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Publication Date

2015

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UNIVERSITY OF CALIFORNIA

Los Angeles

Visual Processing Abnormalities in Anorexia Nervosa and Body Dysmorphic Disorder

A dissertation submitted in partial satisfaction
of the requirements for the degree Doctor of Philosophy
in Neuroscience

by

Wei Li

2015

ABSTRACT OF THE DISSERTATION

Visual Processing Abnormalities in Anorexia Nervosa and Body Dysmorphic Disorder

by

Wei Li

Doctor of Philosophy in Neuroscience

University of California, Los Angeles, 2015

Professor Jamie D. Feusner, Chair

Anorexia Nervosa (AN) and Body Dysmorphic Disorder (BDD) are disorders of body image that share phenomenological and psychological patterns of flawed perception of appearance. Our working model of visual processing dysfunction in AN and BDD describes a primary deficit in configural/holistic visual processing. The consequence of this is a secondary, “inappropriate,” reliance on detailed processing of image features, which is abnormally deployed in situations in which healthy controls deploy configural processing. We hypothesize that this results in a diminished holistic template that is less able to aid in integration, producing a conscious perception dominated by details. We used EEG and fMRI to investigate possible biomarkers of aberrant early visual system activity, that may inform diagnoses, treatments, and therapies in the future.

The aim of my thesis is to understand the neural dynamics underlying visual processing abnormalities in AN and BDD. I used neuroimaging techniques, specifically functional magnetic

resonance imaging (fMRI) and electroencephalography (EEG), to address this research question. Several fMRI studies have shown abnormal brain activation patterns during global encoding of faces and objects for BDD (1–3) and AN (4; 5). In addition to fMRI, I used EEG, which provides superior time resolution and thereby an opportunity to discover biomarkers complementary to the underlying pathophysiology uncovered in fMRI studies. To date, there have been no studies investigating early visual processing in electrophysiological components in either AN or BDD groups, one key area of focus for my dissertation.

In order to determine if individuals with AN and BDD have similar abnormalities in early holistic processing and slower detail processing relative to controls, I investigated amplitude and latency differences in early visual event related potentials (ERP), namely the P100 and N170. These components are thought to reflect configural and detailed processing, respectively, and are abnormal in those with schizophrenia (6) and William's Syndrome (7), two disorders in which individuals may suffer from similar abnormalities in global processing. The results of reduced P100 amplitudes and delayed N170 latency suggests early visual processing deficiencies in AN. Moreover, there was evidence of a possible brain-behavior relationship in the BDD group, as worse insight correlated with reduced N170 amplitude.

Next, I performed a joint analysis of EEG and fMRI signals using a technique called Fusion independent components analysis (ICA) to generate a joint spatiotemporal profile that leverages spatial and temporal resolution advantages of the respective modalities. This allowed us to localize early electrophysiological processes using the high spatial resolution of fMRI, and had yet to be performed in these populations. We found that AN and BDD showed hypoactivity in early and dorsal visual stream systems for low spatial frequencies, suggesting that a common deficiency in holistic processing is operating in primary visual structures as early as 100 ms post-

exposure and extends later in time (170 ms) into dorsal stream higher-order regions. However, the patterns of hypoactivity are not identical; BDD but not AN additionally demonstrated hyperactivity compared to controls in ventral visual stream systems for high spatial frequency houses, and BDD showed hypoactivity in dorsal visual regions for low spatial frequency faces in comparison to participants with AN. Thus, an imbalance in detailed versus configural/holistic processing for non appearance-related stimuli may characterize both disorders, but the defect appears to be more pronounced in BDD.

This dissertation contributes novel findings to the understanding of the pathophysiology underlying visual processing in these disorders, using methods that have not yet been performed in these populations. We found evidence of similar abnormalities between AN and BDD. There were also important differences in electrophysiological and hemodynamic signatures as well, which warrants further investigation. Further experiments that test other ERP components, frequency analyses, and simultaneous EEG-fMRI studies, and replication of the current findings in larger samples, will allow further characterization of neural signatures that can be used as possible biomarkers for more accurate diagnoses and treatment. Deeper understanding of the early visual processing mechanisms in AN and BDD could better inform perceptual treatments, and ERP or fMRI components may have the potential to be used to track and monitor patient symptoms or disease severity in the future.

The dissertation of Wei Li is approved.

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ACKNOWLEDGEMENTS

I would like to thank my coworkers, coauthors, colleagues, and mentors for all their help during my graduate studies. I would like to dedicate this to my family, for which none of this would be possible.

Funding Agency Acknowledgements

My research was partially supported by the UCLA Neuroscience Interdepartmental Program, the UCLA Neuroimaging Training Program, the UCLA Biomathematics Systems and Integrative Biology (SIB) Training Fellowship, and the UCLA Dissertation Year Fellowship. Additional support included a grant from the International OCD Foundation as well as grants from the NIMH: R01MH093535 (Feusner) and R01MH093535-02S2 (Feusner).

Co-author Acknowledgements

I would like to acknowledge and thank the following co-authors for their contributions:

Li W, Arienzo D, & Feusner JD (2013). Body Dysmorphic Disorder: Neurobiological Features and an Updated Model, *Journal of Clinical Psychology and Psychotherapy* **42**, 184–191.

Li W, Lai TM, Bohon C, Loo SK, McCurdy D, Strober M, Bookheimer S, & Feusner J (2015). Anorexia nervosa and body Dysmorphic disorder are associated with abnormalities in processing visual information. *Psychological Medicine*. *In Press*.

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Aberrant Early Visual Neural Activity in Body Dysmorphic Disorder and Anorexia Nervosa.
Manuscript under review in *Frontiers of Human Neuroscience* (Accepted)

Feusner J, Donatello A, Li W, Zhan L, GadElkarim J, Thompson PM, & Leow A (2014).
White matter microstructure in body dysmorphic disorder and its clinical correlates, *Psychiatry research* **211**, 132–140.

Khalsa SS, Craske MG, Li W, Vangala S, Strober M, & Feusner JD (2015). Altered
Interoceptive Awareness in Anorexia Nervosa : Effects of Meal Anticipation, Consumption and
Bodily Arousal. *International Journal of Eating Disorders. In Press*.

**Douglas PK, Lau E, Anderson A, Head A, Kerr W, Wollner M, Moyer D, Li W, Durnhofer
M, Bramen J, & Cohen MS (2013).** Single trial decoding of belief decision making from EEG
and fMRI data using independent components features. *Frontiers in Human Neuroscience* **7**,
392.

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Li W, Arienzo D, & Feusner JD (2013). Body Dysmorphic Disorder: Neurobiological Features and an Updated Model, *Journal of Clinical Psychology and Psychotherapy* **42**, 184–191.

Li W, Lai TM, Bohon C, Loo SK, McCurdy D, Strober M, Bookheimer S, & Feusner J (2015). Anorexia nervosa and body Dysmorphic disorder are associated with abnormalities in processing visual information. *Psychological Medicine*. *In Press*.

Li W, Lai TM, Loo SK, Strober M, Mohammed-Rezazadeh I, Khalsa S, & Feusner J. Aberrant Early Visual Neural Activity in Body Dysmorphic Disorder and Anorexia Nervosa. Manuscript under review in *Frontiers of Human Neuroscience* (Accepted)

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CHAPTER 1

Introduction

1.1 Background and Phenomenology of AN and BDD

AN

Anorexia Nervosa (AN) is an eating disorder that primarily affects adolescent girls and young women. It is characterized by low body weight, distorted body image, and excessive dieting that leads to severe weight loss and fear of weight gain (8). AN affects 0.5-2% of the population and onset typically occurs during adolescence. AN has the highest mortality rate of any psychiatric illness (9; 10), and many sufferers require hospitalization during the course of illness for extreme low weight, cardiac abnormalities, or electrolyte imbalances.

BDD

Body dysmorphic disorder (BDD) is an often-severe psychiatric disorder in which individuals are preoccupied with imagined defects in their appearance, which are not noticeable, or appear slight, to others (8). Individuals with BDD subsequently experience significant distress, disability, and functional impairment, often accompanied by depression and suicidality (11). In addition, they are often delusional in their beliefs (12), and tend to present to plastic surgeons and dermatologists more often than mental health clinicians (13). Even though BDD affects approximately 1–2% of the population (14–17), BDD is understudied and under-recognized relative to other disorders with similar

prevalence. BDD affects males and females equally and usually begins during adolescence, at an average age of 16 (13). BDD has several important phenomenological features including obsessive thoughts and compulsive behaviors, distorted perception, poor insight, and difficulty engaging in treatments (11).

Perceptual Distortions

A common experience of individuals with each of these disorders is distorted perception of appearance. The phenotype of perceptual distortion of one's own body image is an abnormality with multiple possible environmental and neurobiological contributing factors. Neurobiological abnormalities can begin in a feedforward manner with early visual processing deficits in image processing in striate and extrastriate cortices, or as feedback from fronto-striatal or memory systems that impair organizational strategies. Additional abnormalities in emotion regulation areas such as amygdala can bias patients toward misinterpreting emotional expressions, which can further contribute to distorted self-image. Moreover, misallocation of attentional resources to focus on local features at the expense of global processing can result in selective attention to a defect in one's appearance.

The pathophysiology underlying both AN and BDD is complex and likely involves interactions between a variety of social, cultural, developmental, and neurobiological factors, some of which may contribute to development and others to the maintenance of symptoms (18). Deficiencies in visual processing may therefore represent one potential neurobiological factor, which itself is a subset of several likely important contributors toward the underlying phenotype of abnormal appearance perception.

Previous Visual Processing Studies in AN and BDD

In AN, neuropsychological and neuroimaging studies of visuospatial and global/local processing tests as well as naturalistic images have found abnormalities in visual processing. Studies using the Rey-Osterrieth Complex Figures Task (RCFT) have found that individuals with AN draw detailed aspects of the figure first and show less continuity in drawing (19–21). Another study found lower central coherence, a measure of bias towards details at the expense of integrative processing, in a cohort of underweight AN participants, but not after recovery (5). Studies using another neuropsychological task, the Embedded Figures Task (EFT), have found mixed results. Individuals with AN identified the embedded figures more quickly and with higher accuracy than healthy controls, a sign of bias toward detailed processing (19; 22; 23). However, another study found longer times in underweight and weight-restored AN adults relative to healthy controls using a version of the EFT that required holding figures in memory (24).

Several functional and structural imaging studies support these abnormal visual processing findings in AN. An fMRI study using the EFT found greater activation in the fusiform gyrus in AN compared with healthy controls, suggesting a strategy marked by enhanced ventral visual stream activity, which is responsible for detailed image elements. Furthermore, an fMRI study found decreased brain connectivity in a ventral visual network in both underweight and weight restored individuals with AN.(5). Structurally, AN also show decreased gray matter density in the left extrastriate body area, an area in the occipital cortex involved in processing human body parts, compared to controls. These neurocognitive and brain imaging studies suggest the possibility of aberrant visual processing in AN.

Similar to AN, several neuropsychological and neuroimaging studies have found aberrant visual processing function in BDD. One such study tested visual processing using the face inversion effect. The face inversion effect is the phenomenon of slower and less accurate recognition of inverted faces compared to upright faces, due to the absence of a holistic template for inverted faces, necessitating use of detailed processing. A behavioral study found reduced inversion effects for the BDD group compared to controls, suggesting inappropriate use of detailed processing for upright faces (25). BDD participants were also more accurate than controls at detecting changes made to facial features of photos of others' faces (26). Functional magnetic resonance imaging (fMRI) studies using own-face, other-face, and house stimuli point to abnormalities in primary and secondary visual processing systems, particularly when images are filtered to selectively convey configural and holistic information (1–3). These imaging studies suggest imbalances in detailed and holistic processing, in response to appearance and non-appearance related stimuli, and localize these abnormalities to early visual processing regions in the brain.

1.2. Model of visual processing dysfunction in AN and BDD

The human visual system serves as a complex transducer of light into neural activity through a series of key visual processing areas. The visual signal is relayed by the eye through the lateral geniculate nucleus (LGN) to striate cortex (V1), which then is processed along two different pathways: the ventral (detailed processing of form and color) pathway and dorsal (configural processing of motion and space) pathway. The ventral pathway consists of V1, V2, V4, and inferior temporal (IT) cortex and inputs from both magnocellular and parvocellular cell layers, while the dorsal pathway consists

of V1, V2, V5, and MT and inputs mainly from magnocellular cell layers. The information processed in these areas are hierarchical; while V1 cells serve as local spatial filters, IT cells respond to global and configural features, such as shape or even faces. These two functionally specialized and anatomically distinct pathways form the loci of focus for our studies, as our model of visual dysfunction in AN and BDD center on possible deficits in these systems.

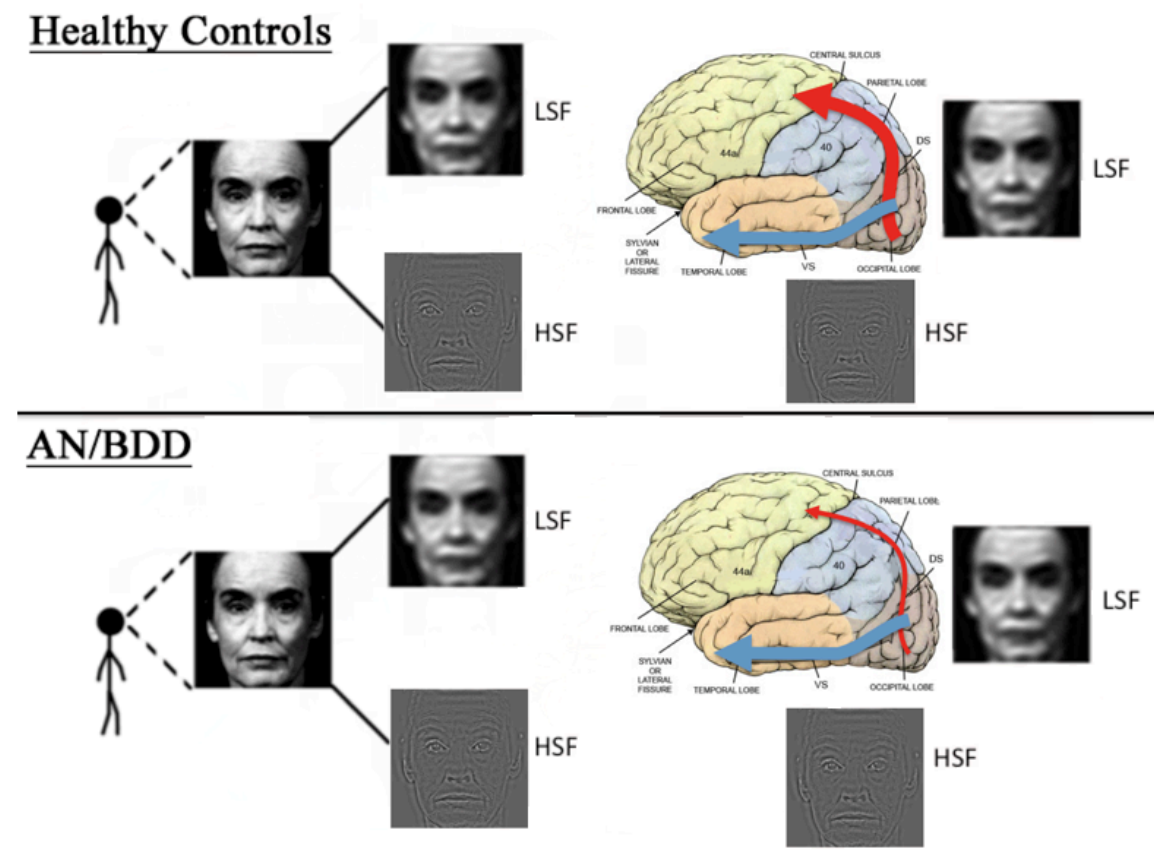


Fig. 1: Working model of visual processing deficit in AN and BDD. Compared with healthy controls, AN and BDD have diminished holistic processing, which may result in an overreliance on detailed processing.

Our working model of visual processing dysfunction in BDD and AN is a primary deficit in configural/holistic processing (18). This may result in a secondary,

“inappropriate,” reliance on featural/detailed processing, which is utilized in situations in which healthy controls normally deploy configural processing. Individuals with AN and/or BDD may realize a conscious perception dominated by details, as a result of a diminished holistic template to aid in integration. fMRI experiments studying BDD (1–3) corroborate this model of visual processing dysfunction. However, a limitation of these prior fMRI studies (due to limited temporal resolution) is that it remains unclear if abnormal performance/brain activation patterns are primarily the result of aberrant early visual cortex activity or are the result of modulation from prefrontal and/or limbic systems. Electroencephalography (EEG) in Chapters 2 and 3 is better suited to discern this, as it can characterize fast changing neuronal dynamics not possible with fMRI.

1.3. Methodology: EEG and fMRI

There are many tools and methods available to interrogate visual processing function in the human brain. The choice of which to use is based on the type of neurophysiology one wishes to measure and the technical limitations inherent in each method.

EEG has been used for decades to study electrical activity in the brain (27; 28). The sources consist of populations of pyramidal neurons and their generation of local field potentials (LFP) as a result of synchronous synaptic activity. The distribution of electrical potentials recorded at the scalp is influenced by the conductivity of the tissue (skull, scalp, cerebrospinal fluid) between the sources and the scalp.

Through averaging of the evoked activity time-locked to an outside stimulus (such as light, sound etc.), scientists have been able to improve the signal-to-noise ratio

of these small evoked potentials and characterize components depending on their polarity and timing relative to the stimulus. In the visual domain, these event related potentials (ERP) can reflect very early processing such as the N75 or the P100 that are impossible to capture or characterize using fMRI. ERPs have the advantage of excellent time resolution (on the order of milliseconds) and have been used extensively in the study of patients with neuropsychiatric disorders (for review see (29)). Some components have high heritability (from .6 to .8) (30; 31) and may prove to be useful as endophenotypes or translational biomarkers. Chapter 2 investigates the use of EEG and ERP, specifically the P100 and N170, to interrogate visual processing deficits in amplitude and latency in AN and BDD patients.

In the latter part of the 20th century, and especially since the 1990's, there has been an explosion in development of noninvasive functional and structural brain imaging methods, mostly centered on magnetic resonance imaging (MRI). Functional MRI (fMRI) maps metabolic and hemodynamic responses, which then infer the underlying local changes in neuronal activity. The most used contrast is the blood oxygenation level dependent signal (32), which is inversely proportional to the level of deoxyhemoglobin content. Thus, following increases in neuronal activity, increases in arterial blood flow lead to increases in venous blood flow, which results in lower deoxyhemoglobin content and an increased BOLD signal. However, the BOLD response is a delayed version of the neurophysiological response, since changes in blood flow occur over a much slower timescale (from hundreds of milliseconds to seconds). For example, the response of V1 neurons begin within 20-50 seconds of the onset of visual stimulus, while the vascular

response is apparent after 1.5-2.5 seconds (33). However, the strength of MRI lies in the high spatial resolution relative to EEG, on the order of millimeters.

In order to integrate ERP and fMRI data, we determined associations between the individual ERP components and their corresponding fMRI spatial maps using independent components analysis (ICA). ICA is a form of blind source separation that separates a signal into a linear combination of statistically independent components. Spatial ICA, when applied to fMRI data, decomposes the signal into independent spatial maps; temporal ICA, on the other hand, finds temporally independent timecourses and can be applied to EEG data. In Chapter 3, we used Fusion ICA, which combines these two ICA techniques by joint estimation of the temporal ERP components and spatial fMRI components (34). We derived a spatiotemporal profile of visual processing in our tasks by first generating ERP waveforms and fMRI spatial maps, then performing Fusion (or joint) ICA. This joint analysis makes use of a shared linear mixing matrix used to derive both the fMRI and EEG sources. These spatial maps were then compared between groups to determine areas of dysfunction, thus integrating temporal information from EEG signals into fMRI spatiotemporal modeling.

1.4 Significance and Implications

The results of these studies suggest a general dysfunction in lower-order stages of visual processing, which be a reflection of a shared, or similar, phenotype that crosses traditional clinical classification boundaries. Clinically, AN and BDD are psychiatric disorders that involve distortion of one's appearance. They overlap in terms of specific areas of appearance concerns as well as severe body image symptoms and low self-esteem. General dysfunction in visual processing found in this study may explain

underlying similarities in perceptual distortions between these two disorders, including focus on symptom-specific areas of appearance concern, increased detail processing (e.g. small defects of the skin in BDD, or areas of cellulite or “fat” on the thighs in AN), and decreased holistic processing (inability to contextualize that the imperfections in appearance features are small relative to one’s whole face or body). Because the areas of dysfunction are linked to ERP components as early as 100 ms post-stimulus, abnormalities in lower level visual processing of basic feature characteristics may occur in AN and BDD individuals’ primary and secondary visual areas before this visual information is transferred forward to higher level memory, emotion, and cognitive areas.

These findings have clinical relevance for informing the development of treatments to address perceptual distortions, e.g., perceptual retraining to address imbalances in early dorsal versus ventral visual streams. Moreover, novel perceptual retraining interventions may be facilitated by real-time simultaneous fMRI and EEG feedback.

Additionally, abnormalities in P100 and N170 components and their corresponding activation maps could serve as markers for visual processing deficiencies as a phenotype or endophenotype that may contribute to AN or BDD symptoms. If so, these could be tested for their ability to predict risk of developing the illness. The P100 and N170 components could also potentially also be used to follow improvements over the course of various treatments.

1.5. Organization of the Dissertation

The layout of the dissertation is as follows.

The overarching goal of my work has been to understand where and when abnormalities occur during visual processing in AN and BDD. In Chapter 2, we investigate electrophysiological correlates using EEG and ERP by focusing on the P100 and N170 visual components and their amplitudes and latencies. Results suggest that individuals with AN and those with BDD have similar deficits in processing configural visual information for appearance- and non appearance-related stimuli, as well as possible inappropriate deployment of detailed processing. We also found associations between these ERP measures and clinical variables.

In Chapter 3, we find connections between the individual ERP components and their corresponding fMRI spatial maps using a relatively new analysis technique called Fusion ICA, which combines EEG and fMRI by joint estimation of the temporal ERP components and spatial fMRI components. We use dual regression to extract individual spatial maps, and found associations between these subject-level activations and face attractiveness in the BDD group. We found that both AN and BDD showed hypoactivity in dorsal visual stream systems for low spatial frequencies, suggesting that a common deficiency in holistic processing is operating in primary visual structures as early as 100 ms post-exposure, which extends later in time (170 ms) into dorsal higher-order processing regions.

In Chapter 4, I present related works completed during my graduate studies. In section 4.1, I present a review article on a neurobiological model for BDD, of which visual processing and neuroimaging are major sections. In section 4.2, I present an article

we published using diffusion tensor imaging (DTI) and probabilistic tractography to investigate white matter integrity in BDD in tracts connecting visual, frontostriatal, and limbic systems.

In Chapter 5, I summarize the findings from my original research. Finally, in Chapter 6 I outline ongoing and future studies.

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CHAPTER 2

This section is adapted from:

Li W, Lai TM, Loo SK, Strober M, Mohammed-Rezazadeh I, Khalsa S, & Feusner J. Aberrant Early Visual Neural Activity in Body Dysmorphic Disorder and Anorexia Nervosa. Accepted in *Frontiers of Human Neuroscience*.

