Psychiatry Research: Neuroimaging xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Associations between cortical thickness, structural connectivity and severity of dimensional bulimia nervosa symptomatology

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ARTICLE INFO

Keywords:
Eating disorders
Structural MRI
Symptom severity
Frontoparietal control network
Orbitofrontal cortex

ABSTRACT

Bulimia nervosa (BN) is a psychiatric illness defined by preoccupation with body image (cognitive 'symptoms'), binge eating and compensatory behaviors. Although diagnosed BN has been related to grey matter alterations, characterization of brain structure in women with a range of BN symptoms has not been made. This study examined whether cortical thickness (CT) values scaled with severity of BN cognitions in 33 women with variable BN pathology. We then assessed global structural connectivity (SC) of CT to determine if individual differences in global SC relate to BN symptom severity. We used the Eating Disorder Examination Questionnaire (EDE-Q) as a continuous measure of BN symptom severity. EDE-Q score was negatively related to global CT and local CT in the left middle frontal gyrus, right superior frontal gyrus and bilateral orbitofrontal cortex (OFC) and temporoparietal regions. Moreover, cortical thinning was most pronounced in regions with high global connectivity. Finally, individual contributions to global SC at the group level related to EDE-Q score, where increased EDE-Q score correlated with reduced connectivity of the left OFC and middle temporal cortex and increased connectivity of the right superior parietal lobule. Findings represent the first evidence of cortical thinning that relates to cognitive BN symptoms.

1. Introduction

Characterized by recurrent binge eating, compensatory behaviors, and over-valuation of body weight and shape, bulimia nervosa (BN) is a serious psychiatric disorder that afflicts 1–2.3% of the population (Hoek and van Hoeken, 2003; Keski-Rahkonen et al., 2009). BN often arises in adolescence (Fairburn and Harrison, 2003; Favaro et al., 2009), and affected individuals demonstrate altered brain activity in response to cognitive control (Marsh et al., 2009), gustatory (Bohon and Stice, 2011) and body processing (Vocks et al., 2010) tasks. Research on normative adolescent development has largely characterized maturation of the cortex, where rapid cortical changes are thought to underpin the increases in cognitive and behavioral capacity observed in this period (Knudsen, 2004). However, adolescence may also increase risk for psychiatric conditions (Giedd, 2008), including BN (for review, see Berner and Marsh, 2014). The average age of onset, paired with reported alterations in functional brain activity, could imply variation in underlying brain structure in BN.

Although several studies have examined associations between BN and brain structure, particularly grey matter volume (GMV), findings are inconclusive (reviewed in Frank, 2015). For instance, some voxel-based morphometry (VBM) studies report increased orbitofrontal and ventral striatal volume in women with BN when compared to healthy controls (Frank et al., 2013; Schäfer et al., 2010). However, manual tracing of striatal structures suggests volumetric reduction of the caudate nucleus and preservation of nucleus accumbens volume in BN (Coutinho et al., 2015). Indeed, another VBM study of BN reports right caudate shrinkage, as well as increased insula and precuneus volume, in affected individuals (Amianto et al., 2013). Examination of group differences across adolescent and adult women has shown reduced local volumes in frontal and temporoparietal regions in bulimic individuals (Marsh et al., 2015). The authors also report diffuse cortical thinning in the BN group, where the most significant reductions were seen in bilateral precentral and inferior frontal gyri. Interestingly, none of these studies observed differences in whole-brain volume (Marsh et al., 2015) and total GMV (Frank et al., 2013; Joos et al., 2010; Wagner et al., 2006) in individuals with BN.

Inconsistent reports of regional GMV alterations may arise, in part,

Abbreviations: BN, bulimia nervosa; CT, cortical thickness; MRI, magnetic resonance imaging; SC, structural connectivity

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https://doi.org/10.1016/j.pscychresns.2017.11.006
Received 1 August 2017; Received in revised form 18 September 2017; Accepted 10 November 2017

from the use of different analytic techniques. While volumetric analysis can be informative when examining deep brain and subcortical structures, the interpretability of volumetric changes in the cortex is limited, as this composite measure comprises two features—thickness and surface area—that arise from distinct genetic factors (Panizzon et al., 2009; Winkler et al., 2010). Furthermore, replication studies show that surface area (SA) can be impacted by expansion or shrinkage of underlying white matter, and variance in GMV in adults is disproportionately influenced by SA relative to CT (Im et al., 2008; Pakkenberg and Gundersen, 1997). These and other methodological challenges may be overcome by surface-based morphometric analysis, which delineates the distinct features of the cortex (e.g., SA, CT, mean curvature), enabling a more precise interpretation of underlying cytoarchitecture (Wagstyl et al., 2015).

CT represents one morphometric feature that is reliably related to cytoarchitecture (e.g., Eickhoff et al., 2005). The measure encapsulates the laminar structure of the cortex, and thickness gradients have been shown to complement the brain's functional sensory hierarchies (Wagstyl et al., 2015). Histological data show that decreased dendritic processes (Nakamura et al., 1985) and soma size (Terry et al., 1987) and increased axonal caliber (Paus, 2010) contribute to cortical thinning. MRI-derived CT alterations have been related to cognitive attributes, including executive function (Burzynska et al., 2012), attention (Westlye et al., 2011) and impulsivity. Moreover, cross-sectional (Lerch et al., 2006; Whitaker et al., 2016) and prospective (Alexander-Bloch et al., 2013a; Raznahan et al., 2011) studies of normative development show that focal changes in CT occur in a coordinated manner across the cortex. This would suggest that regional alterations in CT are not statistically independent but are instead correlated with one another. Thus, examining CT alterations and the correlation, or connectivity, of CT measurements at both the group- and individual-level, may enable more nuanced insight into the neurobiological bases of BN.

