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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