Title Page

**Aberrant Early Visual Neural Activity and Brain-Behavior
Relationships in Anorexia Nervosa and Body Dysmorphic
Disorder**

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**Keywords: Anorexia Nervosa, Body Dysmorphic Disorder, electroencephalography,
visual processing, Dorsal ventral streams**

Abstract word count:

Article body word count: 4452

of figures: 6

of tables: 6

Supplemental information: 1 page

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Abstract:**Background:**

Body dysmorphic disorder (BDD) and anorexia nervosa (AN) share the clinical symptom of disturbed body image, which may be a function of perceptual distortions. Previous studies suggest visual or visuospatial processing abnormalities may be contributory, but have been unable to discern whether these occur early or late in the visual processing stream. We used electroencephalography (EEG) and visual event related potentials (ERP) to investigate early perceptual neural activity associated with processing visual stimuli.

Methods:

We performed EEG on 20 AN, 20 BDD, 20 healthy controls, all unmedicated. In order to probe configural/holistic and detailed processing, participants viewed photographs of faces and houses that were unaltered or filtered to low or high spatial frequencies, respectively. We calculated the early ERP components P100 and N170, and compared amplitudes and latencies among groups.

Results:

P100 amplitudes were smaller in AN than BDD and healthy controls, regardless of spatial frequency or stimulus type (faces or houses). Similarly, N170 latencies were longer in AN than healthy controls, regardless of spatial frequency or stimulus type, with a similar pattern in BDD at trend level significance. N170 amplitudes were smaller in AN than controls for high and normal spatial frequency images, and smaller in BDD than controls for normal spatial frequency images, regardless of stimulus type. Poor insight correlated with lower N170 amplitudes for normal and low spatial frequency faces in the BDD group.

Conclusions:

Individuals with AN exhibit abnormal early visual system activity, consistent with reduced configural processing and enhanced detailed processing. This is evident regardless of whether the stimuli are appearance- or non appearance-related, and thus may be a reflection of general, early perceptual abnormalities. As N170 amplitude could be a marker of structural encoding of faces, lower values may be associated with perceptual distortions and could contribute to poor insight in BDD. Future studies may explore visual ERP measures as potential biomarkers of illness phenotype.

Introduction

Individuals with body dysmorphic disorder (BDD) are preoccupied with perceived defects in their appearance, which are not noticeable or are slight to others (American Psychiatric Association, 2013). They subsequently experience significant distress, disability, and functional impairment, often accompanied by depression and suicidality (Phillips, 2005). In addition, they are often delusional in their beliefs (Eisen et al., 2006), and frequently present to plastic surgeons and dermatologists instead of mental health clinicians. BDD affects approximately 1-2% of the population (Rief et al., 2006; Otto et al., 2001; Faravelli et al., 1997; Bienvenu et al., 2000), yet is still under-studied and under-recognized.

Individuals with anorexia nervosa (AN) also have similar body image distortions, although by DSM definition this relates principally to their body weight or shape (American Psychiatric Association, 2013). Individuals with AN are often convinced that they are overweight and appear “fat,” despite significant evidence to the contrary. They then restrict their caloric intake through self-starvation, which can lead to severe malnutrition, emaciation, and in some cases death (Sullivan, 1995).

Perceptual distortions of appearance may therefore be a cardinal feature across AN and BDD. fMRI studies using own-face (Feusner et al., 2010), other-face (Feusner et al., 2007), and house stimuli (Feusner et al., 2011) all found abnormalities in primary and/or secondary visual processing systems in BDD, particularly for image types that selectively conveyed configural and holistic information. Similar experiments have not been conducted in AN, although several neuroimaging studies suggest abnormal brain activation when visually processing body images (Sachdev et al., 2008; Uher et al., 2005;

Wagner et al., 2003). Multiple studies additionally suggest imbalances in local (detail) vs. global processing in AN (56-61). Moreover, a study investigating the body inversion effect found AN individuals had deficits in discrimination of upright body images, suggesting deficits in configural processing (Urgesi et al., 2013).

Naturalistic visual stimuli, the most studied of which are faces, engage visual processing on multiple levels related to the type of information extracted (Bruce and Young, 1986). Perceptual inputs are analyzed to extract simple features, which are then combined to construct a structural model that can be compared with faces in memory. Two types of visual information, configural and featural, travel through dorsal and ventral visual streams, respectively (Goodale and Milner, 1992). Configural processing can be conceptualized as sensitivity to first order relations (the relative positions of the features), holistic processing of these features into a gestalt, and sensitivity to the relations between the features (such as distance between features) (Maurer et al., 2002). With configural processing, parts are not individually represented but instead recognized as ‘templates’ (Tanaka and Farah, 1993). Featural processing can be conceptualized as the componential analysis of features that can be measured independently from each other, are local in their spatial extent, and are marked by discontinuities (Bartlett et al., 2003). This is also known as local part-based or fragmented-based processing (Schwaninger et al., 2002).

Our working model of visual processing dysfunction in BDD and AN is a primary deficit in configural/holistic processing (Li et al., 2013). This may result in a secondary, “inappropriate,” reliance on featural/part-based processing, which is utilized in situations in which healthy controls normally deploy configural/holistic processing. This may result

in a conscious perception dominated by featural/part-based information (details), as a result of a diminished configural/holistic template to aid in integration. fMRI experiments studying BDD (Feusner et al., 2010, 2011, 2007) corroborate this model of visual processing dysfunction. A limitation of these prior fMRI studies (due to limited temporal resolution) is that it remains unclear if abnormal performance/brain activation patterns are primarily the result of aberrant early visual cortex activity or are the result of modulation from prefrontal and/or limbic systems. Electroencephalography (EEG) is better suited to discern this, as it can characterize fast changing neuronal dynamics that are not possible with fMRI. To date there have been no studies that have investigated early electrophysiological components in response to face or house processing in AN or BDD.

Evidence from a neuroimaging study in BDD, using own- and other-faces (Feusner et al., 2010) suggests dysfunction in early visual systems, including early extrastriate cortex. A similar study using houses stimuli also demonstrated abnormal visual system activation, although in later regions in the visual stream (lingual and parahippocampal gyri) (Feusner et al., 2011). We used face and house stimuli to probe the early visual systems in AN and BDD. Event related potential (ERP) components in response to faces have been well studied in healthy controls, and facial flaws are a common concern in BDD. Houses provide a figure similar in complexity to faces with neutral salience. (Bodies stimuli, although more relevant to appearance concerns for AN subjects, were not used as their P100 and N170 components are not as well studied or characterized as for faces or houses.)

EEG: P100 and N170 event related potential components

The P100 and N170 are visual processing components evoked by presentations of faces and objects. The P100 is the first positive visual evoked potential apparent 80-120 ms post stimulus (Spehlmann, 1965; Herrmann et al., 2005). A study that measured the P100 amplitudes to images of faces and houses, filtered to include only certain spatial frequencies, found the P100 was preferentially larger for low spatial frequency faces/houses and smallest for high spatial frequency faces/houses (Nakashima et al., 2008). Thus, the P100 may index early configural processing.

The N170 is a large negative component that is robustly evoked by face stimuli (Rossion et al., 2000; Bentin et al., 1996), although it also shows varying degrees of activation by other stimuli such as houses, cars, and other objects. It is most prominent in occipito-temporal electrodes, and occurs about 150-180 ms post-stimulus. It may reflect both configural and featural processing (Sagiv and Bentin, 2001; Bentin et al., 1996). Bentin et al. (1996) found the N170 was larger in response to eyes presented in isolation compared to full faces, suggesting the N170 was responsive to featural processing. However, another study found that face representations that require only configural processing generate similar N170 amplitudes as normal photographs of faces (Sagiv and Bentin, 2001). These results can be reconciled by the observation that in most situations faces are primarily processed configurally, whereas analytic, featural processing requires a greater recruitment of neuronal populations, as reflected in a larger N170. Campanella (Campanella et al., 2006) found diminished P100 and N170 components in response to faces in schizophrenia patients; the decreased amplitudes were ascribed to deficits in configural processing, which converges with results from several other studies (Javitt, 2009; Urgesi et al., 2013; Deruelle et al., 1999; Streit et al., 2001; Herrmann et al., 2004).

Our model, in which the primary abnormality is reduced configural processing in BDD and AN, predicts a similar pattern (although perhaps not the same degree) of abnormal EEG responses.

Spatial Frequencies and their relation to configural/featural processing

In our Faces and Houses Tasks, we probed individuals' configural and featural processing by using low-pass (LSF) and high-pass (HSF) spatial frequency-filtered visual images, respectively, as has been performed previously in healthy controls using EEG (Pourtois et al., 2005; Halit et al., 2006). Early vision filters images at multiple spatial scales, tuned to different bandwidths of spatial frequencies. Discrimination and detection of simple sine wave patterns are predicted by the contrast of their individual component spatial frequencies, implying the visual system decomposes the patterns with spatial frequency filters (Campbell and Robson, 1968). Marr (Marr, 1982) proposed that the visual system uses a multiscale representation of the image, constructing a stable, quick, coarse gestalt that is later fleshed out with fine-scale information.

It has been postulated that different levels of spatial frequencies in images convey different types of information for visual processing. LSF images convey information about coarse holistic features such as pigmentation or shading (Morrison and Schyns, 2001) while HSF images convey information about contours and edges. Neurons in primary visual cortex dedicate their first transient responses to processing LSF sinusoidal gratings and later shift their tuning curves to finer information (HSF gratings) (Bredfeldt and Ringach, 2002). Psychophysical evidence indicates that LSF gratings are resolved faster than their HSF analogs (Gish et al., 1986; Parker and Dutch, 1987). Finally, LSF faces have larger holistic effects compared to HSF faces for the whole-part advantage and

composite face paradigms (Goffaux and Rossion, 2006).

Previous functional neuroimaging studies of visual processing in BDD used images filtered to LSF and HSF to selectively activate configural and featural processing, respectively (Feusner et al., 2007, 2011). We analyzed the ERP responses to these images to draw inferences about abnormalities in configural or featural visual processing in AN and BDD. We also included the unaltered (“Normal Spatial Frequency,” or NSF) images as they should engage both configural and featural processing.

Hypotheses

We hypothesized that AN and BDD individuals would demonstrate abnormal early configural processing deficits along with greater reliance on detailed strategies, as both experience appearance-related concerns that could be attributed to perceptual distortions. Thus, we expected lower P100 and N170 amplitudes for AN and BDD relative to controls for normal and low detail faces, which would reflect deficiencies in configural processing. Similarly, we expected delayed N170 latencies for AN and BDD relative to controls for normal and low detail faces, due to secondary, excessive reliance on detailed strategies, which are slower than configural strategies (Goodale and Milner, 1992). We predicted the same patterns for house stimuli; although the previous study in BDD found abnormalities in later visual stream regions, we predicted that similar, earlier aberrant electrophysiological components as for faces might feed forward to contribute to later diminished activation. Abnormal ERP components for house stimuli would therefore reflect general, early visual system deficiencies that are not limited to appearance-related stimuli.

We also predicted that abnormalities in early visual processing associated with

these ERP components would be associated with the clinical variable of poor insight, as aberrant perception would make it difficult for one to refute what they see, even in the presences of contrary evidence. Supporting this, a previous diffusion tensor imaging (DTI) study in BDD found associations between insight and white matter tracts connecting visual systems with emotion and memory systems (Feusner et al., 2014). We hypothesized that for the LSF and NSF images there would be an association between lower insight and lower amplitudes (N170 and P100) and longer latencies (N170) in BDD and AN.

Methods and Materials

Participants

We enrolled 20 individuals meeting DSM-IV-TR criteria for BDD, 20 with AN, and 20 age- and gender-matched healthy controls. All participants were between ages 18-30 and all were unmedicated. Each BDD participant received a clinical evaluation by J.D.F, who has clinical expertise in BDD. Each AN participant received a clinical evaluation by M.S. or S.K., or who have clinical expertise in AN. We used the Mini International Neuropsychiatric Inventory (MINI) to determine comorbid diagnoses (Sheehan et al., 1998). Severity of other psychiatric symptoms was measured using validated clinical scales: the Hamilton Anxiety Rating Scale (HAMA) (Hamilton, 1960), the Brown Assessment of Beliefs scale (BABS, measuring insight about perceived defects and psychiatric illness) (Eisen et al., 1998), and the Montgomery-Asberg Depression Rating Scale (MADRS) (Williams and Kobak, 2008). BDD participants received the BDD version of the Yale–Brown Obsessive–Compulsive Scale (BDD-

YBOCS) (Phillips et al., 1997), and AN participants received the Eating Disorder Examination V16.0D (EDE) (Fairburn et al., 2008).

BDD inclusion/exclusion criteria:

The UCLA Institutional Review Board approved this study. Written informed consent was obtained from all participants. Unmedicated individuals who met criteria for BDD as determined by the BDD Diagnostic Module (32), modeled after the DSM-IV, and who scored ≥ 20 on the BDD-YBOCS were eligible.

AN inclusion/exclusion criteria:

AN participants were unmedicated and were required to be weight-restored (BMI of ≥ 18.5); however, they must have previously met full DSM-IV criteria for AN. We chose to study weight-restored AN individuals to avoid confounds of starvation on brain activity. Eligible participants also had to meet all other current criteria for AN on the MINI, except for amenorrhea.

HC inclusion/exclusion criteria:

HC could not meet any criteria for Axis I disorders, including substance use disorders, on the MINI.

Inclusion/exclusion criteria for all participants:

Participants were free from psychoactive medications for at least 8 weeks prior to entering the study. All had normal or corrected visual acuity, as verified by Snellen eye chart. Exclusion criteria included other concurrent Axis I disorders aside from major depressive disorder, dysthymia, panic disorder, social phobia, or generalized anxiety disorder, as mood and anxiety disorders are frequently comorbid in this population

(Veale et al., 1996; Gunstad and Phillips, 2003; Ruffolo et al., 2006; Zimmerman and Mattia, 1998; Phillips et al., 2006b, 2006a; Hollander et al., 1993; Perugi et al., 1997; Kennedy et al., 1994; Swinbourne and Touyz, 2007).

	Anorexia Nervosa (AN)	Body Dysmorphic Disorder (BDD)	Healthy Control (HC)	p values
N	20	20	20	
Gender (F/M)	18/2	18/2	18/2	
Age	23.40±3.22	24.60±5.13	22.55±4.02	F=1.2, p=.31
Highest Grade Completed	15.00±2.11	16.05±3.47	14.38±2.51	F=1.83, p=.171
BDD-YBOCS (BDD) or EDE (AN) Score	2.48±1.25	29.05±5.38	-	
HAMA	7.30±6.69 ^a	10.20±7.21 ^a	2.05±1.73 ^b	F=10.27, p<.001
MADRS	7.75±9.10 ^a	14.25±7.56 ^a	0.95±1.32 ^b	F=18.74, p<.001
BABS	11.53±5.71 ^a	14.95±3.35 ^b	N/A	t=2.30. df=38 p=.027

Table 1: Demographics and Psychometrics for AN, BDD, and healthy control

(HC) participants. Letter superscripts that are different indicate significant pairwise differences from post hoc t-tests, at p<.05.

Face and House-matching tasks

There were 3 categories of face and house stimuli: HSF, non-filtered (normal spatial frequency – NSF), and LSF; and 1 control condition made of non-filtered circles/ovals (for the faces task) or squares/rectangles (for the houses task) for behavioral responses.

For faces, we used digitized gray-scale photographs of male and female faces. The faces, validated for neutral emotional expression, came from the Macbrain database, Facial Emotional Stimuli, the University of Pennsylvania and the Psychological Image Collection at Stirling. We then filtered these images to various spatial frequencies as previously described (Feusner et al., 2007).

After a 500 ms crosshair presentation, subjects pressed a button corresponding to which of two images match the target image in the top half of the screen, with image duration of 2 sec. (see Fig. 1) (Feusner et al., 2007). There were 72 trials for each category (HSF, NSF, LSF, and shapes), and spatial frequencies were not mixed within each trial. Each face or house had size 8.5cm x 8.5cm, and subtended a visual angle of 4.8°.

EEG Acquisition

All subjects were seated 1 m away from the screen. EEG data were recorded using a high density 256-channel Geodesic Hydrocel Sensor Net (Electrical Geodesics, Inc.) with a sampling rate of 250 Hz in a copper shielded room that was dimly lit. Between experiments, we checked to make sure electrode impedances were below 50kΩ. Data preprocessing included bandpass filtering from 0.1 to 30 Hz for visual ERPs.

Segmentation:

Data were segmented 200 ms before and 500 ms after the presentation of the stimulus for face, and house matching tasks.

Artifact Detection:

Eye blink and movement artifacts were extracted and removed using temporal Independent Component Analysis (ICA) in EEGLAB (Delorme and Makeig, 2004). Segments with > 10 bad channels were removed and interpolated from neighboring electrodes. In addition, channels and segments were visually inspected to account for artifacts missed through automatic detection. We used an interpolation algorithm to reconstruct channels marked as bad by the artifact detection algorithms. Segments were then averaged across each stimuli condition, and grand averaged over all subjects. Event related potentials (ERP) were baseline-corrected using the 200 ms baseline prior to the stimulus onset for correction. All channels were referenced to an average reference of all electrodes except electrooculography (EOG).

Statistical Analyses

Behavioral Analyses:

Accuracy (% correct) and mean correct response times were computed for each condition. We submitted data from the faces and houses task to a mixed measures ANOVA with Group (AN, BDD, or controls) as a between-groups factor and spatial frequency (high, normal, low) and stimulus type (faces, houses) as within-subjects factors. We submitted data from our shapes stimuli to a separate mixed measures ANOVA with stimulus type (circles and squares) as a within-subjects factor and Group (AN, BDD, or controls) as a between-groups factor. (There was no spatial frequency

factor for the shapes, as they were not spatial frequency filtered.) We removed two outliers, defined as cases more than 1.5 times the interquartile range (above or below the 75th or 25th percentile, respectively) on stem and leaf plots in SPSS.

Electrophysiology:

Amplitudes and latencies for P100 and N170 components were measured at a group of right hemispheric occipito-temporal electrodes (TP8, TP10, P8, PO8, P6 CP6, P10); these electrodes were chosen based on previous studies showing the N170 signal is stronger in the right hemisphere versus the left (Rossion et al., 2003; Bentin et al., 1996). Amplitudes were quantified for each condition as the peak voltage measured within 60ms windows centered on 100ms and 170ms for the P100 and N170, respectively. Peak latency was measured as the latency at this peak voltage. These amplitudes and latencies were then submitted to a three way mixed measures ANOVA with group (AN, BDD, controls) as the between groups factor and spatial frequency (high, normal, low) and stimulus type (faces, houses) as the within group repeated measures factor. Because we were interested in group differences, we used estimated marginal means of any significant effects involving group (group, group by spatial frequency, group by stimulus type, and group by stimulus type by spatial frequency) and, following Fisher's LSD procedure, pairwise t-tests (uncorrected) to explore for differences between groups.

We performed Pearson's correlations between BABS scores and LSF and NSF component measures (N170 latency/amplitude, P100 amplitude) for faces and houses, with a significance level set at $p < .05$, one-tailed, Bonferroni-corrected.

Behavioral Results

Reaction time: On the faces/houses tasks, there was a significant spatial frequency effect ($F_{2,53}=257.61$, $p<.001$), but no significant group ($F_{2,53}=1.77$, $p=.18$), stimulus type ($F_{1,53}=.004$, $p=.95$), spatial frequency by group ($F_{4,108}=.58$, $p=.68$), stimulus type by group ($F_{2,53}=.64$, $p=.53$), spatial frequency by stimulus type ($F_{2,53}=2.22$, $p=.12$), or stimulus type by spatial frequency by group effects ($F_{4,108}=.87$, $p=.49$). To follow up on the significant spatial frequency effect, we performed pairwise comparisons among spatial frequencies. There were significantly shorter reaction times for the LSF than the NSF (mean difference=33 ms, $p<.001$) or HSF (mean difference=152 ms, $p<.001$) images, while there were significantly shorter reaction times for NSF than HSF (mean difference=119 ms, $p<.001$) images.

On the shapes stimuli, there were no significant stimulus type ($F_{1,54}<.001$, $p=.99$), group ($F_{2,54}=1.27$, $p=.29$), or stimulus type by group ($F_{2,54}=1.36$, $p=.27$) effects for reaction time.

Accuracy: All groups performed accurately on both face and house tasks as well as the shapes control stimuli (>95% on all tasks). On the faces/houses tasks, there was a significant spatial frequency effect ($F_{2,53}=24.96$, $p<.001$), but no significant group ($F_{2,53}=1.07$, $p=.35$), stimulus type ($F_{1,53}=3.95$, $p=.052$), spatial frequency by group ($F_{4,108}=1.13$, $p=.35$), stimulus type by group ($F_{2,53}=.65$, $p=.52$), spatial frequency by stimulus type ($F_{2,53}=.09$, $p=.91$), or stimulus type by spatial frequency by group effects ($F_{4,108}=2.33$, $p=.06$). To follow up on the significant spatial frequency effect, we performed pairwise comparisons among spatial frequencies. Participants were

significantly more accurate on LSF compared to NSF (mean difference=1.0%, $p<.001$) or HSF (mean difference=1.9%, $p<.001$) images, while they were significantly more accurate on NSF compared to HSF (mean difference=.9%, $p=.007$) images.

On the shapes stimuli, there were no significant stimulus type ($F_{1,54}<1.27$, $p=.26$), group ($F_{2,54}=.41$, $p=.66$), or stimulus type by group ($F_{2,54}=1.61$, $p=.21$) effects on accuracy.

We also examined the effects of task behavioral performance on our ERP measures by testing correlations between reaction time and each measure (P100 amplitude, N170 amplitude, N170 latency). No correlations were significant at a corrected threshold of $.05/3=.016$ (Table S3).

	Anorexia Nervosa (AN)	Body Dysmorphic Disorder (BDD)	Healthy Controls (HC)
Face Accuracy	95.7%	96.3%	96.8%
Face Reaction Time (ms)	855.2±118.2	868.7±106.8	800.3±98.9
House Accuracy	95.9%	96.8%	96.8%
House Reaction Time (ms)	869.9±164.0	837.7±119.0	803.3±119.3
Shape Accuracy	96.4%	95.5%	95.7%
Shape Reaction Time (ms)	769.9±207.6	763.3±72.9	746.0±85.3

Table 2: Accuracy and Reaction times for Face and House tasks, with control stimuli (shapes) as comparison.

P100 Amplitude	
Effect	Statistics
main effect: group	$F_{2,57}=3.70, p=.03$
main effect: stimulus type	$F_{1,57}=.09, p=.76$
main effect: spatial frequency	$F_{2,56}=8.7, p=.001$
interaction effect: stimulus type x spatial frequency	$F_{2,56}=2.81, p=.07$
interaction effect: stimulus type x group	$F_{2,57}=1.71, p=.19$
interaction effect: group x spatial frequency	$F_{4,114}=.85, p=.50$
interaction effect: group x spatial frequency x stimulus type	$F_{4,114}=.21, p=.93$

Table 3: Omnibus mixed measures ANOVA statistics for P100 Amplitude.

Follow-up tests on the group effect found AN had significantly smaller amplitudes than controls ($p=.014$) and BDD ($p=.04$).

