnerable to a variety of stress to the cells that support WM fiber tracts and the specific factors that cause abnormalities in the various disorders and what role nerve growth and development play will have to be identified.

A small sample size is also a significant limitation of this study, nonetheless, significant regions were found, beyond what should be attributable to chance alone, and this is the first study to report on WM functionality in BN. Additionally, it is difficult to determine what alterations exist prior to illness onset, as studying participants before the onset of the disorder is very difficult, or what alterations occur during course of the illness and may even persist beyond recovery. Studies after recovery will be a next step toward identification of potential trait disturbances.

Other potential limitations are the influence of hormonal status on WM functionality, as well as variables such as cortisol, hydration, or electrolytes. We study participants during the first 10 days of the menstrual cycle to reduce effects of gonadal hormones, participants are in a strict treatment program that ensures normal food intake including fluids and lab values are normal. We believe that those criteria reduce confounding effects, although we do not have for instance serum cholesterol or gonadal hormone values. DTI is a relatively new technique and we cannot further exclude that certain physiologic variables may confound results.

Lastly, the relationships between WM functionality measures with behavior suggest that one may determine the other, but the exact mechanism that may cause altered WM function or how WM may affect behavior, are far from explained. Specifically, how WM functionality might determine anxious traits and altered brain reward function will require further study.

Conclusion

This is the first study thus far to investigate WM functionality in BN. Controlling for comorbid diagnoses, medication use and BMI, WM FA was reduced and ADC increased in BN, suggesting that the disorder is associated with deficiencies in WM

functionality. Such abnormalities could contribute to heightened anxiety in BN, as well as mood disturbance and altered reward processing.

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