In addition to the limitations of volumetric morphometry analysis, the use of case-control designs may not fully characterize dysfunctional neural circuitry in BN. Psychiatric nosology has begun to adopt a dimensional approach (Insel et al., 2010), aligning with evidence that psychiatric disorders exist on a continuum and are often comorbid with one another (Caspi et al., 2014; Kessler et al., 2005). Moreover, translational neuroscience research indicates that alterations in cognitive processes scale with underlying neural circuitry (Cuthbert, 2014). Thus, while diagnostic cut-offs benefit treatment and prevention efforts, categorical approaches may not capture the full range of individual differences between affected individuals, which could result in the exclusion of meaningful variance in brain measures. Dimensionality in BN has previously been evaluated through group comparisons of healthy, 'subclinical' bulimic, and bulimic women (Stice et al., 1998, 1996). However, other models conceptualize binge eating as a dichotomous component (i.e., an individual either binges or does not) and body image concerns and drive for thinness as continuous constructs (Williamson et al., 2002). More recently, Brooks et al. (2012) proposed impulse control as a dimensional component, or trait, of disordered eating behavior, which may scale with alterations in underlying neural circuitry. Thus, examination of the distribution of cognitive and attitudinal features of BN, as opposed to frequency counts of bingeing and purging, may capture aspects of the condition that exist at varying degrees in the population. Although preliminary fMRI research of reward processing supports a dimensional model in full and subclinical BN (Bohon and Stice, 2011), the question of whether anatomical alterations scale with BN symptoms remains unanswered.

The present study utilizes a novel dimensional approach to assess alterations in CT across women with a wide range of BN pathology. We also aimed to quantify the structural connectivity of CT at the group level and examine how individual contributions to this group-level connectivity (Saggar et al., 2015) are related to BN symptom severity. To provide a continuous measure of BN symptom severity, participants completed the Eating Disorder Examination Questionnaire (EDE-Q; Fairburn and Beglin, 1994), which indexes cognitions about weight, shape and eating. We hypothesized that EDE-Q score would be negatively related to both global and local measurements of cortical thickness, localized to frontal, temporal and parietal lobules.

2. Methods

2.1. Design and participants

Thirty-seven right-handed women ($M_{age} \pm SD = 22.6 \pm 4.13$ y, 62% White) with normal or corrected-to-normal vision and a range of BN symptoms participated in the study. Participants were recruited from George Mason University, an outpatient eating disorder clinic and the community via online and posted advertisements. Seventeen participants completed a diagnostic phone interview as a part of a separate study (Fischer et al., 2017), which was used to determine the presence of bulimic symptoms and compatibility for MRI scanning. Exclusion criteria included neurological disorders or traumatic brain injury, metallic implants, psychosis or substance dependence, and pregnancy. Participants provided written, informed consent and received monetary compensation for their time. All procedures complied with the ethical standards of the Human Subjects Review Board at George Mason University and the Declaration of Helsinki, revised in 2008.

To assess BN symptoms, participants completed the Eating Disorder Examination interview (EDE; Cooper and Fairburn, 1987) and the substance dependence and psychosis modules of the Structured Clinical Interview for DSM-IV (First et al., 2002). The EDE provides an initial diagnosis of anorexia and bulimia nervosa, binge-eating disorder (BED) and eating disorder not otherwise specified (EDNOS) based on DSM-IV diagnostic criteria. Participants also completed the EDE-Q, which assesses eating disorder attitudes and behaviors over the past 28 days. Items relating to eating disorder attitudes are completed on a 7-point, forced-choice scale. The EDE-Q has a four-factor structure, comprised of eating concern, weight concern, shape concern and restraint subscales. Importantly, we operationalized BN symptom severity with global EDE-Q score as opposed to any one subscale, or alternative combination of subscales, as all subscales contain items relevant to BN. Because we oversampled for women with BN symptoms and validated these with the EDE, EDE-Q score conceivably reflects severity of BN as opposed to any eating disorder. Self-report data related to depressive (Quick Inventory of Depression (QIDS); Rush et al., 2003) and anxiety (State and Trait Anxiety Inventory (STAI); Spielberger and Sydeman, 1994) symptoms were also collected. These data and demographic information are presented in Table 1.

2.2. Exclusions

Four participants were excluded from all analyses. Two subjects were outliers based on age and were excluded to eliminate effects of aging on the EDE-Q-CT relationship. Two subjects were excluded because of a technical problem, leaving 33 participants for analysis of local CT. One subject was an outlier based on global mean CT, and she was excluded from both global CT and structural connectivity analyses, which both incorporate measurements of global CT. Outliers had values three standard deviations above or below the mean.

2.3. MRI data acquisition & FreeSurfer reconstruction

MRI data were collected on a Siemens 3T Allegra scanner (Erlangen, Germany) with a one-channel, quadrature birdcage head coil. T1-weighted structural scans were obtained using a three-dimensional, magnetization-prepared, rapid-acquisition gradient echo (MPRAGE) pulse sequence with sagittal acquisition (160 1-mm thick slices, flip angle = 9°, matrix size = 256 × 256, FOV = 260 mm^2, TR = 2300 ms, TE = 3.37 ms). Scans were reviewed by a neuroradiologist for anatomical abnormalities.