N170 Amplitude	
Effect	Statistics
main effect: group	$F_{2,57}=3.74, p=.03$
main effect: stimulus type	$F_{1,57}=11.42, p=.001$
main effect: spatial frequency	$F_{2,56}=34.24, p=.001$
interaction effect: stimulus type x spatial frequency	$F_{2,56}=.45, p=.64$
interaction effect: stimulus type x group	$F_{2,57}=.02, p=.56$
interaction effect: group x spatial frequency	$F_{4,114}=3.54, p=.009$
interaction effect: group x spatial frequency x stimulus type	$F_{4,114}=.068, p=.41$

Table 4: Omnibus mixed measures ANOVA statistics for N170 Amplitude.

Follow-up tests on the group effect found AN had significantly smaller amplitudes than controls ($p=.011$) and BDD had a trend for smaller amplitudes than controls ($p=.055$). Follow-up tests on the group by spatial frequency effect found AN had significantly smaller amplitudes vs controls for HSF ($p=.001$) and NSF ($p=.034$) images, while BDD had significantly smaller amplitudes vs. controls for NSF ($p=.034$) images.

N170 Latency	
Effect	Statistics
main effect: group	$F_{2,57}=3.39, p=.041$
main effect: stimulus type	$F_{1,57}=8.18, p=.006$
main effect: spatial frequency	$F_{2,56}=25.05, p=.001$
interaction effect: stimulus type x spatial frequency	$F_{2,56}=8.01, p=.001$
interaction effect: stimulus type x group	$F_{2,57}=.37, p=.69$
interaction effect: group x spatial frequency	$F_{4,114}=1.44, p=.23$
interaction effect: group x spatial frequency x stimulus type	$F_{4,114}=.68, p=.61$

Table 5: Omnibus mixed measures ANOVA statistics for N170 Latency.

Follow-up tests on the group effect found that AN had significantly longer latencies than controls ($p=.016$) and BDD had a trend for longer latencies than controls ($p=.059$).

		Faces			Houses		
	Spatial Frequency	AN	BDD	Controls	AN	BDD	Controls
P100 mean	LSF	$1.35\pm.29$	$3.72\pm.63$	$2.82\pm.56$	$2.17\pm.46$	$3.05\pm.68$	$3.2\pm.54$

amplitudes	NSF	1.45±.27	3.77±.53	2.81±.63	1.45±.27	3.77±.53	2.81±.63
(μV)	HSF	1.33±.22	3.33±.53	2.78±.51	1.33±.22	3.33±.53	2.78±.51
N170 mean	LSF	.72±.25	.93±.41	1.77±.59	.12±.5	.47±.37	.25±.61
amplitudes	NSF	.66±.22	1.15±.57	2.08±.61	.21±.51	.67±.40	.63±.58
(μV)	HSF	.98±.27	2.76±.57	3.29±.81	.47±.41	.84±.41	2.39±.71
N170 mean	LSF	165.2±4.77	164.6±3.30	157.6±3.50	177.6±4.94	176±3.24	161.6±3.56
latencies	NSF	164.8±4.55	158.6±2.54	155±3.53	173.8±4.97	170.8±3.24	163.8±3.77
(ms)	HSF	174.6±3.78	177.6±2.16	173±3.12	177.6±4.74	174.6±2.43	171.2±3.94

Table 6: Means and SEMs for P100 amplitudes, N170 amplitudes, and N170 latencies

ERP waveforms for both faces and houses are shown in Fig. 2.

Electrophysiological results

P100 amplitude

We found a significant group effect ($F_{2,57}=3.70$, $p=.031$) and spatial frequency effect ($F_{2,56}=8.70$, $p=.001$). (Statistics for all main and interaction effects can be found in Table 3.) To follow up the significant group effect, we performed group pairwise comparisons. The AN group had significantly lower amplitudes than BDD (mean difference=1.48, $p=.014$) and controls (mean difference=1.23, $p=.04$). The BDD group did not significantly differ from the controls ($p=.66$).

We investigated this further with a post hoc analysis using time–frequency analysis, specifically event-related spectral perturbations (ERSP), to understand if differences in alpha or theta power or intertrial coherence could explain the AN amplitude difference. However, we did not find any significant differences between

groups. Additionally, there were no differences in sleep or tiredness ratings. (See Supplemental Information).

N170 amplitude

We found a significant group effect ($F_{2,57}=3.74$, $p=.030$), spatial frequency effect ($F_{2,56}=34.24$, $p=.001$), stimulus type effect ($F_{1,57}=11.42$, $p=.001$), and group by spatial frequency effect ($F_{4,114}=3.54$, $p=.009$). (Statistics for all main and interaction effects can be found in Table 4.)

To follow up the significant group effect, we performed group pairwise comparisons. The AN group had significantly lower amplitudes than controls (mean difference=1.32, $p=.011$), while the BDD group had a trend for lower amplitudes than controls (mean difference=.98, $p=.055$). The AN group did not significantly differ from the BDD group ($p=.50$).

To follow up on the significant group by spatial frequency effect, we performed group pairwise comparisons for each spatial frequency. The AN group had significantly lower N170 amplitudes for HSF and NSF images compared to controls (HSF: $p=.001$, NSF: $p=.045$), while the BDD group had significantly lower N170 amplitudes than controls for NSF images ($p=.034$).

N170 latency

We found a significant group effect ($F_{2,57}=3.39$, $p=.041$), stimulus effect ($F_{1,57}=8.18$, $p=.006$), spatial frequency effect ($F_{2,56}=25.05$, $p=.001$), and spatial frequency by stimulus type effect ($F_{2,56}=8.013$, $p=.001$). (Statistics for all main and interaction effects can be found in Table 5.)

To follow up the significant group effect, we performed group pairwise comparisons. The AN group had significantly longer latencies than controls (mean difference=8.57, $p=.016$), while the BDD group had a trend for longer latencies than controls (mean difference=6.67, $p=.059$). The AN group did not significantly differ from the BDD ($p=.585$).

See Table 6 for all means and SEMs for P100 amplitudes, N170 amplitudes, and N170 latencies.

Correlations with Clinical Variables:

There were significant positive correlations between BABS and N170 amplitudes for NSF ($r=.54$, $p=.002$) and LSF faces ($r=.48$, $p=.006$) in the BDD group, of which the former survived multiple comparisons (Fig. 5). (There were no significant outliers as determined by leverage values.)

Discussion:

This is the first EEG study in BDD, and the first study to investigate early visual processing components of P100 and N170 in either BDD or in AN. Results suggest that individuals with AN may have deficiencies in visual processing of configural information and enhanced detailed processing, as reflected in decreased P100 amplitudes and delayed N170 latencies, respectively. Because these abnormalities are evident irrespective of stimulus type or spatial frequency, they may be indications of general, early perceptual abnormalities. These effects are likely associated with low-level stimulus characteristics

that are unrelated to appearance. Our results suggest that there may also be a similar deficiency in BDD, for which there was trend level significance for all three ERP measures, in the same direction as in AN. In the BDD group there is evidence for a relationship between diminished structural encoding of faces and greater perceptual distortions, as decreased N170 amplitudes on the faces task correlated with worse insight.

AN individuals showed significantly decreased P100 amplitudes compared to controls and BDD. They also showed significantly decreased N170 amplitudes compared to controls, specifically for high and normal spatial frequencies. In this time frame, this could represent an abnormality in very early configural processing, originating in dorsal extrastriate visual processing areas. This could explain the propensity of AN subjects to fixate on particular “fat” body parts at the exclusion of the whole, as well as the estimation of their size as larger than they actually are (Skrzypek et al., 2001). We found AN had a trend for greater event related desynchronization (ERD) compared to controls (See Supp. Information), which suggest AN could be compensating for their configural deficits through increased attention, effort, or arousal. AN individuals also had significantly delayed N170 latencies, which may be a reflection of enhanced detailed processing. Moreover, the fact that these abnormalities were evident across faces and houses suggests that this represents a general effect for all image types.

We also found that BDD, similar to AN, had significantly lower N170 amplitudes relative to controls for normal spatial frequency images. The BDD group additionally demonstrated significant positive correlations between N170 amplitude and BABS scores for NSF and LSF faces for BDD subjects, such that lower (less negative) amplitude is associated with worse insight (higher BABS scores). The BABS is a seven-item clinician

administered interview that measures the amount of delusional thinking, belief, and insight in clinical populations. Thus, diminished N170 amplitudes, which could be a marker of abnormal structural encoding of faces, leading to an incomplete generation of a complete facial representation, which in turn contributes to perceptual distortions.

Previous research found associations between higher BABS scores and low fractional anisotropy and high mean diffusivity of the inferior longitudinal fasciculus and forceps major (Feusner et al., 2014), as well as lower accuracy on the Navon task in global-local trials (Kerwin et al., 2014), suggesting a consistent association between neural and neuropsychological signatures and poor insight across several studies in BDD.

Previous neuropsychological and neuroimaging studies on visual/visuospatial processing in AN and BDD suggest imbalances in detail and configural processing. Superior attention to detail and poor central coherence compared with controls was observed in both active and recovered AN participants (Roberts et al., 2013; Tenconi et al., 2010). A pattern in the current study of delayed N170 latencies for AN support previous findings of weak central coherence in AN (Lopez et al., 2008, 2009; Kim et al., 2011; Smeets et al., 1999). Our results provide a better estimation of when these abnormalities may occur, as we see differences as early as 100ms after stimulus presentation.

Previous ERP studies in AN using visual stimuli focused on later components associated with emotional responses (Pollatos et al., 2008)(Dodin and Nandrino, 2003). One study found that individuals with AN had larger amplitude and longer latency P300s in response to body images, interpreted as hyperarousal in information processing (Dodin

and Nandrino, 2003), whereas another that focused on N200 and P300 signals in response to emotional faces found abnormalities in emotional processing (Pollatos et al., 2008).

If these findings of abnormal ERP patterns are replicated in future studies, they have the potential to provide useful biomarkers that could be translated to clinical use. If this is the case, they may be more practical than biomarkers from neural patterns generated from fMRI experiments, due to lower cost, higher temporal resolution, and efficiency of EEG. These biomarkers of early visual components would be advantageous because they are less likely to be affected by emotional, subjective, or motivational factors, relative to psychometric measurements, and potentially provide a dimensional “bio-signature” of an important phenotype shared by AN and BDD. Findings from this study would therefore have relevance for informing the development of treatments to address perceptual distortions such as perceptual retraining; these would require different strategies depending on the pathophysiological mechanism driving the symptoms. In addition, these markers can be monitored over time to assess treatment efficacy in common practices to treat these disorders such as cognitive behavioral therapy. In previous studies, EEG and ERPs have been used as biomarkers for Alzheimer’s and Mild Cognitive impairment (MCI) (Jackson and Snyder, 2008) as well as for detecting early visual processing deficits in schizophrenia (Knebel et al., 2011). Thus, abnormalities, or brain-behavior relationships, in P100 or N170 components in AN or BDD could serve as trait markers underlying their visual processing deficits; this could lead to more accurate prediction of AN or BDD risk and diagnosis. In addition, since persistent perceptual disturbance has been found to be a strong predictor of relapse in AN and bulimia nervosa (Keel et al., 2005), it could potentially also be used prognostically.

This study has several limitations. The recordings are observed at the scalp level, so we cannot specify exactly which cortical regions are dysfunctional in these subjects. We also investigated weight-restored AN participants, so results may not be able to be generalized to individuals in the underweight state. Moreover, we cannot determine if effects in the current study are the result of their previous starvation state. Because it is difficult for weight-restored individuals with AN to estimate the previous duration of time they were in the underweight state, we did not have this data available for regression analyses. (Although we examined correlations with lowest BMI attained, we found no significant associations.) In the future, a longitudinal study could track this with better precision in order to explore relationships with duration of starvation state.

Future studies can use source analyses in conjunction with ERPs to further localize, with more precision, abnormalities in the brain. In addition, since images of faces and houses could still elicit higher level processing from emotion or memory areas, using stimuli such as Gabor patches could be more fruitful to investigate lower-level visual processing. Furthermore, joint analyses integrating different neuroimaging modalities such as fMRI or sMRI can enable inferences to be made on both hemodynamic and electrical sources of neural activity.

In the interest of classifying psychopathology across multiple domains of analysis, our results suggest an electrophysiological underpinning behind the symptoms of distorted body image in AN and BDD. These can form the basis of additional dimensions by which we can understand these various disorders that can be used in conjunction with current psychometric and behavioral methods. As a result, new treatments may be developed based on the mechanisms underlying the symptoms; for

example, perceptual retraining with visual stimuli may be more effective for individuals with more severe visual distortions. Thus, this data can be used both as biomarkers of abnormal visual processing and to provide a deeper understanding of abnormal brain activation patterns in these disorders involving body image.

Acknowledgements:

Funding for this work was supported by a grant from the National Institutes for Mental Health (NIMH): R01MH093535 (Feusner) and R01MH093535-02S2 (Feusner) and a grant from the International OCD Foundation (Li). Mr. Li was also supported by a Dissertation Year Fellowship from the UCLA Graduate Division.

We would like to thank Dr. Mark Cohen and Dr. Shafali Jeste for allowing us to use their EEG system and software.

Financial Disclosures:

This study was funded by grant NIH MH093535-02S1 (Feusner) and a grant from the International OCD Foundation (Li). All authors report no biomedical financial interests or potential conflicts of interest.

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ERSP: Event Related Synchronization and Desynchronization

To complement our event related potential (ERP) analyses, we also performed time-frequency analyses using event related spectral perturbances (ERSP) to characterize ongoing EEG rhythmic activity and their frequency power spectrum over time. ERSs provide information about modulations of oscillatory activity not phase-locked to the stimulus, as are ERPs (Pfurtscheller and Lopes da Silva, 1999). We chose to examine event-related synchronization (ERS) and desynchronization (ERD) in the alpha (8-12 Hz) and theta (4-7 Hz) ranges during the first 200 ms post-stimulus; ERD and ERS are considered to be due to decreases or increases in synchrony of the underlying neuronal populations, respectively (Pfurtscheller and Lopes da Silva, 1999). During visual processing, alpha and theta normally respond in opposite ways; theta synchronizes while alpha desynchronizes, relative to baseline (Pfurtscheller et al., 1996). The alpha ERD (and corresponding theta ERS) is thought to be a reflection of activation of cortical areas related to sensory processing, and could be the result of increased attention, effort, or arousal (Pfurtscheller and Lopes da Silva, 1999). We used these frequency measures to better understand the effects of these cognitive and attentional variables on the early visual processing occurring in AN and BDD.

We also used intertrial coherence (ITC) to measure the consistency of phase across trials at each frequency and time point (Makeig et al., 2002). In this way, we are able to investigate any abnormalities in phase synchronization or phase consistency across trials in AN and BDD.

Methods

Single trials (from .5s before stimulus to 2s after) were convolved time locked to

a complex morlet wavelet, setting the number of cycles to be 3 in 1 second. This resulted in 3 Hz as the lowest frequency analyzed. Spectral power modulations were measured relative to a baseline of 200 ms pre-stimulus. We collapsed all three spatial frequencies for these analyses, as we did not have any a priori hypotheses about spatial frequency, and to increase number of trials for the analysis. Comparisons were performed using averaged power or ITC values from time-frequency windows chosen around the frequency and time ranges of interest (Alpha: 8-12 Hz, Theta: 4-7 Hz, P100: 72-128 ms, N170: 140-196 ms). We performed a 4 way ANOVA, with Group (AN, BDD, controls), Electrode (Oz, Pz), Frequency (Alpha 8-12 Hz, Theta 4-7 Hz), and Component (P1, N170) as factors. Significant ANOVAs were submitted to post hoc one-way ANOVAs and Tukey tests to compare pairwise effects of interest.

Results

We found a trend for a group by frequency interaction effect ($F_{2,471}=2.745$, $p=.065$) for the faces task. Post-hoc univariate ANOVAs performed on the individual frequencies showed a trend for a significant difference in the alpha range ($F_{2,235}=3.017$, $p=.051$). Pairwise comparisons found that this was driven by AN having greater alpha desynchronization compared with controls ($p=.041$).

We did not find any significant differences in ITC between groups.

Correlations with Face Ratings

Based on the group results findings, we performed *post hoc* Pearson correlation analyses within the AN group between alpha power and participants' subjective ratings of the attractiveness, aversiveness, and degree to which thoughts of self were triggered when viewing the face stimuli (collected after the experiment). There were no significant

outliers as determined by leverage values. We found a significant positive correlation between alpha power and aversiveness ratings ($r=.67$, $p=.017$). Thus, lower alpha power (which occurs with desynchronization and may reflect increased attention, effort, or arousal) is associated with lower subjective aversiveness of the face.

Correlations with Sleep and Tiredness Ratings

We also performed post-hoc Pearson correlation analyses on the significant measures from the ERP analyses (N170 Amplitude Faces HSF, N170 Latency Houses LSF, P100 Amplitude Faces LSF, P100 Amplitude Faces NSF, and P100 Amplitude Faces HSF) with sleep and tiredness ratings for AN and BDD groups. However, we found no significant associations.

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Figures:

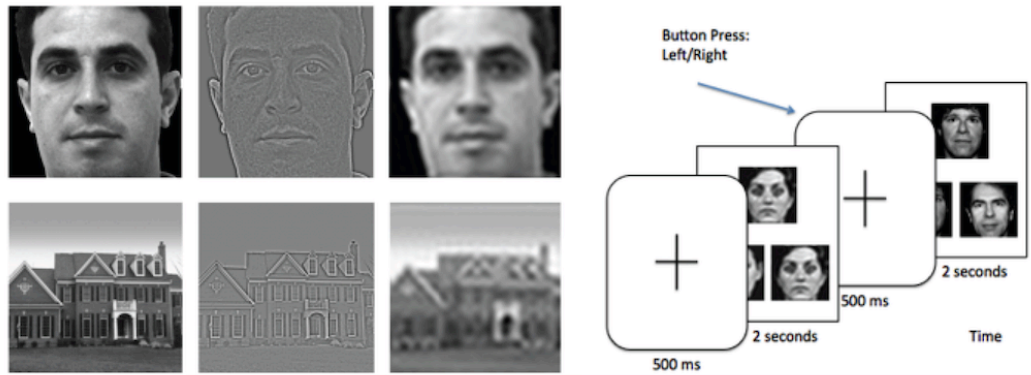


Fig. 1. Left: Example of stimuli used in the experiment, filtered to normal, high, and low spatial frequencies. Right: Task paradigm, consisting of a face or house matching task.

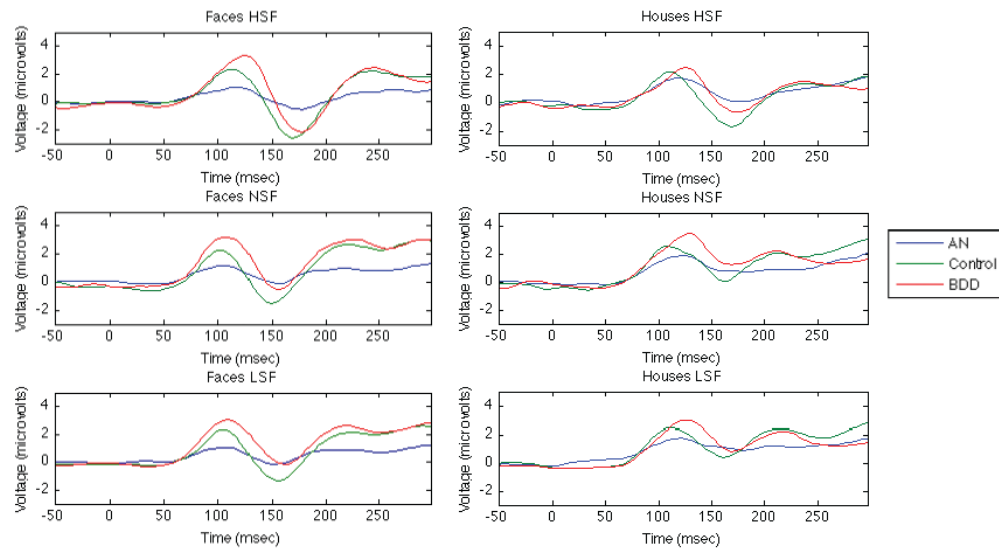


Fig. 2 Group averaged ERP components for Face and House Tasks. The first 50ms are the baseline period, stimulus presentation at time=0.

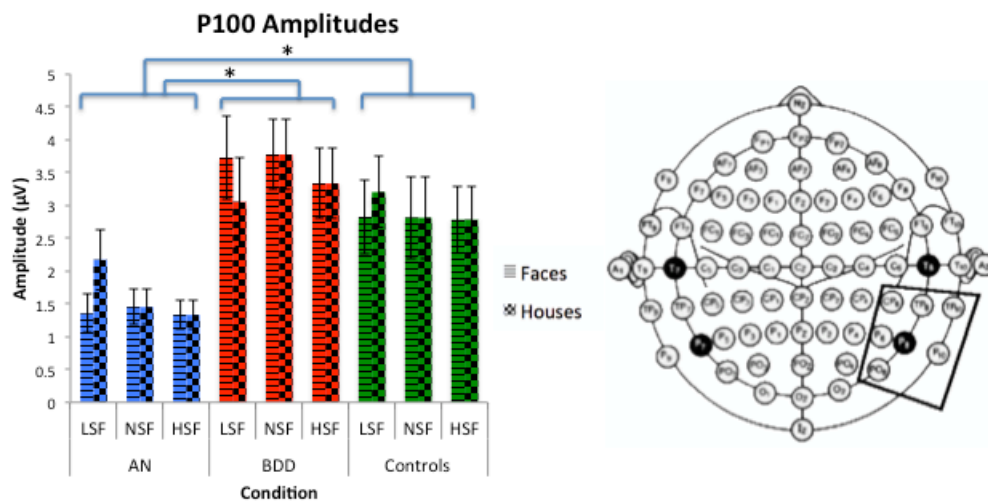


Fig. 3. P100 amplitudes across stimulus type (Faces/Houses), Group (AN, BDD, and Controls), and spatial frequency (LSF=low spatial frequency; NSF=normal spatial frequency; HSF=high spatial frequency). Asterisks denote significant group effects, $p < .05$, showing AN have smaller P100 amplitudes than BDD or controls for all image types.

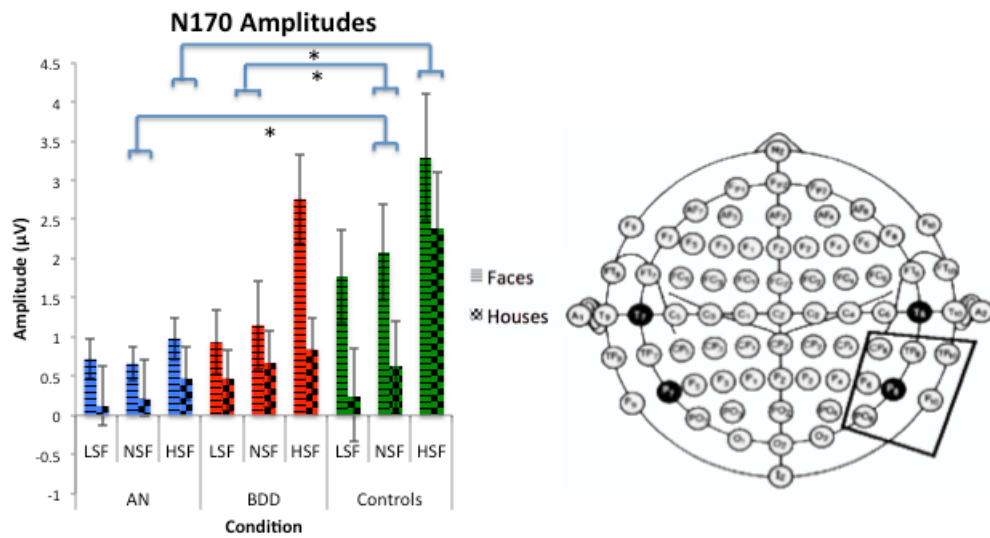


Fig. 4. N170 amplitudes across stimulus type (Faces/Houses), Group (AN, BDD, and Controls), and spatial frequency (LSF=low spatial frequency; NSF=normal spatial frequency; HSF=high spatial frequency). Asterisks denote significant group by spatial frequency effects, $p < .05$, showing AN have smaller N170 amplitudes than controls for HSF and NSF images, while BDD have smaller N170 amplitudes than controls for NSF images.

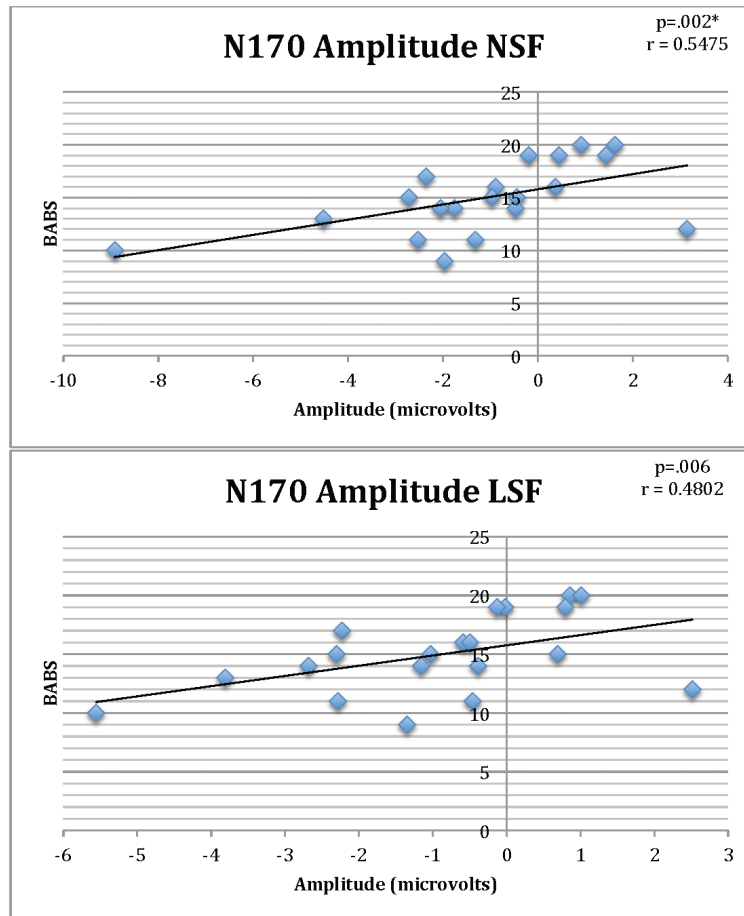


Fig. 6 Correlations of BABS scores and N170 amplitudes for NSF and LSF faces in individuals with BDD. Lower (less negative) amplitude is associated with worse insight (higher BABS scores). *Survives Bonferroni corrections for multiple comparisons

CHAPTER 3

This section is adapted from:

Li W, Lai TM, Bohon C, Loo SK, McCurdy D, Strober M, Bookheimer S, & Feusner J (2015). Anorexia nervosa and body Dysmorphic disorder are associated with abnormalities in processing visual information. *Psychological Medicine*. In Press.

Anorexia nervosa and body dysmorphic disorder are associated with abnormalities in processing visual information

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Background. Anorexia nervosa (AN) and body dysmorphic disorder (BDD) are characterized by distorted body image and are frequently co-morbid with each other, although their relationship remains little studied. While there is evidence of abnormalities in visual and visuospatial processing in both disorders, no study has directly compared the two. We used two complementary modalities – event-related potentials (ERPs) and functional magnetic resonance imaging (fMRI) – to test for abnormal activity associated with early visual signaling.

Method. We acquired fMRI and ERP data in separate sessions from 15 unmedicated individuals in each of three groups (weight-restored AN, BDD, and healthy controls) while they viewed images of faces and houses of different spatial frequencies. We used joint independent component analyses to compare activity in visual systems.

Results. AN and BDD groups demonstrated similar hypoactivity in early secondary visual processing regions and the dorsal visual stream when viewing low spatial frequency faces, linked to the N170 component, as well as in early secondary visual processing regions when viewing low spatial frequency houses, linked to the P100 component. Additionally, the BDD group exhibited hyperactivity in fusiform cortex when viewing high spatial frequency houses, linked to the N170 component. Greater activity in this component was associated with lower attractiveness ratings of faces.

Conclusions. Results provide preliminary evidence of similar abnormal spatiotemporal activation in AN and BDD for configural/holistic information for appearance- and non-appearance-related stimuli. This suggests a common phenotype of abnormal early visual system functioning, which may contribute to perceptual distortions.

Received 28 September 2014; Revised 31 December 2014; Accepted 2 January 2015

Key words: Dorsal/ventral visual streams, electroencephalography, event-related potential, face processing, house processing, joint ICA.

Introduction

Individuals with body dysmorphic disorder (BDD) and those with anorexia nervosa (AN) express distortions in how the body is perceived, which suggests underlying abnormalities in visual information processing. In BDD, the cardinal diagnostic psychopathology is pre-occupation with perceived defects in appearance, which are unnoticeable, or slight, to others (APA, 2013). Sufferers experience significant distress, disability, and functional impairment, often accompanied by depression and, in many, suicidality (Phillips, 2005). The pathophysiology is likely complex (Monzani *et al.* 2012), including frontostriatal dysfunction (Rauch *et al.*

2003; Feusner *et al.* 2010a), emotion recognition (Buhlmann *et al.* 2002, 2004; Feusner *et al.* 2010c), and atypical visual processing (Feusner *et al.* 2007, 2010c). Regarding the latter, functional magnetic resonance imaging (fMRI) studies using own-face (Feusner *et al.* 2010a), other-face (Feusner *et al.* 2007), and house stimuli (Feusner *et al.* 2011) point to abnormalities in primary and secondary visual-processing systems, particularly when images are filtered to selectively convey configural and holistic information. In accord with these results, one preliminary EEG study found increased N170 latencies in BDD subjects, suggesting increased use of detailed visual processing (Li *et al.* 2013).

Several behavioral studies in BDD suggest imbalances in global (configural and/or holistic) and local (detailed) visual processing, although the results are not entirely consistent. Several of these studies have tested the inversion effect, which is the phenomenon

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that recognition of inverted faces (or other naturalistic stimuli) is normally slower and less accurate compared to upright faces, due to the absence of a holistic template for inverted faces. One study found reduced face inversion effects in BDD compared to controls for long- but not short-duration stimuli, suggesting a greater propensity for detailed and piecemeal processing of faces, whether upright or inverted (Feusner *et al.* 2010b). Another study found that individuals with BDD had superior recognition of inverted famous faces relative to controls; this reduced inversion effect may also be an indication of greater focus on single facial features (Jefferies *et al.* 2012). A study using inverted faces, scenes, and bodies found that individuals with high degree of body dysmorphic concerns also had reduced inversion effects (Mundy & Sadusky, 2014). Individuals with BDD were found to be slower and less accurate on the Embedded Figures Test (EFT) and the Navon task, suggesting abnormal global and local processing (Kerwin *et al.* 2014). However, a study examining holistic processing using the face inversion effect, composite face effect, and Navon task, found that the BDD and control groups performed similarly on all three tasks (Monzani *et al.* 2013). Thus, while evidence exists for abnormal global and/or local processing, the findings are still somewhat inconclusive. This may be attributed to differences in experimental conditions (e.g. stimulus duration), insufficient power, or else there may be nuances due to heterogeneity within BDD samples.

In AN, the image distortion is the perception of excess weight and fatness, culminating in a marked restriction of energy intake and lowering of body mass. Several studies (although not all) investigating neurocognition in AN have found enhanced local (detail) processing at the expense of visuospatial processing that is more global and integrated (Lopez *et al.* 2008; Urgesi *et al.* 2013). On the Rey–Osterrieth Complex Figures Task, which requires recall and re-creation of a complex figure, AN performed worse (Lopez *et al.* 2009; Kim *et al.* 2011) or equal (Sherman *et al.* 2006; Lopez *et al.* 2008; Castro-Fornieles *et al.* 2009; Danner *et al.* 2012; Stedal *et al.* 2012) relative to controls. Several of these studies found that those with AN drew detailed aspects of the figure first and showed less continuity in reproduction (Sherman *et al.* 2006; Lopez *et al.* 2008; Stedal *et al.* 2012). Individuals with AN have also been found to be faster and more accurate on the EFT, suggesting superior detail-focused processing (Jolliffe & Baron-Cohen, 1997; Booth *et al.* 2003). Other studies have found superior attention to detail and poor central coherence compared with controls, in active and recovered AN participants and their sisters (Tenconi *et al.* 2010; Roberts *et al.* 2013). Several functional and structural imaging studies support

these abnormal visual-processing findings in AN. An fMRI study using the EFT found greater activation in the fusiform gyrus in AN compared with healthy controls (Fonville *et al.* 2013), suggesting a strategy marked by enhanced ventral visual stream activity, which is responsible for detailed image elements (Iidaka *et al.* 2006). Furthermore, an fMRI study by Favaro *et al.* (2012) found decreased brain connectivity in a ventral visual network in both underweight and weight-restored individuals with AN, but hyperconnectivity within the somatosensory network only in the underweight group. Structurally, AN also show decreased gray-matter density in the left extrastriate body area, an area in the occipital cortex involved in processing human body parts, compared to controls (Suchan *et al.* 2010). These neurocognitive and brain-imaging studies suggest the possibility of aberrant visual processing in AN, although the body of research is still growing.

Thus, a potentially important clinical phenotype in AN and BDD is perceptual distortion of appearance. Both disorders tend to display a common pattern of abnormalities in visual processing and visuospatial organization, manifesting as over-attention to details with less global perception and feature integration (Madsen *et al.* 2013). However, no study has directly compared visual processing in these disorders.

A limitation of fMRI studies is their relatively poor temporal resolution, typically on the order of 2–3 s. Because of this it remains unclear if abnormal neural activation or connectivity patterns in visual systems result primarily from aberrant early visual cortex activity, or are due primarily to modulation from pre-frontal and/or limbic systems. This question, however, is well suited for electroencephalography (EEG), which, unlike fMRI, allows characterization of fast-changing neuronal dynamics. EEG has a time resolution in the order of milliseconds, but has limited spatial resolution, while fMRI has the capability to localize, with higher spatial resolution, changes in blood oxygenation in the brain in the order of millimeters. Therefore, a combination of fMRI and EEG can be used to generate a joint spatiotemporal profile that leverages spatial and temporal resolution advantages of the respective modalities.

Herein we report what is, to the best of our knowledge, the first use of this dual modality approach to study visual processing in BDD and AN. We analyzed the P100 component of the event-related potential (ERP), which indexes first-order processing localized to V1 and V2 and early dorsal visual stream (Itier & Taylor, 2004), and the N170, which indexes higher level visual processing and structural encoding, and has sources including the ventral visual stream and posterior fusiform gyrus (Pascual-Marqui, 1999). (As our principal interest was in early visual processing, we

did not study P300 or N400.) We used independent component analysis of task-related fMRI data in combination with ERP data from a separate session, using the same stimuli and paradigm to perform joint independent component analysis (jICA). jICA combines data from these two modalities by joint estimation of the temporal ERP components and spatial fMRI components (Calhoun *et al.* 2006) (see online Supplementary Information). For task stimuli, we used faces and houses. Faces are appearance-related stimuli that have been extensively studied using fMRI and EEG (Bentin *et al.* 1996; Costen *et al.* 1996; Bartlett *et al.* 2003). We chose to use face rather than body images, as visual EEG profiles in response to body images have not been well characterized. Houses have a visuospatial complexity similar to faces, but they are of neutral salience, and have been previously studied using fMRI and EEG (Epstein & Kanwisher, 1998; Iidaka *et al.* 2006; Desjardins & Segalowitz, 2013). We hypothesized that AN and BDD will differ from healthy controls (HC) in configural processing of unaltered face and house stimuli (normal spatial frequency; NSF), and in processing the same stimuli when they are filtered to contain only low spatial frequency (LSF) information. Although our overarching hypothesis was that AN and BDD may express similar abnormal visual-processing phenotypes, we did not expect to prove phenotypic or endophenotypic equivalence, both due to the preliminary nature of this study and the complexity inherent within psychiatric diagnostic categories.

We tested three specific primary hypotheses:

- (1) AN and BDD would demonstrate hypoactivity compared with HC: (a) in early dorsal stream regions for the P100 component; and (b), ventral stream regions for the N170 component. We predicted that this would be observed for LSF faces and houses, as well as NSF images because they contain LSF information.
- (2) Symptom severity in both groups will correlate negatively with activity in early dorsal and ventral stream regions for NSF and LSF joint P100 and N170 components.
- (3) Neither BDD nor AN will differ from HC in visual system response to high spatial frequency (HSF) images, as these were not detected in previous fMRI studies using HSF faces and houses (Feusner *et al.* 2007, 2011).

Method and materials

We recruited 15 AN, 15 BDD, and 15 HC participants, of equivalent age and sex, from UCLA and local treatment centers, as well as from the community through print and online advertisements. Diagnoses of clinical

participants were confirmed through detailed interviews conducted by three of the authors (J.F., M.S. and C.B.), which included the Mini International Neuropsychiatric Interview (MINI) to determine a primary diagnosis of AN and/or co-morbid diagnoses (Sheehan *et al.* 1998). The BDD Diagnostic Module (Phillips *et al.* 1995), a 6-item clinician-administered structured interview based on DSM-IV criteria for BDD, was used to make a primary diagnosis of BDD. Severity of concurrent psychiatric symptoms was measured using validated clinical scales [Hamilton Anxiety Rating Scale (HAMA; Hamilton, 1960); Brown Assessment of Beliefs Scale (BABS; Eisen *et al.* 1998); Montgomery–Asberg Depression Rating Scale (MADRS; Williams & Kobak, 2008)]. BDD participants also received the BDD version of the Yale–Brown Obsessive–Compulsive Scale (BDD-YBOCS; Phillips *et al.* 1997), and AN participants received the Eating Disorder Examination V16.0D (EDE; Fairburn *et al.* 2008). We did not administer the EDE to BDD participants, nor did we administer the BDD-YBOCS to AN participants, as these scales have not been validated in these populations.

Inclusion/exclusion criteria

Participants were free from psychoactive medications for at least 8 weeks prior to entering the study. Individuals who met criteria for BDD by the BDD Diagnostic Module (Phillips *et al.* 1997) modeled after the DSM-IV were eligible. AN participants were weight-restored [body mass index (BMI) ≥ 18.5], but they were required to have previously met full DSM-IV criteria for AN at some point in their lifetime, as determined by the MINI. We chose to study weight-restored AN individuals to avoid confounds of starvation on brain activity. For individuals with co-morbid diagnoses, they were required to have had a primary diagnosis of AN or BDD based on symptom severity to be eligible. (See online Supplementary Information for additional inclusion/exclusion criteria; and Table 1 and online Supplementary Table S8 for categories and specific areas of BDD appearance concerns, respectively.)

Face- and house-matching task

All participants performed a visual matching task in the fMRI scanner, and then performed the same tasks during a separate EEG session on a separate day. Participants were recalled for the EEG session after a mean of 191.8 ± 305.7 days (range 1–1006). The mean interval between sessions was not significantly different among groups ($F_{2,42} = 2.08$, $p = 0.14$). The stimuli (Fig. 1) were face and house photographs that were NSF, or filtered to LSF or HSF, and circles/ovals or squares/rectangles as control images (see Feusner *et al.*

Table 1. Demographics and psychometrics for anorexia nervosa (AN), body dysmorphic disorder (BDD), and healthy control (HC) participants.

Demographics	AN	BDD	HC	Statistical values
Total subjects (N)	15	15	15	
Gender (F/M)	13/2	13/2	13/2	
Age, years	23.6 ± 3.46	24.93 ± 5.15	22.07 ± 3.85	$F = 1.7, p = 0.18$
Years of education	14.79 ± 2.22	16.36 ± 3.86	14.3 ± 2.45	$F = 2.0, p = 0.15$
EDE score	2.96 ± 1.42	N.A.	N.A.	
BDD-YBOCS score	N.A.	29.07 ± 4.79	N.A.	
BABS score	12.31 ± 6.51	14.6 ± 3.31	N.A.	$t = 1.19, p = 1.20$
HAMA score	6.67 ± 5.98 ^a	9.2 ± 6.91 ^a	2.27 ± 1.94 ^b	$F = 6.3, p = 0.003$
MADRS score	8.93 ± 9.14 ^a	14 ± 6.78 ^a	1.07 ± 1.22 ^b	$F = 13.6, p < 0.0001$
Body mass index	20.36 ± 1.61 ^a	22.92 ± 3.68 ^b	21.43 ± 1.85	$F = 3.8, p = 0.03$
BDD appearance concerns (number of individuals in each category)		Face only: 7 Non-face only: 5 Face and non-face: 3		

EDE, Eating Disorder Examination V16.0D; BDD-YBOCS, BDD version of the Yale–Brown Obsessive–Compulsive Scale; BABS, Brown Assessment of Beliefs Scale; HAMA, Hamilton Anxiety Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; n.a., not available.

^{a,b} Different superscript letters indicate significant pairwise differences from *post-hoc t* tests at $p < 0.05$.

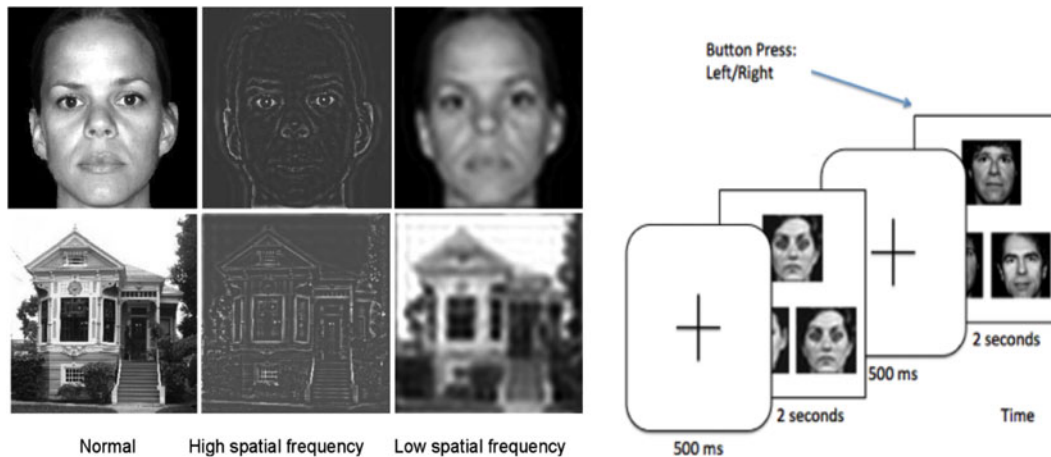


Fig. 1. Left: Example stimuli used in the experiment, consisting of digital images filtered to normal, high, and low spatial frequencies. Right: Task paradigm, consisting of a face- or house-matching task.

2007). During the presentation, participants pressed a button corresponding to which of two images matched the target image in the top half of the screen. The face and house orders, for NSF, LSF, and HSF, were counter-balanced across participants. There were 72 trials for each category; each trial consisted of a 500 ms crosshair, then 4 s of face or house presentation (2 s for the EEG session, given constraints on total time) during which button responses were recorded.

EEG acquisition and processing

All participants were seated 1 m from the screen. EEG data were recorded using a high-density 256-channel

Geodesic Hydrocel Sensor Net (Electrical Geodesics Inc., USA) with a sampling rate of 250 Hz, in a dimly lit, copper-shielded room. Between experiments, electrode impedances below 50 k Ω were ensured by reapplying saline solution to high-impedance electrodes. Data preprocessing included bandpass filtering from 0.1 to 30 Hz for visual ERPs.

Artifact detection: See online Supplementary Information.

Segmentation: Data were segmented 200 ms before and 500 ms after stimuli presentation. Segments were averaged across each stimuli condition, and grand averaged over all participants. ERP were baseline-corrected using the 200 ms baseline prior to

the stimulus onset. All channels were referenced to an average reference of all electrodes except electro-oculography.

fMRI acquisition and processing

Blood oxygen level dependent (BOLD) contrast images were acquired using a 3-T Trio MRI system (Siemens AG, Germany). We used a T2*-weighted echoplanar imaging gradient-echo pulse sequence (repetition time, 2.5 s; echo time, 25 ms; flip angle, 80°; acquisition matrix, 64 × 64 pixels; field of view, 192 × 192 × 120 mm; in-plane voxel size, 3 × 3 mm; section thickness, 3 mm; 0.75-mm intervening spaces; and 28 total sections). There were 133 whole-brain images per subject per run. We also obtained matched-bandwidth and high-resolution Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) T1-weighted images for each subject to provide detailed brain anatomy during structural image acquisition.

For processing and analysis of the fMRI data, we used Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library (FSL) (<http://www.fmrib.ox.ac.uk/fsl>). Preprocessing steps are described in the online Supplementary Information.

We used FEAT (fMRI Expert Analysis Tool version 5.4; FSL) for general linear model analyses. At the individual subject level, we modeled the hemodynamic response function using a convolution of the experimental paradigms of each stimulus type *v.* crosshair baseline with the canonical hemodynamic response function and its temporal derivative (Aguirre & Farah, 1998). Motion correction was performed by adding 24 motion parameters, modeling the six rigid body motion parameters, their temporal derivatives, and their squares (Friston *et al.* 1996). We thresholded the *z* score images using clusters determined by $z > 2.3$ and a corrected cluster significance threshold of $p < 0.05$.

jICA

Inputs to jICA were BOLD responses to HSF, NSF, and LSF stimuli, contrasted to crosshair baseline, registered to the MNI brain. These contrasts were submitted to jICA using the Fusion ICA Toolbox (FIT) (<http://icatb.sourceforge.net>) in Matlab, and were combined with the ERP waveforms as described previously (Calhoun *et al.* 2006). We performed ICA using the Infomax algorithm, a gradient descent algorithm to maximize entropy of the output of single layer neural network (Lee & Sejnowski, 1997), to generate the shared unmixing matrix and the fused ERP and fMRI sources (Calhoun *et al.* 2006). We used principal components analysis to reduce dimensionality from subjects to components. Fifteen joint components were estimated

from ERP time courses and fMRI activation maps. The jICA mixing matrix's rows consist of each participant's concatenated data; thus, the maximum number of components extracted from each group is 15 since this was the number of participants in each group. Fifteen independent components (ICs) thus maximizes the extent of separation between sources for this sample size.

Within-group jICA components

From the IC decomposition, we extracted P100 and N170 ICs using a template-matching algorithm that calculated similarity scores for each component. These scores were calculated by comparing each IC against the average ERP at 100 ms windows taken symmetrically around time-points 100 and 170 ms. We then submitted the IC with the largest similarity score for each component (P100 or N170) for analysis with dual regression.

To reduce the number of multiple comparisons, we restricted between-group comparisons by using masks constructed from each respective spatial frequency contrast using a group GLM analysis for each group. We created masks from thresholded images (*z* scores > 1.7), from which we combined the two compared groups' masks and then binarized the results.

Dual regression

We used Matlab's GIFT Toolbox's Spatiotemporal Reconstruction tool to create subject-level ICs from each group spatial map, by adopting a dual regression procedure (as previously described in Filippini *et al.* 2009; see online Supplementary Information).

Statistical analyses

We performed permutation tests between groups to test for statistical differences using Statistical nonparametric Mapping (SnPM, <http://warwick.ac.uk/snpm>), with 10 000 iterations. We used a Bonferroni-corrected significance threshold of $\alpha = 0.016$ to account for pairwise comparisons for each of our specific hypotheses; although our hypotheses only included two group pairwise comparisons (AN *v.* controls and BDD *v.* controls) we used a more conservative threshold of $\alpha = 0.05/3 = 0.016$ to additionally account for the *post-hoc* AN *v.* BDD comparison.

Correlations with clinical variables

We calculated correlations between individual subject spatial map average intensity values and global scores on the EDE (for AN) and BDD-YBOCS (BDD), for NSF and LSF joint P100 and N170

components. We Bonferroni-corrected for multiple comparisons ($\alpha = 0.05/8 = 0.00625$).

Results

Demographics and psychometrics (Table 1)

All participants were unmedicated. All AN participants met DSM-IV criteria for restricting type; one had co-morbid generalized anxiety disorder (GAD). Of the BDD participants, two had co-morbid major depressive disorder (MDD), three had dysthymic disorder, one had panic disorder, one had MDD and GAD, and one had MDD, GAD, and social anxiety disorder. In the BDD group, three had facial concerns, one had non-facial concerns, and 11 had facial and non-facial concerns.

Behavioral results

There were no significant differences among groups for accuracy or response times for the EEG or fMRI tasks (Accuracies and reaction times can be found in Table S1 and Fig. S1.)

Within-group jICA results

For AN, BDD, and HC groups the P100 component has associated activations in lingual gyrus and middle occipital cortex, while the N170 component has activations in fusiform gyrus, lingual gyrus, and inferior/middle occipital cortex. This is consistent with previous findings using EEG source localization that localized the P100 (Itier & Taylor, 2004) to early visual cortices and the N170 (Pascual-Marqui, 1999) to mainly the posterior fusiform gyrus. Online Supplementary Figs S2 and S3 show example components for the P100 and N170 components, respectively, in AN, BDD and HC derived from jICA (thresholded at $|Z| > 3.5$ for display purposes). Supplementary Figs S4 and S5 show spatial maps as a linear sum of individual maps weighted by their ERP time-courses. (See supplementary Information for a spatiotemporal movie.)

Between-group jICA results: faces task

P100 component

There were no statistically significant differences among groups for any spatial frequencies for the joint P100 component.

N170 component

Compared to HC, AN and BDD groups each showed statistically significant hypoactivity in similar dorsal visual stream systems (precuneus, lateral occipital cortex) for LSF faces in the joint N170 component

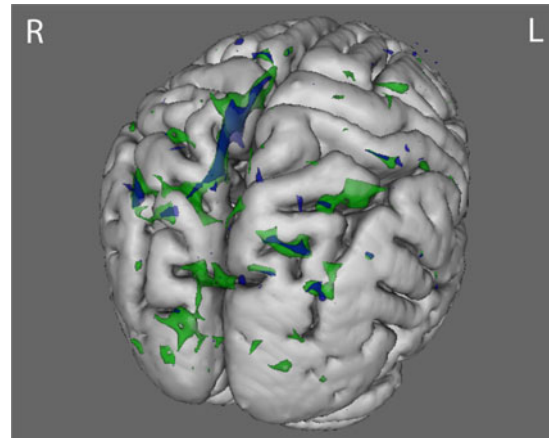


Fig. 2. N170 joint component for low spatial frequency face stimuli. The body dysmorphic disorder group (green) demonstrated hypoactivity ($p < 0.016$) compared with healthy controls in regions including lateral occipital cortex, occipital pole, and precuneus. The anorexia nervosa group (blue) demonstrated hypoactivity ($p < 0.016$) compared with healthy controls in the precuneus and the lateral occipital cortex. See online Supplementary Table S4 for local maximally significant coordinates.

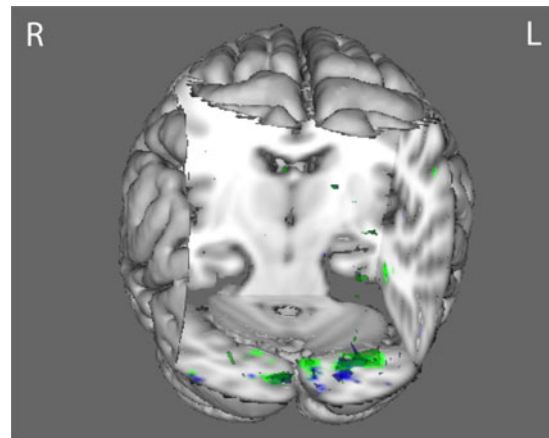


Fig. 3. P100 joint component for low spatial frequency house stimuli. The body dysmorphic disorder group (green) and the anorexia nervosa group (blue) both demonstrated hypoactivity ($p < 0.016$) compared with healthy controls in regions including the middle temporal gyrus, the occipital fusiform gyrus, and the inferior temporal gyrus. See online Supplementary Table S5 for local maximum coordinates.

($p < 0.016$) (Fig. 2 and online Supplementary Table S3).

Between-group jICA results: houses task

P100 component

Compared with HC, AN and BDD groups each showed statistically significant hypoactivity in similar

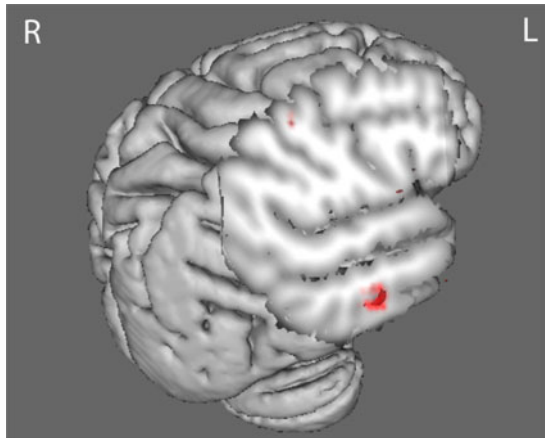


Fig. 4. N170 joint component for high spatial frequency house stimuli. The body dysmorphic disorder group (red) demonstrated hyperactivity ($p < 0.016$) in regions including the temporal fusiform cortex compared with healthy controls. See online Supplementary Table S6 for local maximum coordinates.

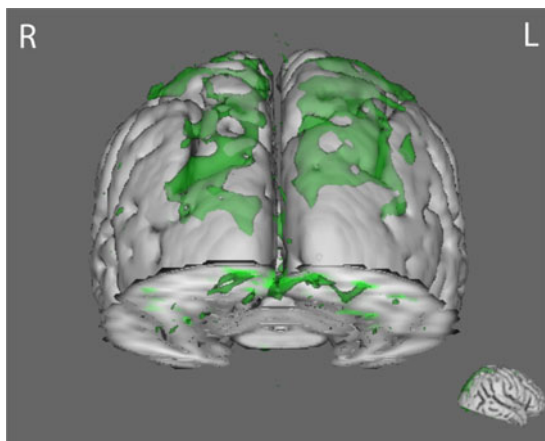


Fig. 5. N170 joint component for low spatial frequency house stimuli. The body dysmorphic disorder group (green) demonstrated hypoactivity ($p < 0.016$) compared with healthy controls in regions including the occipital fusiform cortex, lateral occipital cortex, and frontal pole. See online Supplementary Table S7 for local maximum coordinates.

early visual regions (occipital fusiform gyrus) for LSF houses in the joint P100 component ($p < 0.016$) (Fig. 3 and online Supplementary Table S4).

N170 component

Compared with HC, the BDD group demonstrated statistically significant hyperactivity in regions including the posterior temporal fusiform cortex (part of the ventral visual stream) for HSF houses in the joint N170 component ($p < 0.016$) (Fig. 4 and online Supplementary Table S5). The BDD group

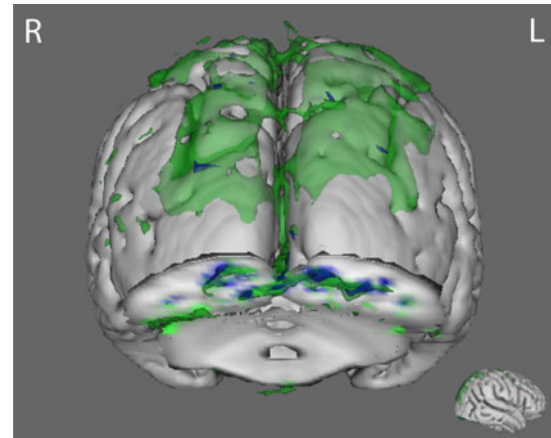


Fig. 6. N170 joint component for low spatial frequency house stimuli using a lower statistical threshold ($p < 0.05$). The body dysmorphic disorder group (green) demonstrated hypoactivity compared with healthy controls in regions including the occipital fusiform cortex, lateral occipital cortex, and frontal pole. The anorexia nervosa group (blue) demonstrated hypoactivity in occipital fusiform cortex, occipital pole, and precuneus.

demonstrated statistically significant hypoactivity compared with HC in early ventral visual stream areas (occipital fusiform, temporal occipital fusiform, and lateral occipital cortices), and dorsal visual stream areas (superior parietal lobule) for LSF houses in the joint N170 component stimuli (Fig. 5 and online Supplementary Table S6). By contrast, the AN group showed hypoactivity compared with HC in early ventral visual stream areas as well (occipital fusiform cortex, occipital pole, and precuneus), but only at a lower p threshold of $p < 0.05$ (Fig. 6).

Post-hoc AN v. BDD comparisons

Although not among our primary hypotheses, we conducted *post-hoc* comparisons directly between AN and BDD. The BDD group demonstrated statistically significant hypoactivity compared with AN in left lateral occipital cortex for the LSF houses in the joint N170 component ($p < 0.016$) (see online Supplementary Fig. S6 and Table S7). There were no other statistically significant differences for the other spatial frequencies and joint ERP components.

Correlational analyses

Activity for LSF faces in the joint N170 component in the AN group correlated negatively with global EDE scores: $r = -0.55$, $p = 0.04$, suggesting that lower activity for faces that only contain global and configural information was associated with worse eating disorder

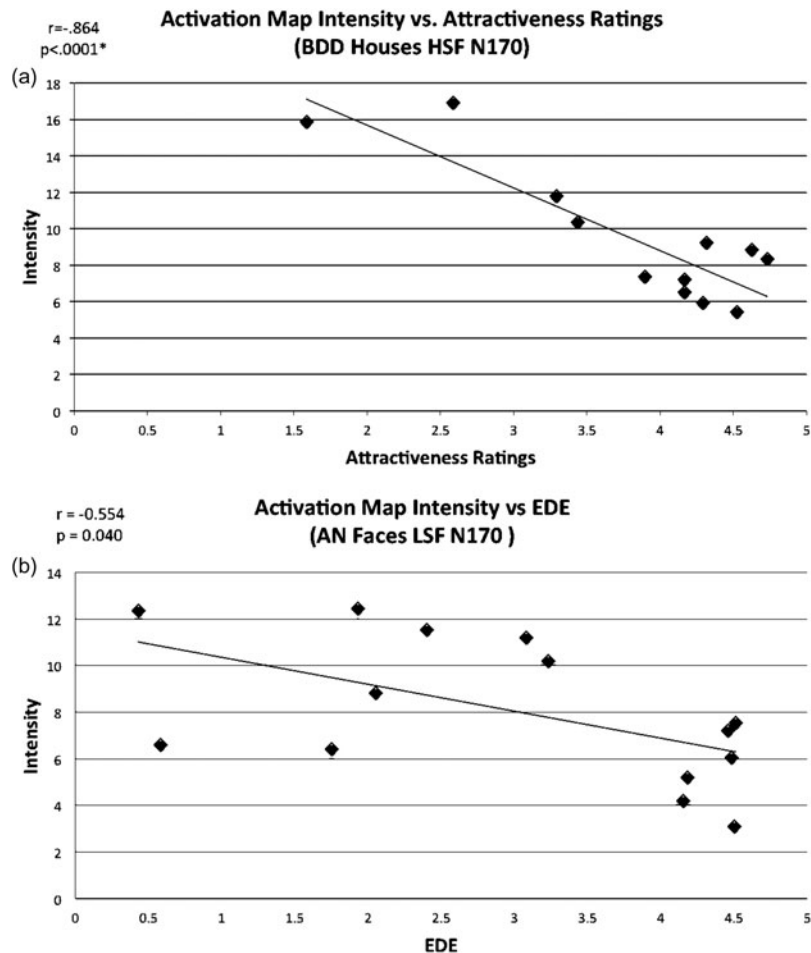


Fig. 7. (a) Scatterplot showing significant negative correlation ($q = 0.035$ after false discovery rate correction) between mean activation map intensities and attractiveness ratings for the body dysmorphic disorder (BDD) group for high spatial frequency (HSF) houses in the joint N170 component. (b) Scatterplot showing negative correlation ($p = 0.04$) between mean activation map intensities and Eating Disorder Examination V16.0D (EDE) ratings for the anorexia nervosa (AN) group for low spatial frequency (LSF) faces in the joint N170 component. The correlation was not significant after multiple comparison correction.

symptoms. However, this did not survive correction for multiple comparisons.

As exploratory *post-hoc* analyses, we calculated correlations between mean scores on ratings of face attractiveness, aversiveness, and degree to which the face triggered thoughts of their own appearance (obtained immediately after the fMRI session) and individual subject spatial map averages for all joint components that were significantly different among groups. There was a significant correlation between face attractiveness ratings for the BDD group and activation for HSF houses in the joint N170 component. [$q = 0.035$, corrected for multiple comparisons using false discovery rate (FDR)] (Fig. 7).

Because the BDD and AN groups differed significantly on depression, anxiety, and BMI (see Table 1), we conducted *post-hoc* analyses investigating the relationship between MADRS, HAMA, and BMI

(and BABS scores, although not significantly different), and all joint components that were significantly different among groups. There were no significant correlational findings, using FDR correction with a q threshold of 0.05. (See online Supplementary Table S2 for full correlation results with psychometric scores.)

Discussion

To the best of our knowledge, this is the first study to investigate visual processing concurrently in individuals with AN and in those with BDD for appearance- and non-appearance-related images, and the first to use joint analysis of fMRI and EEG data to study brain activation patterns in these clinical populations. We found that both AN and BDD showed hypoactivity in dorsal visual stream systems for LSFs, suggesting that a

common deficiency in holistic processing is operating in primary visual structures as early as 100 ms post-exposure, which extends later in time (170 ms) into dorsal higher-order processing regions. However, the patterns of hypoactivity are not identical; BDD demonstrated hyperactivity when compared with controls in ventral visual stream systems for HSF houses, but they showed hypoactivity in dorsal visual regions for LSF faces in comparison to participants with AN.

In line with our hypothesis, individuals with BDD and those with AN demonstrate hypoactivity in early secondary visual-processing regions when viewing faces that contain only LSF information, corresponding to electrical activity in the N170 component. But contrary to our hypotheses, we did not find hypoactivity in the P100 component profile for faces, which suggests that abnormalities in face visual processing may not manifest until the structural encoding that occurs ~170 ms after stimulus presentation.

Also in line with our hypotheses, BDD individuals demonstrate hypoactivity in primary and secondary visual regions for the P100 and N170 components, respectively, in response to LSF houses. This suggests deficient activation for configural/holistic information in the dorsal visual stream within the first 200 ms of visual processing, even for stimuli that are appearance neutral. Contrary to prediction, in response to HSF house images, individuals with BDD demonstrate hyperactivity in the fusiform gyrus (part of the ventral visual stream) in the N170 component, suggesting greater engagement of detailed processing. As we did not find this in our previous fMRI studies of BDD (Feusner *et al.* 2007, 2010c, 2011), the general linear modeling we used in those studies may not have had the sensitivity necessary for its detection, as jICA specifically isolates fMRI activations linked to electrophysiological activity at predefined time-points. The results herein suggest a general imbalance for detailed *v.* configural/holistic processing of visual information.

We observed similar hypoactivity in visual systems for LSF house images in participants with AN, but with some exceptions. In the P100 profile, they show hypoactivity in early visual areas, although more limited relative to that observed in participants with BDD. In the N170 profile, participants with AN did not show significant differences in activation at the (corrected) threshold of $p < 0.016$; however, they did show hypoactivity in primary visual areas at a lower threshold of $p < 0.05$. These support previous findings of poor central coherence and diminished holistic and configural processing in individuals with AN, for bodies (Lopez *et al.* 2008; Urgesi *et al.* 2013) and complex figures (Lopez *et al.* 2009; Kim *et al.* 2011). We did not, however, find evidence of increased detailed processing in AN, from our HSF condition.

The *post-hoc* direct comparison of AN to BDD did not reveal significant differences in these primary visual areas, but there was lower activity in a superior portion of the left lateral occipital cortex in BDD compared to AN. One possibility is that AN is characterized by similar deficient activity in primary visual regions as seen in BDD, although of slightly lower magnitude and extent. Yet in later, dorsal stream structures, BDD may have reduced activity compared to AN, possibly signifying a greater deficiency in configural processing. Finally, although the AN group did not demonstrate the same ventral visual stream hyperactivity compared with controls as observed for BDD, the direct AN to BDD comparison was not statistically significant. Thus, an imbalance in detailed *v.* configural/holistic processing for non-appearance-related stimuli may characterize both disorders, but the defect appears to be more pronounced in BDD.

These findings may indicate a possible deficit in magnocellular pathway systems that normally construct a low-resolution holistic template of the visual field, which in turn may contribute to the distorted perceptions underlying appearance concerns in both disorders. However, similarities in abnormal neural activity as elicited by this experiment does not prove that AN and BDD have identical pathophysiology contributing to their respective clinical phenotypes. This is a preliminary study in these disorders, so further behavioral, connectivity, and neuropsychological research should be conducted to fully elucidate their differences.

The observation that case-control differences were more pronounced for the house than the face images is somewhat unexpected, given how often those with BDD perceive defects in their own faces. One possible explanation is that faces on average have more emotional and social saliency than houses, and this may also be more variable person-to-person. Such variability could introduce noise into the ERP responses from top-down modulation, resulting in a more heterogeneous signal (the specific emotional and cognitive reactions to faces would not likely be directly detected in this study, as we chose to focus solely on early visual joint components). The house stimuli, in contradistinction, may have allowed for a more consistent, less modulated response in visual systems and thus be more sensitive to underlying abnormalities.

The study has several limitations. First, the small sample size may have hindered full independent components decomposition. Second, although we collected the fMRI and EEG data using the same stimuli, task, and participants, they were not collected concurrently. This invites the possibility of subjective and experimental differences between sessions, although the normalization step when performing the jICA accounts for linear effects of habituation. However, concurrent

fMRI-EEG studies have their own limitations, such as significant artifacts due to gradient and heartbeat noise. Third, although we chose face images for appearance-related stimuli as the N170 and P100 are well characterized, faces are more likely to be salient for participants with BDD. It is possible that this may have differentially affected attention. The N170 and P100 joint components are less likely than later components to be affected by top-down modulation, although it remains a possibility. Moreover, the BDD group may have misinterpreted neutral face expressions as being angry or contemptuous, as has been observed in other BDD studies (Buhlmann *et al.* 2006), which, in turn, may have resulted in between-group differences in image salience or emotion. The BDD group had higher average anxiety and depression scores than both AN and HC participants, although this is unlikely to account for differences in activation patterns given a lack of significant correlations between component activation and these ratings. Finally, it remains unknown due to the cross-sectional design of the study if the differences found reflect intrinsic variations that enhance risk of illness, or epiphenomena of illness or correlates of other neural processes.

The results of this study suggest the possibility that a general visual-processing phenotype may operate in psychiatric disorders that involves distortion of one's appearance and is accompanied by emotional distress and related self-esteem concerns (Madsen *et al.* 2013). The phenotype may explain the peculiar, increased attention given to miniscule defects seen on the skin (in BDD), or areas of perceived cellulite, or 'fat', on thighs and stomach (in AN), and the inability to process these perceptions contextually, i.e. to see them as inconsequential relative to the body as a whole (Madsen *et al.* 2013). The finding in the BDD group that greater degree of activation for high detail stimuli is associated with lower face attractiveness ratings supports this interpretation; enhanced detail processing may lead to a greater likelihood of flaw detection, and hence lower perception of attractiveness. The fact that this relationship was significant for house stimuli and not face stimuli is somewhat unexpected, but may be due to the aforementioned possibility of greater neural signal variability related to differences in salience of the faces. For the AN group, lower activation for LSF faces is associated with worse eating disorder symptoms, suggesting a possible link between deficiencies in global and configural processing and clinical symptomatology, although this correlation did not survive correction for multiple comparisons. As the neural differences observed are linked to ERP components as early as 100 ms post-stimulus, we speculate that abnormalities exist in BDD and AN in primary and secondary visual brain regions before this

information is transferred forward to areas that form and regulate memory, emotion, and cognitive schemas.

The results, although preliminary given the small sample and need for replication, suggest potential translational implications. The results may have promise in informing study of these phenotypes as biomarkers of risk, persistence of symptom-conferring pathophysiology, or endophenotypes. Finally, they may inform the development of novel, adjunctive perceptual remediation therapies targeting impairment in early dorsal *v.* ventral visual streams.

Supplementary material

For supplementary material accompanying this paper visit <http://dx.doi.org/10.1017/S0033291715000045>.

Acknowledgements

This work was funded by NIH MH093535-02S1 (Feusner). Dr Strober received support from the Resnick Endowed Chair in Eating Disorders.

Declaration of Interest

None.

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CHAPTER 4

4.1. Review Article: Body Dysmorphic Disorder: Neurobiological Features and an Updated Model

This section is adapted from:

Li W, Arienzo D, & Feusner JD (2013). Body Dysmorphic Disorder: Neurobiological Features and an Updated Model, *Journal of Clinical Psychology and Psychotherapy* **42**, 184–191.

Zeitschrift für Klinische Psychologie und Psychotherapie

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der körperdysmorphen Störung

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Zeitschrift für Klinische Psychologie und Psychotherapie

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Body Dysmorphic Disorder: Neurobiological Features and an Updated Model

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Abstract. Body dysmorphic disorder (BDD) affects approximately 2 % of the population and involves misperceived defects of appearance along with obsessive preoccupation and compulsive behaviors. There is evidence of neurobiological abnormalities associated with symptoms in BDD, although research to date is still limited. This review covers the latest neuropsychological, genetic, neurochemical, psychophysical, and neuroimaging studies, and synthesizes these findings into an updated (yet still preliminary) neurobiological model of the pathophysiology of BDD. We propose a model in which visual perceptual abnormalities, along with frontostriatal and limbic system dysfunction, may combine to contribute to the symptoms of impaired insight, obsessive thoughts, and compulsive behaviors expressed in BDD. Further research is necessary to gain a greater understanding of the etiology of BDD symptoms and their evolution over time.

Key words: BDD, neurobiology, pathophysiology, etiology, model

Körperrydymorphe Störung: Neurobiologische Aspekte und ein aktualisiertes Modell

Zusammenfassung. Die Körperdymorphe Störung (KDS) betrifft ungefähr 2 % der Bevölkerung und ist durch wahrgenommene Defekte im Aussehen sowie einer zwanghaften Beschäftigung und ritualisierten Verhaltensweisen gekennzeichnet. Es gibt mittlerweile Belege dafür, daß die KDS mit neurobiologischen Abnormalitäten einhergeht, obwohl die Forschung in diesem Bereich bis heute immer noch begrenzt ist. Dieser Beitrag gibt einen Überblick über neuropsychologische, genetische, neurochemische, psychophysische und bildgebende Studien und trägt diese Befunde in einem aktualisierten (bislang vorläufigen) neurobiologischen Modell zur Pathophysiologie der KDS zusammen. Wir schlagen ein Modell vor, in welchem sowohl visuelle Wahrnehmungsabnormalitäten sowie Dysfunktionen im frontostriatalen und limbischen System zu Symptomen wie geringer Krankheitseinsicht sowie eindringlicher Gedanken und zwanghafter Verhaltensweisen der KDS beitragen. Weitere Forschung ist nötig, um ein tieferes Verständnis für ätiologische Faktoren von KDS-Symptomen sowie deren Entwicklung über die Zeit zu erhalten.

Schlüsselwörter: BDD, Neurobiologie, Pathophysiologie, Ätiologie, Modell

Body dysmorphic disorder (BDD) is an often severe psychiatric disorder in which individuals are preoccupied with imagined defects in their appearance, which are not noticeable, or which appear slight, to others (American Psychiatric Association, 2000). They subsequently experience significant distress, disability, and functional impairment, often accompanied by depression and suicidality (Phillips et al., 2005). In addition, they are often delusional in their beliefs (Eisen, Phillips, Coles, & Rasmussen, 2004), and tend to present to plastic surgeons and dermatologists more often than mental health clinicians (Phillips, Didie, Feusner, & Wilhelm, 2008).

BDD affects approximately 1–2% of the population (Bienvenu et al., 2000; Faravelli et al., 1997; Otto, Wilhelm, Cohen, & Harlow, 2001; Rief, Buhlmann,

Wilhelm, Borkenhagen, & Braehler, 2006), yet is still understudied and underrecognized. BDD has several important phenomenological features including obsessive thoughts and compulsive behaviors, distorted perception, poor insight, and difficulty engaging in treatments (Phillips, 2005). The pathophysiology behind BDD is complex and likely involves interactions between a variety of factors, some of which may contribute to development and others to the maintenance of BDD symptoms. However, the field of neurobiological research in BDD is still young, and there are many gaps in our knowledge of how BDD symptoms are formed and evolve over time.

This review explores the research findings regarding neurobiological abnormalities that may be associated with the etiology and pathophysiology of BDD. These include

neurobiological factors that pertain to neurocognitive functioning, neurochemistry, brain activation relative to visual processing, morphometry, and genetic factors that have been associated with BDD. We attempt to synthesize the evidence from these various domains to generate a preliminary, heuristic model that integrates research findings to date.

Neurocognitive Functioning

Some of the earlier research done in BDD to assess neurobiological functioning involved tests of neurocognitive functioning. Three different studies have been performed in BDD using neuropsychological measures to investigate domains of memory, executive functioning, motor functioning, and/or visuospatial functioning (Deckersbach et al., 2000; Dunai, Labuschagne, Castle, Kyrios, & Rossell, 2010; Hanes, 1998).

Hanes (1998) tested individuals with BDD and obsessive-compulsive disorder (OCD) on measures of memory, executive function, and motor function (Hanes, 1998). He found that individuals with BDD and those with OCD performed poorly relative to healthy controls on tests of executive function, including response inhibition and planning, but performed normally on measures of verbal memory (Rey Auditory Verbal Learning Task [RAVLT]), visuospatial construction and memory (Rey-Osterrieth Complex Figure Test [RCFT]), verbal fluency, and motor function (Hanes, 1998).

Another study testing verbal and nonverbal memory found that individuals with BDD performed poorer than controls on the California Verbal Learning Test and the RCFT (Deckersbach et al., 2000). On the RCFT, group differences in free recall were mediated by deficits in organizational strategies; the BDD group selectively recalled details instead of larger organizational design features. The authors interpreted this deficit in memory organization strategy to be most likely attributed to abnormalities in executive functioning and frontostriatal circuit dysfunction. However, as this task involves viewing and encoding a complex visual figure, it is also possible that earlier perceptual abnormalities in global and/or local visual processing and/or differences in selective attention may have contributed to poor performance. The findings in this study may have clinical implications, as individuals with BDD tend to focus on details of their appearance at the expense of global aspects. These abnormalities, which may implicate organizational difficulties, abnormal selective attention, and/or aberrant perception, may contribute to, or be involved in the maintenance of, BDD symptoms.

Dunai et al. (2010) investigated executive functioning in BDD by having participants complete a battery of tasks that tested planning, organization, working memory, and

motor speed (Dunai et al., 2010). BDD participants made significantly more between-search errors on the Spatial Working Memory Task and had slower subsequent thinking times in a Stockings of Cambridge test, used to probe deficits in planning. These deficits in executive functioning also support a role of frontostriatal dysfunction in BDD.

Other neuropsychological studies in BDD have focused on processing of emotional or otherwise highly salient stimuli. Individuals with BDD appear to have deficits in facial emotion recognition. One study found that in self-referent situations, BDD patients were more likely to misinterpret neutral faces as angry or contemptuous, compared with controls (Buhlmann, Etcoff, & Wilhelm, 2006). This may implicate brain regions and systems involved in facial emotion perception such as the inferior frontal cortex, right parietal cortex, occipitotemporal cortex, insula, striatum, and/or amygdala, as potentially dysfunctional in BDD (Adolphs, Demasio, Tranel, & Demasio, 1996; Gur, Skolnik, & Gur, 1994; Sprengelmeyer, Rausch, Eysel, & Przuntek, 1998). However, functional neuroimaging studies have yet to be conducted to investigate the role of these regions in emotion regulation in BDD. These findings are also consonant with the clinical observation that individuals with BDD often have self-referential delusions or overvalued ideas with regard to other people's emotional response to their perceived flaws. In another study, subjects were asked to interpret various ambiguous scenarios. BDD subjects were more likely to report general situations, social situations, and body-focused situations as threatening, which was not observed for controls (Buhlmann, Wilhelm, et al., 2002). In an emotional Stroop task, BDD subjects had greater Stroop interference (more delayed response) for words related to their disorder and appearance ideal – that is *beauty* or *attractive* (Buhlmann, McNally, Wilhelm, & Florin, 2002). However, a study of negative priming found no difference between BDD and healthy control subjects in terms of cognitive inhibition as measured by response latencies, for appearance-related “threatening” words (Wilhelm, Buhlmann, & McNally, 2003).

In sum, most studies of neurocognition in BDD have found evidence of abnormal executive functioning (specifically, planning, organization, and response inhibition), which implicates frontostriatal systems. There is also evidence of abnormalities in facial emotional recognition, and possibly heightened sensitivity to appearance-related stimuli and perceived social threats.

Neurochemistry

There is a small body of evidence for the role of serotonin in BDD. Marazziti et al. found decreased serotonin transporter binding density in OCD-related disorders, including BDD (Marazziti, Dell'Osso, & Presta, 1999).

There is evidence from both controlled and uncontrolled studies that serotonin reuptake inhibitor (SRI) medications are effective treatments for BDD (see Ipser, 2010; Phillips & Hollander, 2008, for reviews). Treatment with medications that have serotonin reuptake inhibition often result in less frequent and intense preoccupations, better control over impulsivities, and decreased BDD-related distress (Allen et al., 2008; Phillips & Hollander, 2008). Other evidence for the involvement of serotonin in BDD includes a case study in which BDD symptoms were exacerbated during dietary depletion of tryptophan (a serotonin precursor) (Barr, Goodman, & Price, 1992). Another case study found a serotonin agonist, psilocybin, led to decreased BDD symptoms (Hanes, 1996).

The role of serotonin in the pathogenesis of BDD is as of yet uncertain. The strongest evidence of an association with serotonin is that BDD symptoms are often improved through treatment with SRIs. However, all of the aforementioned studies only provide indirect evidence of a relationship between serotonergic systems and BDD, and do not prove that serotonergic abnormalities underlie BDD pathophysiology.

Genetics and Heritability

Thus far there have been limited studies investigating genetic factors underlying BDD. Nevertheless, heredity and genetic factors do appear to contribute to BDD; for example, 8 % of individuals with BDD have a family member also diagnosed with BDD, a statistic 4–8 times the prevalence in the general population (Bienvenu et al., 2000). A twin study in females that utilized self-report measures of dysmorphic concerns and concerns about body odor and body malfunction, from a UK twin registry, found genetic factors accounted for approximately 44 % of the variance of dysmorphic concerns (Monzani et al., 2011). The same group found in another twin study that up to 64 % of the covariation between body dysmorphic and obsessive-compulsive traits was accounted for by common genetic factors (Monzani et al., 2012).

Additional evidence for a heritable connection with OCD comes from family studies. In one study, 7 % of BDD patients had a first-degree relative with OCD (Phillips, Gunderson, Mallya, McElroy, & Carter, 1998). There is a six times higher lifetime prevalence of BDD in first-degree relatives of OCD probands, compared with relatives of controls (Bienvenu et al., 2000).

In terms of specific genes, there has only been one preliminary study published to date in BDD, using candidate genes. Richter et al. (2004) found an association between the GABA (A)-gamma-2 1(A) allele and BDD, as well as comorbid BDD-OCD (Richter et al., 2004). The same study demonstrated an association of BDD with the serotonin transporter promoter polymorphism short allele.

Overall, these studies show that susceptibility for BDD, among other factors, may be heritable. Moreover, there may be shared genetic traits between BDD and OCD.

Visual Processing

Abnormal visual information processing is a phenotype that may contribute to the phenomenology of BDD. Clinically, individuals with BDD experience distortions of self-perception of appearance. This likely causes or contributes to preoccupation with physical defects, the conviction of disfigurement and ugliness, and subsequently to poor insight or delusionality. These phenomenological observations, as well as the neuropsychological study demonstrating impaired performance on the RCFT mediated by greater reproduction of detailed relative to global design features (Deckersbach et al., 2000), suggest possible disturbances in visual perception and/or visuospatial information processing.

The first functional neuroimaging study to investigate visual perception in BDD examined visual processing of others' faces (Feusner, Townsend, Bystritsky, & Bookheimer, 2007). Twelve BDD subjects and 13 healthy controls underwent functional magnetic resonance imaging (fMRI) while matching photographs of others' faces. Some of the faces were digitally altered to remove the high or low spatial frequencies, to create images that contained configural or detail information, respectively. This study found left hemisphere hyperactivity in an extended face-processing network for normal and low spatial frequency images. This pattern, in contrast to the generally right hemisphere-dominant pattern for healthy controls (Haxby et al., 1994), suggests greater detail encoding and analysis relative to holistic and configural processing, even for face images that contain a low level of detail. Abnormal interhemispheric sharing of information may also be involved. Another interesting finding in the study was abnormally high activation of amygdalae in the BDD group for the low and high spatial frequency images. In contrast, the control group showed normal activation of the amygdalae for the NSF task, and reduced activity for the low and high spatial frequency images. This suggests an abnormal hyperresponsivity of the amygdala in BDD relative to controls, for images that contain low and high levels of detail.

Another investigation of other-face processing, this one a psychophysical study, showed that individuals with BDD have abnormalities in identity recognition for faces with emotional expressions (Feusner, Bystritsky, Helleman, & Bookheimer, 2010). The poor performance in the BDD group did not depend on the type of emotional expression. This suggests general abnormalities in visual information processing of faces, which may be more pronounced when a face, in general, has an emotional expression.

Feusner et al. (2010) conducted an fMRI study of own-face processing in 17 individuals with BDD and 16 healthy controls. They found abnormal hypoactivity in the BDD group in the visual cortex (striate and extrastriate regions) for low spatial frequency images, and hyperactivity in frontostriatal systems (orbitofrontal cortex and caudate) for normal images (Feusner, Moody, et al., 2010). In addition, BDD symptom severity as measured by the BDD version of the Yale-Brown Obsessive-Compulsive Disorder Scale (BDD-YBOCS) (a measure of severity and impairment from obsessive thoughts, compulsive and avoidant behaviors, and insight) (Phillips et al., 1997), was correlated with frontostriatal activity and activity in the extrastriate visual cortex. Despite the BDD group rating the viewing of their face as being highly aversive, they did not demonstrate greater amygdala or insula activity. This study provides preliminary evidence of similar aberrant orbitofrontal-striatal circuit activity in BDD and OCD (Rotge et al., 2008), which may be associated with obsessive thoughts and compulsive behaviors in both cases.

The same group conducted another fMRI experiment to investigate abnormalities in visual processing in BDD for non-appearance-related stimuli (Feusner, Hembacher, Moller, & Moody, 2011). Fourteen BDD subjects and 14 healthy controls were scanned while they matched photographs of houses that were normal, or contained only high or low spatial frequency information. The BDD group relative to the control group showed abnormal hypoactivity in secondary visual processing systems for low spatial frequency images. This provides evidence of abnormal global and holistic processing (as this type of information is conveyed by low spatial frequency images), for non-appearance-related stimuli, suggesting more general abnormalities in visual processing.

An imbalance between local (detail) and global (holistic) processing in BDD was also found in a psychophysical study of inverted faces (Feusner, Moller, et al., 2010). Eighteen BDD subjects and 17 healthy controls performed a face recognition task with sets of upright and inverted (upside-down) faces. Normally, recognition of inverted faces is less accurate and slower relative to upright faces, which is attributed to the absence of a holistic template for inverted faces (Farah, Tanaka, & Drain, 1995); this is termed the *face inversion effect*. Results from this study indicated that the inversion effect for response time was smaller in BDD subjects than controls during the long-duration stimuli (due to faster processing of inverted faces than controls), but was not significantly different during the short-duration stimuli. This suggests that BDD individuals may have a propensity to engage in highly detailed processing of faces, whether upright or inverted. Controls, on the other hand, may primarily engage holistic processing for upright faces, yet have to rely on detailed processing for inverted faces. If so, this may have conferred the BDD group's advantage in

speed of responses for inverted faces. This was only observed for the long viewing duration condition, likely because this condition allowed sufficient time for encoding of details. For short-duration stimuli, on the other hand, there was likely insufficient time to process details, only allowing for holistic processing. The fact that the inversion effect was normal in BDD subjects for short viewing durations therefore suggests that an imbalance in detail versus holistic processing may be a dynamic phenomenon that emerges only in situations in which viewing durations are long. Clinically, this occurs on a daily basis in most individuals with BDD, as they often spend many minutes or even hours at a time viewing themselves in mirrors and other reflective surfaces (Phillips, 2005).

The ability to detect aberrancies in facial features or asymmetry is another aspect of visual processing that has been investigated in BDD. Evidence that BDD may involve perceptual distortions for own-face processing comes from a study in which BDD subjects perceived distortions of digital images of their faces that were not actually present (Yaryura-Tobias et al., 2002). Another study investigated the ability to detect asymmetry in BDD (Reese, McNally, & Wilhelm, 2010). This has clinical relevance, as some individuals with BDD perceive defects of their appearance related to asymmetry. In addition, a theory of symptom formation in BDD relates to the possibility that individuals have enhanced aesthetic sensitivity (Veale, 2009), which could include noticing imperfections including asymmetry that are not noticed by others. To investigate this, Reese et al. (2010) enrolled 20 BDD subjects, 20 OCD patients, and 20 healthy controls who viewed sets of others' faces that were altered in symmetry (Reese et al., 2010). Individuals with BDD were not significantly more accurate or faster than healthy controls in detecting differences in facial symmetry. In another study (Stangier, Adam-Schwebe, Muller, & Wolter, 2008), it was found that the BDD group was more accurate in detecting changes in aesthetic features of others' faces. An important difference between the Stangier et al. (2008) and Reese et al. (2010) studies is that in the former, the view time was limited to 200 ms and in the latter, the view time was unlimited and subjects were not told to respond as quickly as possible. In addition, in the Stangier et al. (2008) study, the subjects were asked to identify changes in facial *details* (with the exception of distance between the eyes, which is more of a configural judgment). In the Reese et al. (2010) study, judging facial symmetry would most likely engage configural processing. Thus, enhanced detail processing in BDD may explain performance advantages relative to controls for inverted faces as well as for change detection for facial features of others' faces. The difficulty in synthesizing the results from these experiments comes from the fact that they used different tasks, time durations, own or others' face stimuli, and end point measures (accuracy or reaction time), all which may affect outcomes.

In summary, there is evidence of abnormal visual processing in BDD. The findings in the functional neuroimaging studies suggest imbalances in detailed versus global/configural processing marked by abnormalities in primary and/or secondary visual cortical, temporal, and prefrontal systems. Moreover, this overall pattern is evident for own-face, other-face, and inanimate object stimuli. The behavioral (psychophysical) studies provide evidence for enhanced detail processing, with reduced face inversion effect and enhanced ability to detect changes in facial features.

Morphometric and Other Neuroimaging Studies

There have only been three small studies in BDD that have investigated volumetric brain morphometry. A study of females with BDD compared with healthy controls found greater total white matter and a relative leftward shift in caudate asymmetry (Rauch et al., 2003). A study of males also found greater total white matter, as well as a smaller anterior cingulate and orbitofrontal cortex and a trend for larger thalamic volumes (Atmaca et al., 2010). Both studies provide evidence for abnormalities in frontostriatal systems. The third study (Feusner et al., 2009) did not find volumetric differences between groups, but found that symptom severity as measured by the BDD-YBOCS correlated significantly with volumes of the left inferior frontal gyrus (IFG) and the right amygdala.

A small single-photon emission computed tomography (SPECT) study was performed in 6 BDD subjects (Carey, Seedat, Warwick, van Heerden, & Stein, 2004). It showed relative perfusion deficits in bilateral occipital as well as anterior temporal regions, and asymmetric perfusion in the parietal lobes.

Neurobiological Model for Pathophysiology of BDD

Here we attempt to integrate the presented findings into a preliminary model for understanding the pathophysiology of BDD as it pertains to neurobiological abnormalities. As with most psychiatric disorders, the governing pathophysiology for BDD is complex and unlikely to be encompassed by a single domain. Importantly, neurobiological models alone are also likely to be insufficient in explaining such a complex disorder; interpersonal, cognitive-behavioral, psychodynamic, and cultural contributions are also critical factors to consider.

In BDD, aberrant interactions between networks and regions as well as neurotransmitter and neurochemical systems may have etiological roles, or else may represent

secondary sequelae of the illness. Up to this point, the limited research into this disorder, particularly due to the fact that most studies have involved a small number of subjects and have not been replicated, precludes drawing firm conclusions about the neurobiology of BDD and hampers the development of a well-supported model. However, from the extant research there are patterns that have begun to emerge across studies. One pattern is that of abnormalities in frontostriatal systems, as evidenced by neurocognitive (impaired executive functioning) and functional and structural neuroimaging studies. Similar patterns of frontostriatal hyperactivity and dysfunction are evident in many studies of OCD (for reviews, see Menzies et al., 2008; Whiteside, Port, & Abramowitz, 2004). In addition, improvement of BDD symptoms through modulation of the serotonergic system with SRIs, similar to that in OCD, could be the result of mechanistic action at the level of frontostriatal circuits or the limbic system (Blair, Habib, & Flament, 2006; Furmark et al., 2002). Another pattern that has emerged involves abnormalities in visual processing for appearance and non-appearance-related stimuli, as evidenced by findings in functional neuroimaging and psychophysical studies. These appear to follow a pattern of enhanced detail and/or impaired global and configural processing. In addition, there is evidence of abnormal emotional processing, as evidenced by impairments in facial emotional recognition and abnormal patterns of amygdala activity. There is also emerging evidence that there may be heritable genetic factors involved in BDD, and possibly a heritable link between BDD and OCD.

A preliminary neurobiological model of BDD symptoms thus needs to take into account abnormalities that span domains of perception, emotional processing, planning, organization, response inhibition, and patterns of obsessive thoughts and compulsive behaviors. Abnormalities in visual perception, originating in primary and secondary visual processing systems, may represent a sensory deficit that provides an initial distorted percept. This may subsequently be modulated by impaired emotional processing and aberrant frontostriatal systems (including impaired response inhibition and visuospatial organization), which could give rise to an inability to inhibit obsessive thought patterns and to concomitant urges to perform compulsive and avoidant behaviors. A distorted perception, further erroneously validated by impaired perception of others' emotional reactions toward them (thus contributing to poor insight and delusionality) would then be maintained and perpetuated over time by an inability to control thoughts and behavioral patterns.

Future Research Directions

To help test and refine this and other models, further neurobiological research in BDD is imperative. In

particular, as most studies thus far have been cross-sectional, it is not possible to discern if the pathophysiological deficits are etiological or secondary to other aspects of the illness that have developed over time. To elucidate this, longitudinal studies of children at risk will be useful, particularly in relation to developmental changes that occur during adolescence, when the onset of the disorder typically occurs. In addition, studies of unaffected first-degree relatives will help identify likely inherited phenotypes and endophenotypes. A better integration of brain imaging modalities such as electroencephalography (EEG), magnetoencephalography (MEG), fMRI, and structural evaluations (diffusion tensor imaging and volumetric/cortical thickness) could uncover important structure–function relationships, as well as help develop a better understanding of the time course and dynamics of brain activity. Once dysfunctional systems have been identified (e.g., specific circuits within frontostriatal systems, and/or subsystems of visual processing networks such as dorsal or ventral visual stream), further neurochemical investigations of neurotransmitter systems that may mediate abnormalities would be useful. In addition, because of the evidence of shared heredity and overlap in phenomenology and comorbidity, direct comparisons of individuals with BDD with those with OCD could elucidate specific neurobiological factors that may represent these shared traits or susceptibility factors. Similar investigations should also be conducted across other possibly related disorders such as eating disorders and social phobia.

Conclusions

BDD appears to be a complex disorder in which heritable factors related to dysmorphic concerns and obsessive-compulsive traits, as well as other biological susceptibilities, may combine in certain individuals with family, interpersonal, and cultural experiences to lead to the development of BDD. Neurobiological dysfunctions span several domains that have been studied thus far, including neurocognitive, neurochemical, visual and emotional processing systems, and genetics. We propose a neurobiological model for BDD that includes visual and emotional processing abnormalities and frontostriatal and limbic system dysfunction. These may combine to contribute to the symptoms of perceptual distortions and impaired insight, as well as obsessive thoughts and compulsive behaviors. Further research is necessary to gain a greater understanding of the etiology of BDD symptoms and their evolution over time, and will be important in aiding intervention strategies and the development of improved treatments.

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Recent advances in MRI technology have allowed the investigation of both cortical function (fMRI) and white matter structure (Diffusion Tensor Imaging, or DTI) in vivo. DTI can be used to quantify measures of water diffusion such as anisotropy, which reflects the integrity and orientation of tissue at the voxel level, since the water motion is restricted along the direction of the axons. Furthermore, tractography allows characterization of fiber tracts that connect across neighboring voxels, which can infer the strength and integrity of connections between brain regions. A better understanding of structure-function relationships for the visual system, as well as the microstructural abnormalities that may underlie the functional deficits we observed in Chapters 2 and 3, may provide insight on which areas of the brain architecture are affected in AN and BDD and suggest targets for followup treatment and intervention. For example, white matter abnormalities in tracts connecting limbic and visual processing systems (i.e. the inferior longitudinal fasciculus) might suggest dysfunction in emotional processing of stimuli to and from visual cortex.

In Chapter 4.2, we investigate white matter integrity using diffusion imaging in BDD through the use of DTI and probabilistic tractography, of which the author contributed much of the coding and implementation in MATLAB.

4.2. White Matter Microstructure in Body Dysmorphic Disorder and its Clinical Correlates

This section is adapted from:

Feusner J, Donatello A, Li W, Zhan L, GadElkarim J, Thompson PM, & Leow A (2014). White matter microstructure in body dysmorphic disorder and its clinical correlates, *Psychiatry research* **211**, 132–140.

Published in final edited form as:

Psychiatry Res. 2013 February 28; 211(2): 132–140. doi:10.1016/j.psychres.2012.11.001.

White matter microstructure in body dysmorphic disorder and its clinical correlates

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Abstract

Body dysmorphic disorder (BDD) is characterized by an often-delusional preoccupation with misperceived defects of appearance, causing significant distress and disability. Although previous studies have found functional abnormalities in visual processing, frontostriatal, and limbic systems, no study to date has investigated the microstructure of white matter connecting these systems in BDD. Fourteen medication-free BDD participants and 16 healthy controls were scanned using diffusion-weighted MRI. We utilized probabilistic tractography to reconstruct tracts of interest, and tract-based spatial statistics to investigate whole brain white matter. To estimate white matter microstructure we used fractional anisotropy (FA), mean diffusivity (MD), and linear and planar anisotropy (c_l and c_p). We correlated diffusion measures with clinical measures of symptom severity and poor insight/delusional. Poor insight negatively correlated with FA and c_l and positively correlated with MD in the inferior longitudinal fasciculus (ILF) and the forceps major (FM). FA and c_l were lower in the ILF and IFOF and higher in the FM in the BDD group, but differences were nonsignificant. This is the first diffusion-weighted MR investigation of white matter in BDD. Results suggest a relationship between impairments in insight, a clinically important phenotype, and fiber disorganization in tracts connecting visual with emotion/memory processing systems.

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Financial Disclosures

None of the authors have any conflicts of interest to report.

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Keywords

diffusion tensor imaging; probabilistic tractography; high angular resolution diffusion imaging; inferior longitudinal fasciculus; inferior fronto-occipital fasciculus; forceps major

1. INTRODUCTION

Body dysmorphic disorder (BDD) is a psychiatric disorder in which individuals are preoccupied with misperceived defects of their appearance (American Psychiatric Association., 2000). Believing that they look disfigured and ugly, they suffer significant distress and functional impairment. BDD affects approximately 0.7–2.4% of the population (Faravelli et al., 1997; Rief et al., 2006; Koran et al., 2008; Buhlmann et al., 2010) and is associated with high lifetime rates of hospitalization (48%) (Phillips and Diaz, 1997) and suicide attempts (22%–27.5%) (Veale et al., 1996; Phillips and Diaz, 1997; Phillips et al., 2005). Insight is usually impaired and 36–60% of BDD patients are delusional (Gunstad and Phillips, 2003; Phillips et al., 2005; Mancuso et al., 2010). Despite the severity of this disorder, knowledge of the underlying abnormalities in brain function and structure is still in its early stages.

An important symptom domain in BDD, for which there is emerging evidence, is distortion of visual perception. Distortion of self-perception of appearance may contribute to the conviction of disfigurement and ugliness and subsequent poor insight or delusionality. Clinically, individuals with BDD focus on details of their appearance at the expense of global aspects. A neuropsychological study using the Rey-Osterrieth Complex Figure Test demonstrated that patients with BDD selectively recalled details instead of larger organizational design features (Deckersbach et al., 2000). Individuals with BDD may also have perceptual distortions for own-face processing; in one study they perceived distortions of digital images of their faces that were not actually present (Yaryura-Tobias et al., 2002).

A previous functional magnetic resonance imaging (fMRI) study (performed in the same participants as the current study) found that individuals with BDD demonstrated abnormalities in visual processing (striate and extrastriate visual cortex) and frontostriatal systems (orbitofrontal cortex and caudate) when viewing their face (Feusner et al., 2010). There was also evidence of abnormalities in emotion processing systems. In addition, BDD symptom severity was correlated with frontostriatal activity and activity in extrastriate visual cortex. Abnormalities in visual systems may therefore represent early stage abnormalities (“bottom-up”) and/or may be the result of “top-down” modulation from emotional processing and/or prefrontal systems.

An earlier fMRI study in BDD using others’ faces as stimuli also found a pattern of abnormal information processing, including left hemisphere hyperactivity in an extended face-processing network (Feusner et al., 2007). This pattern, in contrast to the generally right hemisphere-dominant pattern for healthy controls (Haxby et al., 1994), suggests greater detail encoding and analysis relative to holistic and configural processing. Abnormal interhemispheric sharing of information may be involved, which may also contribute to aberrant visual processing.

The objective of the current study was to explore anatomical white matter connections involved in these neural systems that have been previously found to show abnormal activity in BDD. These white matter tracts include those likely involved in the integration of information between visual processing and the limbic as well as prefrontal systems, and those involved in interhemispheric sharing of information.

The only other studies in BDD that have investigated white matter include three small studies of volumetric brain morphometry. Two of these (Rauch et al., 2003; Atmaca et al., 2010), but not the third (Feusner et al., 2009) found greater total white matter in the BDD group relative to healthy controls.

To our knowledge, no study to date has investigated white matter microstructure in BDD using diffusion tensor imaging (DTI). However, several DTI studies have investigated white matter integrity in obsessive-compulsive disorder (Szeszko et al., 2005; Cannistraro et al., 2007; Yoo et al., 2007; Menzies et al., 2008; Saito et al., 2008; Garibotto et al., 2010; Bora et al., 2011; Nakamae et al., 2011), which is believed to be related to BDD (Hollander and Wong, 1995; Phillips et al., 2010). Several of these studies (Yoo et al., 2007; Saito et al., 2008; Garibotto et al., 2010; Bora et al., 2011; Nakamae et al., 2011), but not others (Szeszko et al., 2005; Cannistraro et al., 2007; Menzies et al., 2008), found abnormal fractional anisotropy (FA) in the corpus callosum. Across the studies with positive findings, however, there were inconsistencies in regard to both location and direction (higher or lower FA) of the abnormalities within the corpus callosum. Two studies in social anxiety disorder, also thought to be related to BDD (Fang and Hofmann, 2010) suggested abnormalities of FA in the uncinate fasciculus (Phan et al., 2009; Baur et al., 2011). One study in anorexia nervosa, also conceptualized to be related to BDD (Cororve and Gleaves, 2001), found abnormalities in the fimbria-fornix (Kazlouski et al., 2011). Overall, a consistent pattern of white matter abnormalities has not emerged in these related disorders. Thus we based our hypotheses for the current study on the aforementioned functional brain imaging studies in BDD suggesting abnormal activity in extended visual processing systems, in addition to performing exploratory analyses across the white matter of the entire brain.

Magnetic resonance diffusion imaging can provide information on white matter microstructure and anatomical connectivity by measuring the diffusion profile of water molecules. The DTI technique fits an ellipsoid (or “tensor”) to local water diffusivity, providing an estimate of the magnitude and orientation of water diffusion at each voxel. From this, white matter integrity measures based on the three “eigenvalues” of the reconstructed ellipsoid (representing the magnitude of water diffusivity along the three principal directions of the ellipsoid), such as the fractional anisotropy (FA; a measure of preferential directionality of water diffusion) and mean diffusivity (MD; a measure of overall diffusivity), and can be derived (Torrey, 1956; Stejskal, 1965).

One limitation of the standard FA is that it is not designed to probe subvoxel fiber architecture. Thus, low FA values may reflect either abnormal individual fiber integrity (e.g., fiber demyelination) or greater dispersion of fibers (e.g., fiber crossing or mixing, or other disorganization). To help differentiate these, we included DTI-derived geometric indices, linear and planar anisotropy (c_1 and c_2) (Westin et al., 2002), to better quantify the shape of diffusion tensors beyond standard FA and MD.

Based on the previous BDD studies outlined above, we hypothesized that BDD participants would exhibit microstructural white matter abnormalities relative to controls in tracts involved in integration of information between limbic and visual processing systems, between prefrontal systems and visual processing systems, and those involved in interhemispheric sharing of information. We therefore examined the inferior longitudinal fasciculus (ILF), which connects anterior temporal cortex structures (including the amygdala and hippocampus) to the occipital lobe; the inferior fronto-occipital fasciculus (IFOF), which connects prefrontal regions to the occipital lobe; and the forceps major (FM), which connects the right and left occipital lobes (Catani and Schotten, 2008). Moreover, we predicted significant correlations would exist between the degree of microstructural abnormalities in these tracts and important clinical phenotypes of BDD symptom severity as

well as poor insight/delusionality. We also performed an exploratory voxel-wise analysis of all white matter tracts.

2. METHODS

2.1. Participants

The UCLA Institutional Review Board approved the study protocol. Fourteen unmedicated participants with BDD and 16 healthy controls, aged 20 to 48 years, provided informed consent and participated (Table 1). BDD and control participants of equivalent sex, age, and level of education were recruited from the community (all had participated in a previous fMRI study of own-face processing (Feusner et al., 2010)). All were right-handed as determined by the Edinburgh Handedness Inventory (Oldfield, 1971). Diagnoses were made by J.D.F. who has clinical expertise with this population using the Body Dysmorphic Disorder Module (Phillips et al., 1995), a reliable diagnostic module modeled after the Structured Clinical Interview for Diagnostic and Statistical Manual (DSM) Disorders. In addition, we performed a clinical psychiatric evaluation and screened participants with the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998).

Exclusion criteria for all participants included: substance abuse or dependence within the past 12 months, lifetime neurological disorder, pregnancy, or any current medical disorder that may affect cerebral metabolism. We excluded BDD participants with any concurrent Axis I disorder besides dysthymia, major depressive disorder (MDD), or generalized anxiety disorder (GAD); as depression and anxiety are frequently comorbid in BDD, we believed that a sample excluding these would not be representative. However, we required that BDD be the primary diagnosis as defined by the MINI. Healthy controls could not have any current or past Axis I disorder, as determined by the MINI. We administered the BDD version of the Yale-Brown Obsessive-Compulsive Scale (BDD-YBOCS) (Phillips et al., 1997), a validated scale widely used to evaluate symptom severity in BDD (scores ranging from 0 to 48). We administered the Brown Assessment of Beliefs Scale (BABS), a measure of insight and delusionality that has been tested for validity and reliability in this population (Eisen et al., 1998). BABS Scores range from 0 to 24. Higher scores indicate poorer insight (more convinced about their appearance being defective and less able to recognize that their appearance concerns are attributable to a mental illness). A score of 18 with a score of 4 on item 1 (how convinced the person is that he/she is accurate) is classified as delusional. The 17-item Hamilton Depression Rating Scale (HAM-D-17), a widely used and well-validated scale (Hamilton, 1960), was used to measure depressive symptoms.

All participants with BDD were required to have a score of 20 or higher on the BDD-YBOCS. Participants were free from psychoactive medications for 8 weeks or longer prior to the study and were not receiving cognitive-behavioral therapy.

All diffusion data were age- and gender-corrected using General Linear Model Univariate in SPSS, with gender as a fixed factor and age as continuous predictor.

2.2. Imaging data acquisition

We used a 3-T Allegra MRI scanner (Siemens Medical Solutions USA, Inc, Malvern, Pennsylvania). Diffusion-weighted MR imaging data were acquired using single-shot spin-echo echo-planar imaging (EPI) (field of view=240mm; voxel size=2.5×2.5×3.0mm, with 0.75 mm gap; TR/TE=7400/96ms; flip angle 9°). We collected 44 contiguous axial slices aligned to the anterior commissure–posterior commissure line along 34 gradient-sensitizing directions with $b=1000\text{s/mm}^2$ and one minimally diffusion-weighted scan.

2.3. Data processing

All DTI data were visually inspected for motion artifacts to ensure quality, followed by Eddy current correction using FSL (http://www.fmrib.ox.ac.uk/fsl/fdt/fdt_eddy.html). Diffusion tensors were constructed using the MedInria software (<http://www.sop.inria.fr/asclepios/software/MedINRIA/>) to obtain three eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) and three eigenvectors (v_1, v_2, v_3). The eigenvector (v_1) associated with the largest eigenvalue (i.e., the axial diffusivity) is usually assumed to represent local fiber direction. FA is mathematically defined as:

$$FA = \sqrt{\frac{3}{2} \left(\frac{(\lambda_1 - \bar{\lambda})^2 + (\lambda_2 - \bar{\lambda})^2 + (\lambda_3 - \bar{\lambda})^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2} \right)}; \bar{\lambda} = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} \quad (1)$$

Its values range from 0 (no directional dependence of diffusion) to 1 (diffusion along a single direction), and are considered a general measure of white matter integrity. MD ($\bar{\lambda}$ in equation (1)) quantifies the overall water diffusivity and is defined as the average of the 3 eigenvalues.

2.3.1. Geometric indices—DTI white matter integrity indices are usually defined based on the eigenvalues of the tensor, and thus are rotationally invariant. While the FA distinguishes only between isotropic and anisotropic diffusion profiles, c_p and c_l (Westin et al., 2002) further determine whether diffusion profiles are planar/“pancake” shaped (high c_p), or linear/“cigar” shaped (high c_l). In white matter regions with highly coherent fiber orientations, water diffusion is mainly restricted along the direction corresponding to the largest DTI eigenvalue and as a result c_l (mathematically defined as: $c_l = (\lambda_1 - \lambda_2)/\lambda_1$) (Westin et al., 2002) takes values close to 1. In the planar case the diffusion is mostly restricted to the plane spanned by the two eigenvectors corresponding to the two largest eigenvalues (λ_1 and λ_2 , which would be large relative to λ_3), and as a result c_p (mathematically defined as: $c_p = (\lambda_2 - \lambda_3)/\lambda_1$) (Westin et al., 2002) takes values close to 1. Thus, the magnitudes of c_l and c_p provide estimates of fiber tract organization.

2.4. Fiber reconstruction using tractography

For tract-specific analyses, we used probabilistic tractography to compare mean white matter integrity measures between BDD and control participants for: a) the inferior fronto-occipital fasciculus (IFOF), which connects prefrontal regions to the occipital lobe; b) the inferior longitudinal fasciculus (ILF), which connects anterior temporal cortex structures (including the amygdala and hippocampus) to the occipital lobe; and c) the forceps major (FM), which connects the right and left occipital lobes (Catani and Schotten, 2008). In addition, we investigated the relationship between these tract diffusion measures and two important clinical variables in BDD: symptom severity (BDD-YBOCS) and degree of insight/delusional (BABS).

For the probabilistic tractography we used a high angular resolution diffusion imaging (HARDI) method, the tensor distribution function (TDF), to reconstruct the imaging data (Leow et al., 2009) and to perform tractography. To this end, we utilized a standard probabilistic tractography algorithm with necessary modifications to accommodate data processed using TDF (GadElkarim et al., 2011) (see Supplementary Information for full details). Tract reconstruction was performed in individual subjects' diffusion image space, using anatomical landmarks as described below (see also Fig. S1). Interrater reliability for FA was $r=0.95$, which was established between investigators (D.A. and W.L.) on a set of data from 6 randomly chosen subjects (3 from the BDD set and 3 from the healthy controls),

for which ROIs were separately drawn by each investigator to reproduce the tracts and extract the diffusion measures.

2.5. Tract reconstruction protocol

2.5.1. IFOF—A para-sagittal plane at the level of the mid-cingulum was selected in the B0 image. A coronal slice was then selected at the anterior edge of the thalamus. On the corresponding color-coded tensor map, a region of interest (ROI) was drawn around the cluster of voxels in the superior-medial part of the temporal lobe that represent anteriorly-to-posteriorly oriented white matter tracts (i.e., color-coded green).

We then visually inspected all fibers passing through this seeding ROI. Fibers that did not connect the frontal lobe with the occipital lobe were then excluded. Operationally, we defined the frontal lobe to be the brain tissue anterior to the anterior edge of the thalamus, and occipital lobe posterior to the mid-point between the posterior edge of the parieto-occipital sulcus and the posterior edge of the posterior cingulum.

2.5.2. ILF—For the ILF and forceps major we followed and slightly modified the method used in (Wakana et al., 2007). We first selected a sagittal slice at the level of the mid-cingulum in the B0 image and identified the parieto-occipital sulcus. A coronal plane was selected halfway between the posterior edge of the parieto-occipital sulcus and the posterior edge of the posterior cingulum. The first ROI was drawn in the equivalent color-coded tensor space to include the occipital lobe (and exclude the parietal lobe). If difficult to visualize in any particular participant, the boundary between the occipital and parietal lobes was defined by linearly extrapolating the parieto-occipital sulcus medially to the lateral edge of the brain.

The second ROI was defined in the anterior temporal lobe. A sagittal slice at the level of the mid-cingulum was select from the B0 image. A coronal slice was then selected at the posterior edge of the genu of the corpus callosum. In this slice, if the temporal lobe was connected to the frontal lobe then the next coronal slice anteriorly that was not connected was selected. On this slice, the second ROI was drawn to include the entire temporal lobe.

2.5.3. FM—These ROIs were drawn in the same manner as the first ROI for the ILF. The first ROI was drawn to select the occipital lobe in the right hemisphere. The second ROI was drawn in the same way on the left hemisphere.

2.6. White matter integrity measures and data analysis

For each tract-of-interest, we plotted the reconstructed fibers and extracted mean white matter integrity measures of FA MD, c_f , and c_p . In the absence of *a priori* hemisphere-specific hypotheses, we analyzed bilateral (left+right) tracts for the ILF and IFOF (the FM is a midline structure). *Post hoc* analyses were then conducted for the left and right ILF and IFOF. We performed two-way ANOVAs with group as one factor and tract (ILF, IFOF, and FM) as the other (repeated measures) factor to compare mean values for each measure. Huynh-Feldt adjustments for sphericity were used when appropriate.

For the BDD group, we computed Pearson correlation coefficients between integrity measures and BDD-YBOCS and BABS scores. We used a Bonferroni-corrected significance level of $\alpha=0.017$ ($0.05/3$), two-tailed, for testing *a priori* hypotheses on bilateral ILF, IFOF and FM for each measure; and a Bonferroni-corrected significance level of $\alpha=0.0125$ ($0.05/4$), two-tailed, for the *post hoc* analyses for right and left ILF and IFOF tracts.

2.7. TBSS

We conducted exploratory voxel-wise analyses comparing FA, MD and eigenvalues in whole-brain white matter between the two groups using the TBSS program in FSL (Smith et al., 2006). TBSS utilizes nonlinear registration to project measures-of-interest onto an alignment-invariant tract representation (the “mean skeleton”). From this normalized template, voxel-wise statistical comparisons were performed between groups using Randomise v2.1, with the Threshold-Free Cluster Enhancement option (<http://www.fmrib.ox.ac.uk/fsl/randomise/index.html>). This produced *P*-value images, fully corrected for multiple comparisons. We used a significance threshold of $\alpha=0.05$.

3. RESULTS

3.1. Demographics and psychometrics

Two BDD participants had comorbid GAD, one had comorbid MDD, and three had both GAD and MDD or dysthymia. All BDD participants had preoccupations with perceived facial defects.

3.2.1 Between group tractography results—There were no significant between-groups differences in the ILF, IFOF, or the FM for FA, MD, c_l or c_p , although there was a trend for a group-by-tract interaction effect in the FM for c_l ($F_{1,9, 53}=2.47$, $P=0.097$). Although not statistically significant, there was a consistent pattern in the BDD group relative to healthy controls of lower FA and c_l in the ILF and IFOF and higher FA and c_l in the FM.

3.2.2 Additional *post hoc* analysis of comorbidity—Because there were 6 BDD subjects with a comorbid anxiety and/or depressive disorder, we performed a repeated measures ANOVA with comorbidity status as one factor and tract as the repeated measures factor for each of FA, MD, c_l , and c_p . Means for these diffusion measures were similar between comorbid and noncomorbid groups for the ILF, IFOF, and FM (Table S3). ANOVA results demonstrated no significant effect of comorbidity. There was only a significant comorbidity by tract effect for FA ($F_{2,24}=3.95$, $P=0.033$): however, post hoc *t*-tests revealed no significant differences between comorbid and noncomorbid groups for the ILF ($t=0.72$, d.f.=12, $P=0.49$), IFOF ($t=0.67$, d.f.=12, $P=0.51$), or FM ($t=0.47$, d.f.=12, $P=0.65$).

3.3. TBSS results

Voxel-wise analyses in the whole-brain white matter using TBSS did not detect any significant group differences.

3.4.1. Correlation results—There were significant negative correlations in the ILF and FM between BABS scores and both FA and c_l and significant positive correlations in the ILF and FM between BABS scores and MD (see Table 3 and Figs. 1, S2, and S3). There were no significant correlations in these tracts between any diffusion measures and BDD-YBOCS scores (Table S1 in Supplementary Information). This suggests that there is a stronger association between white matter microstructure and insight (as measured by the BABS), rather than symptoms of obsessional thoughts and compulsive behaviors (primarily measured by the BDD-YBOCS), in these tracts.

3.4.2. Additional, *post hoc* correlation analyses—Because four BDD participants had a comorbid depressive disorder and all had some degree of depressive symptomatology, we additionally calculated Pearson correlation coefficients between HAM-D-17 scores and the diffusion measures. There were no significant correlations between HAM-D-17 and FA,

MD, c_f or c_p for any tract (Table S2 in Supplementary Information), suggesting that there are stronger associations between white matter microstructure and insight, rather than depressive symptomatology, in these tracts.

For the correlation analyses with BABS scores, one data point met criteria as an outlier for MD in the FM, based on the z-score method for outlier detection ($Z=3.1$) (Barnett and Lewis, 1984; Iglewicz and Hoaglin, 1993). We recalculated the Pearson correlation coefficient without this data point and found that there was still a strong positive correlation between BABS and MD ($r=0.53$, $P=0.062$), although it was no longer statistically significant.

4. DISCUSSION

This represents the first investigation of white matter microstructure in BDD using diffusion-weighted MRI. We found that the clinical measure of poor insight correlated negatively with FA and c_f and positively with MD in the ILF, which connects visual with emotional processing systems. Poor insight also correlated negatively with FA and c_f and positively with MD in the FM, which connects right and left visual processing systems.

In order to better understand white matter architecture beyond the standard measures of FA and MD, we utilized additional metrics for investigating fiber tract organization: c_f and c_p . The finding of a negative correlation between poor insight and both FA and c_f suggests that greater fiber dispersion (which would contribute to both lower c_f and FA) is associated with worse insight. Our results therefore suggest a more specific relationship between fiber architecture, rather than individual fiber integrity, and poor insight in BDD.

These correlations were present despite the observation there were no significant between-groups differences detected in these tracts. This likely reflects the idea that phenotypes, such as poor insight in this case, may map better to brain pathophysiology than DSM or ICD-10 diagnostic categories. Such categorical constructs are increasingly recognized to have limited validity (Insel and Cuthbert, 2009), particularly as they may represent heterogeneous groupings of symptom clusters or dimensions. Poor insight, as a dimension of observable behavior that cuts across many diagnostic boundaries (Goldberg et al., 2001), may prove to be an important phenotype with links to aberrant neurobiology.

In BDD, poor insight is considered to be on a continuum with delusionality (Phillips et al., 1994; Phillips et al., 2006; Mancuso et al., 2010). This may represent a dimensional phenotype of psychosis in BDD (Phillips, 2004). Poor insight/delusionality usually manifests as erroneous convictions that one or more appearance features are defective and ugly (Phillips et al., 1993; Phillips et al., 1994). Insight is typically poor in most individuals with BDD, with 36–60% of patients classified as delusional (Eisen et al., 2004; Phillips, 2004; Phillips et al., 2006; Mancuso et al., 2010). Delusional variants appear to exist on a continuum with nondelusional variants, as they are similar in most demographics, clinical features, and course of illness (Phillips et al., 2006; Mancuso et al., 2010). Case reports suggest that individuals with BDD fluctuate between overvalued ideations and delusionality (Phillips and McElroy, 1993). Insight/delusionality is an important clinical variable; individuals who are more delusional seem less likely to seek and remain in treatment (Eisen et al., 2004) and, when controlling for symptom severity, have lower educational attainment (Eisen et al., 2004; Phillips et al., 2006). Because poor insight is typically related to what they perceive, and studies show abnormalities in visual processing systems in BDD (Feusner et al., 2007; Feusner et al., 2010; Feusner et al., 2011), one possibility is that a distorted visual perception of appearance is difficult to refute, and may contribute to their level of conviction. The structural neurobiology of systems involved in visual perception in BDD may therefore be relevant to understanding poor insight/delusionality.

One such structural system is the ILF, which connects the temporal lobe with the occipital lobe (Catani et al., 2003; Catani and Schotten, 2008). Long fibers in this tract connect the anterior temporal lobe with posterior occipital regions (Catani et al., 2003). The occipital branches of the ILF extend to extrastriate cortical regions in the dorso-lateral occipital lobe, lingual and fusiform gyri, and the cuneus, while temporal branches extend medially near the amygdala, hippocampus, and uncus/parahippocampal gyrus. Feed-forward and feed-back information may be carried on this tract (Schmahmann and Pandya, 2006). Feed-forward connections may function to consolidate visual memories (Shinoura et al., 2007; Ross, 2008). Feed-back connections likely carry signals regarding emotional valence of stimuli to the visual cortex, resulting in enhanced visual processing of emotionally salient stimuli. This has been demonstrated in neuroimaging studies in which amygdala activation was found to correlate with activation in the visual cortex (Morris et al., 1998; Pessoa et al., 2002), and this correlation is attenuated in patients with amygdala damage (Vuilleumier et al., 2004). Moreover, pre-existing representation of face identity in memory may influence early stages of visual encoding (Righart et al., 2011). In this way, top-down modulation on earlier visual processing systems by memory representations may overlap with perceived facial information. The ILF therefore is involved in visual processing, and may have a role in face recognition (Fox et al., 2008) as well as facial emotion recognition (Philippi et al., 2009).

Our finding of significant correlations between fiber dispersion in the ILF and poor insight suggests that worse insight/delusionality may be associated with reduced fiber organization in pathways involved in integration between emotional signals and visual perception. We conjecture that the observed higher degree of fiber dispersion in ILF may be due to reduced alignment of long ILF fiber bundles that connect visual- and emotion-processing systems, or alternatively due to aberrant connections within shorter, local fibers that travel with ILF during part of their course. The correlation between fiber dispersion and poor insight was greater on the left, although the functional significance is unclear.

The previous fMRI study in BDD of own-face perception (Feusner et al., 2010), performed in the same individuals as in the current study, found hypoactivity in regions of the left extrastriate visual cortex that are likely connected to anterior temporal lobe structures via the ILF. Hypoactivity was found in these regions specifically for face images that represented only low spatial frequency information. It is possible then that feed-forward and/or feed-back of information between perceptual and emotional/memory systems may be disturbed in BDD. This may affect specific elements of perception such as the ability to perceive the whole, which may subsequently contribute to worse insight/delusionality.

In the same study, there was no significant amygdala (or insula) hyperactivity, despite the BDD participants rating own-face viewing as highly distressing and aversive. This also suggests impaired connections between perceptual and emotional systems in BDD. Other studies in BDD have found misinterpretations of facial expressions (Buhlmann et al., 2004; Buhlmann et al., 2006), and impairment in identity recognition of faces with emotional expressions (Feusner et al., 2010). These studies lend additional evidence to impairments in integration of visual and emotional information.

Poor insight also correlated with fiber dispersion in the FM. This tract appears to be involved in transferring visual inputs from one hemisphere to the other (see (Doron and Gazzaniga, 2008) for review). Other evidence for disturbed right/left hemisphere function in BDD comes from a previous fMRI study of other-face visual processing, in which there was a left-hemisphere dominant pattern (Feusner et al., 2007). In addition, a test of global-local visual processing in BDD revealed slower performance in the BDD relative to the control group, particularly when participants were required to switch between identifying local and global stimuli (Kerwin et al., 2011), which likely requires interhemispheric transfer of

information. It is possible, then, that poor insight in BDD may also be related to visuospatial abnormalities mediated by fiber disorganization in the FM.

The findings from the current study may signify that poor integration of information between systems subserved by the ILF and the FM, related to fiber disorganization, may be associated with inability to accurately perceive and/or contextualize visual stimuli in individuals with BDD. When individuals view their own appearance, impaired feed-forward or feed-back information transfer in the ILF may result in a failure to update visual memories accurately. This may result in persistent yet distorted visual templates of appearance flaws, as a result of, for example, previously viewing themselves in extreme lighting conditions or even from past blemishes such as acne that had since resolved. In addition, impaired interhemispheric information transfer in the FM may impair ability to integrate global and local visual information; this may result in a piecemeal perception of their appearance features and an inability to perceive that whatever slight defects exist are small relative to the whole. These resultant distorted visual perceptions may be difficult to refute, translating to poor insight or even delusionality about their appearance. This level of conviction may be resistant to attempts of others to reassure them that their appearance does not appear defective and ugly (which family members and friends often try to do), because they take the reality of their visual experience for granted. Further, this may trigger other symptoms such as dysphoria about perceived ugliness, anxiety and self-consciousness around others, and compulsive behaviors to fix or hide their appearance.

Although no previous study has investigated white matter integrity using diffusion imaging in BDD, studies in other clinical populations have found abnormalities in the ILF. Multiple studies in schizophrenia have found low FA in the ILF, as well as other white matter tracts (Hubl et al., 2004; Ashtari et al., 2007; Mitelman et al., 2007; Cheung et al., 2008; Michael et al., 2008; Clark et al., 2011). Several of these have found associations between positive (Mitelman et al., 2007; Michael et al., 2008) and negative symptoms (Michael et al., 2008) and low FA in the ILF, and associations between, auditory (Hubl et al., 2004) and visual hallucinations (Ashtari et al., 2007) and low FA in the left ILF. Some of these studies also found lower FA in the left IFOF in schizophrenics (Cheung et al., 2008; Clark et al., 2011). Despite many phenomenological differences between BDD and schizophrenia, they share some clinical phenotypes such as poor insight, delusional thinking, distorted perception, as well as evidence of abnormalities in global visual processing and visual integration (see (Silverstein and Keane, 2011) and (Butler et al., 2008) for reviews).

This study has several limitations. Small sample size may have resulted in low power, which may explain why significant differences were not detected between groups for the DTI measures. The cross-sectional design limits our understanding of whether the correlative relationships between white matter architecture and clinical symptoms has a causative role in BDD symptoms, or are the secondary effects of having BDD. It is also not possible to determine whether the findings in the ILF have significance for feed-forward and/or feed-back relationships, as information carried in this tract may be bidirectional (Schmahmann and Pandya, 2006). The acquisition parameters of our diffusion sequence included a gap of .75mm in the z plane, which may have reduced the ability to reconstruct fibers using tractography, especially for those tracts that are oblique to the z plane. Because we extracted white matter tracts using a protocol based on ROI drawings using anatomical landmarks (Wakana et al., 2007), variations in ROI placement may result in different tracts, an inherent limitation of DTI-tractography (Hagmann et al., 2003).

The current study has several strengths. Our hypotheses were informed by a functional imaging study of own-face processing in the same individuals with BDD (Feusner et al.,

2010). All participants were unmedicated, reducing possible confounds observed with psychotropic medications in other DTI studies (Yoo et al., 2007).

In conclusion, we detected significant correlations between fiber dispersion and poor insight/delusional in the ILF and FM in individuals with BDD. This clinical symptom in BDD, with important prognostic implications, may therefore be associated with fiber disorganization in tracts that communicate between visual perceptual and emotion/memory processing systems. Future larger studies are warranted to confirm these findings, and also in order to further investigate white matter architecture and integrity and how they relate to phenotypes underlying different symptom dimensions in BDD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by grants from the National Institute of Mental Health (5K23 MH079212, 1R01 MH093535, and 1R01 MH085900 – Dr. Feusner), a grant from the International Obsessive Compulsive Foundation (Dr. Feusner), and a UCLA Faculty Research Grant (Dr. Feusner). Dr. Leow was partially supported by a grant from the National Alliance for Research on Schizophrenia and Depression (NARSAD- G5749). None of the funding sources had any involvement in the study design; in the collection, analysis or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

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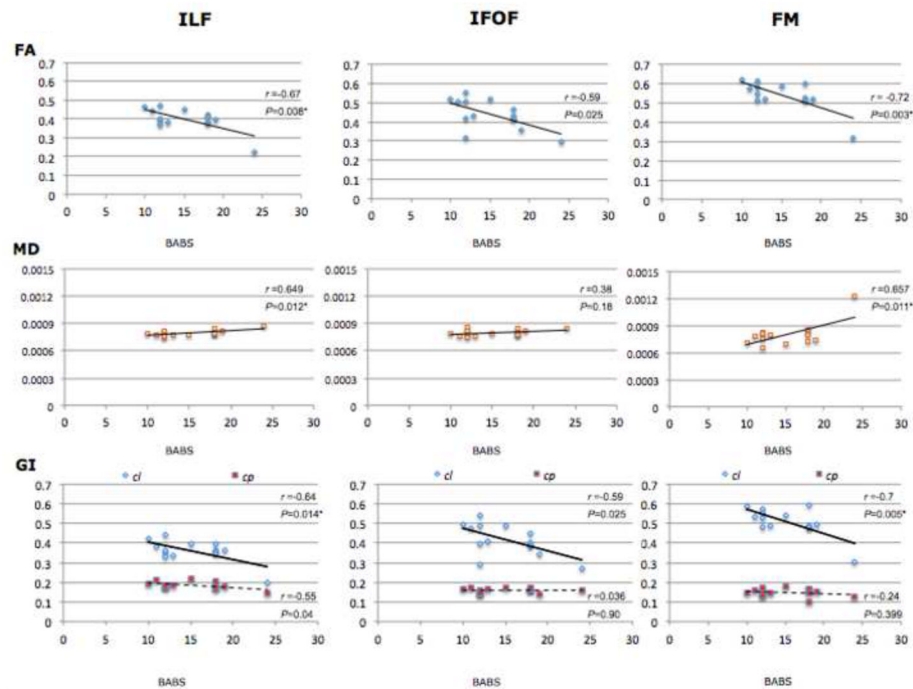


Fig. 1. Correlations between white matter diffusion measures and poor insight/delusionality in bilateral white matter tracts in BDD group (N=14)

Correlation between scores on the BABS (a measure of degree of poor insight/delusionality) and FA, MD, c_l and c_p in bilateral ILF, IFOF, and FM BABS = Brown Assessment of Beliefs Scale; FA = fractional anisotropy; MD = mean diffusivity; GI = geometric indices; c_l = linear anisotropy; c_p = planar anisotropy; ILF = inferior longitudinal fasciculus; IFOF = inferior longitudinal fasciculus; FM = forceps major

* Indicates significant P values after Bonferroni correction for multiple comparisons

Table 1

Demographics and psychometric scores

Characteristics	BDD group (N=14)	Control group (N=16)	P value ^a
Age, mean years (SD)	26.6 (4.9)	27.3 (5.3)	0.7
Female/male	7/7	8/8	>0.99
Education, mean years (SD)	15.5 (2.8)	16.9 (2.3)	0.150
BDD-YBOCS score, mean (SD)	29.85 (4.4)	N/A	N/A
BABS score, mean (SD)	15 (3.9)	N/A	N/A
HAMD-17 score, mean (SD)	10 (6.7)	1.25 (1.48)	<0.0001

Abbreviations: BDD: body dysmorphic disorder; BDD-YBOCS: BDD version of the Yale-Brown Obsessive-Compulsive Scale; BABS: Brown Assessment of Beliefs Scale

HAMD-17: The 17-item Hamilton Depression Rating Scale

^a two-sample t-tests for age, education and HAMD-17; χ^2 test for gender

Table 2

Mean (\pm SD) values for BDD and healthy control groups for white matter diffusion measures in the ILF, IFOF, and the FM^a

	ILF	IFOF	FM	df	error	F	P
FA							
BDD	0.40 \pm (0.062)	0.44 \pm (0.079)	0.54 \pm (0.075)				
Healthy controls	0.41 \pm (0.058)	0.45 \pm (0.051)	0.52 \pm (0.046)				
group				1	28	0.029	0.87
group-by-tract				2	56	1.81	0.17
MD^b							
BDD	0.00081 \pm (0.00003)	0.00081 \pm (0.00004)	0.00082 \pm (0.00014)				
Healthy controls	0.00082 \pm (0.00007)	0.00081 \pm (0.00005)	0.00078 \pm (0.00004)				
group				1	28	0.178	0.68
group-by-tract				1.7	49	1.44	0.246
c_l							
BDD	0.36 \pm (0.058)	0.42 \pm (0.079)	0.51 \pm (0.072)				
Healthy controls	0.37 \pm (0.052)	0.43 \pm (0.056)	0.48 \pm (0.048)				
group				1	28	0.000	0.98
group-by-tract				1.9	53	2.47	0.097
c_p							
BDD	0.18 \pm (0.018)	0.16 \pm (0.013)	0.15 \pm (0.020)				
Healthy controls	0.19 \pm (0.015)	0.16 \pm (0.017)	0.16 \pm (0.021)				
group				1	28	2.12	0.156
group-by-tract				2	56	1.65	0.20

^aResults presented for repeated measures ANOVA with group (BDD or healthy control) as one factor and tract (ILF, IFOF, and FM) as the other

^bIn units of mm²/s factor. Huynh-Feldt adjustments for sphericity were used.

BDD = body dysmorphic disorder; ILF = inferior longitudinal fasciculus; IFOF = inferior longitudinal fasciculus; FM = forceps major; FA = fractional anisotropy; MD = mean diffusivity; c_l = linear anisotropy; c_p = planar anisotropy

Table 3

Correlations in the BDD group between BABS scores and diffusion measures in the ILF, IFOF, and the FM

ILF	FA			MD			c_l			c_p		
	r	P		r	P		r	P		r	P	
Bilateral	-0.67	0.008*		0.649	0.012*		-0.64	0.014*		-0.55	0.04	
<i>post hoc</i>												
Left	-0.68	0.006*		0.629	0.016*		-0.697	0.0055*		-0.33	0.246	
Right	-0.62	0.017		0.605	0.022		-0.52	0.053		-0.64	0.013*	
IFOF	FA			MD			c_l			c_p		
	r	P		r	P		r	P		r	P	
Bilateral	-0.59	0.025		0.38	0.18		-0.59	0.025		0.036	0.90	
<i>post hoc</i>												
Left	-0.42	0.127		0.269	0.352		-0.43	0.124		0.123	0.675	
Right	-0.56	0.035		0.422	0.133		-0.55	0.041		-0.094	0.749	
FM	FA			MD			c_l			c_p		
	r	P		r	P		r	P		r	P	
	-0.72	0.003*		0.657	0.011*		-0.70	0.005*		-0.242	0.399	

Abbreviations: BDD = body dysmorphic disorder; BABS = Brown Assessment of Beliefs Scale; FA = fractional anisotropy; MD = mean diffusivity; c_l = linear anisotropy; c_p = planar anisotropy; ILF = inferior longitudinal fasciculus; IFOF = inferior fronto-occipital fasciculus; FM = forceps major

* Indicates significant P values after Bonferroni correction for multiple comparisons

CHAPTER 5

Summary and Synthesis of Original Research Completed

AN and BDD are severe body image disorders in which individuals perceive nonexistent or minor flaws in their appearance, resulting from distortions in perception. Multiple studies have pointed to visual processing abnormalities as potential contributors to these distortions in both these disorders. My research expands on this existing body of work through characterizing electrophysiological, hemodynamic and structural features associated with visual perception. In addition, I have conducted the first studies (Chapters 2 and 3) to directly compare the neurobiology in AN and BDD.

Chapter 2 describes an investigation of the amplitudes and latencies of early visual ERP components of AN and BDD individuals using EEG. This is the first study of its kind to study the P100 and N170 and to compare these measures between AN and BDD. We found AN had significantly smaller P100 amplitudes compared to BDD and controls, and that poor insight correlated with smaller N170 amplitude in the BDD group. These results suggest abnormalities in early visual processing in AN. Moreover, there was evidence of brain-behavior relationship in the BDD group, as worse insight correlated with reduced N170 amplitude.

In Chapter 3, we extended these ERP findings by using a technique called Fusion ICA that searches for joint associations between the EEG and fMRI data. This results in a spatiotemporal profile that isolates the P100 and N170 components and their corresponding fMRI spatial maps. We found AN and BDD groups demonstrated similar hypoactivity in early secondary visual processing regions and the dorsal visual stream when viewing low spatial frequency faces linked to the N170 component, as well as in

early secondary visual processing regions when viewing low spatial frequency houses, linked to the P100 and N170 components. Additionally, the BDD group exhibited hyperactivity in fusiform cortex when viewing high spatial frequency houses, linked to the N170 component. These results augment previous fMRI findings of abnormal visual processing in BDD by adding temporal information through fusion of EEG and fMRI data, while also providing preliminary evidence of similar abnormal spatiotemporal activation in AN and BDD for configural/holistic information for appearance- and nonappearance-related stimuli.

In Chapter 4, we expand the scope of our investigation into structural differences in white matter tracts using DTI and tractography. We found significant correlations between fiber dispersion in two structures: inferior longitudinal fasciculus (ILF) and the forceps major (FM), and poor insight. The former suggests worse insight may be associated with reduced fiber organization in pathways that integrate emotion and visual perception, while the latter suggests poor insight could be associated with disorganization in interhemispheric transfer of information.

Integrating these findings, we find evidence for abnormal configural and detailed processing mechanisms in both AN and BDD. AN shows diminished configural processing as evidenced by reduced P100 amplitudes in the ERP study and hypoactivity in dorsal regions for P100 and N170 components for faces and houses in the Fusion study. In addition, AN shows signs of enhanced detail processing as evidenced by delayed N170 latencies across all spatial frequencies. BDD show similar diminished configural processing, with similar hypoactivity for faces and houses on the Fusion study, but the spatial extent is larger and covers more dorsal stream structures such as precuneus

and lateral occipital cortex. This could be evidence for a more widespread deficiency in visual processing in BDD. Moreover, the brain-behavior correlate of worse insight with decreased N170 amplitude in BDD but not AN suggests that the N170 amplitude could be a more useful candidate biomarker or relevant endophenotype in BDD, particularly as the BDD group had significantly worse insight (higher BABS scores) than AN. However, this could be attributed to our AN sample being weight-restored in order to avoid the confounds of starvation on brain activation and morphometry, and thus they may have a greater degree of recovery and/or represent a less ill sub-group than the typical AN population. Finally, both AN and BDD show evidence of enhanced detail processing, through delayed N170 latencies in AN, and hyperactivity in fusiform cortex while viewing HSF houses in BDD.

The results mirror findings of disrupted configural processing in schizophrenia (1), autism and William's Syndrome (2), all disorders with early visual sensory processing deficits and an inability to integrate global aspects of images. This suggests that although these disorders manifest with overall dissimilar behavioral profiles than BDD and AN, and hence different classifications in the Diagnostic and Statistical Manual (DSM), there may be a common neural phenotypes or endophenotypes of dysfunction within early visual systems. This conceptualization is consistent with a dimensional understanding of psychopathology, such as that outlined in the Research Domain Criteria (RDoC) strategic plan to study mental disorders proposed by the National Institute of Mental Health. Moreover, therapies targeting this particular visual processing dimension, such as perceptual retraining, might prove promising in treatment for a range of disorders that share this particular phenotype.

Beyond these findings of abnormal function in visual systems, we also found compromised structural white matter connections from the DTI study between visual areas and higher level systems involved in emotion and memory, and between right and left visual cortex. Similar to the ERP study, we found correlations between worse insight and measures of fiber disorganization (lower FA, and lower linear anisotropy). This provides evidence for a link between white matter integrity and a key clinical phenotype in BDD.

A more elaborated model from our original one, based on the findings from the DTI study, suggests that their distorted body image could in part be related to feed-forward information from aberrant visual processing regions, whose conveyance may be further distorted or hindered due to disorganized fiber tracts; this could lead to emotional dysregulation and/or formation of visual memories based on distorted lower-level perception. Alternatively, or in addition, impaired feedback connections between emotion or memory regions and visual systems may lead to impaired updating of older memories. This may manifest as persistent memory templates consisting of previous visual memories that were particularly emotionally disturbing. These may continue to influence their conscious perception when looking at themselves (in the present), yet this is unbeknownst to them. An example is an individual who perceives gross skin blemishes such as acne, which perhaps he/she actually had in the past, despite the fact that in the present they are no longer visible to others. In other words, their “screen is not refreshing” fast enough.

AN and BDD are complex disorders that cannot be fully characterized by visual processing deficiencies as they are undoubtedly influenced by the individual’s

psychological state and past experiences. It is important therefore to note that visual processing deficiencies are likely just one dimension among several neurophysiological dysfunctions that could span early sensory processing up to higher-order cognitive and emotional processes.

There are several apparent discrepancies between the studies that are important to clarify. At first glance, it may seem that with the larger spatial extent of abnormal hypoactivity in BDD compared to AN in the Fusion study one might expect to have observed a greater reduction in the P100 or N170 in the ERP study, but in fact we see the lowest amplitudes in the AN group. It must be remembered, however, that the ERP contribution to the component in the fusion ICA analysis mainly provides a temporal marker, and the link between the BOLD signal and EEG is not clear. fMRI reflects only the complementary features of neuronal activity, through metabolism, oxygenation, and blood flow. EEG and fMRI sources might be spatially distinct, as the neuronal population and the vascular network supplying the blood might be separated in space. In addition, other processes such as glial cell metabolism or neurotransmitter release might require energetic support that causes hemodynamic changes in the absence of EEG activity. Thus, the results we found in the Fusion study may measure complementary or orthogonal signals relative to what we found in the ERP study. Further research, perhaps aided by source localization, is needed to understand how and if these signals co-localize.

There are other factors that may cause these discrepancies. First, measurements of amplitudes and latencies are crude, as brain processing occurs over long periods of time so focusing solely on peaks is somewhat arbitrary. Second, although fusion ICA may paint a more complete representation in that it takes into account and decomposes the

entire waveform, our decomposition in our study may not have been optimal as the number of components was limited by the number of subjects.

Nevertheless, fusion ICA may have greater sensitivity to detect between-group differences over traditional GLM analyses; it does not require a priori regressors or models. One study in our lab (Leow et al., under review) found hyperactivity in BDD subjects in the ventral visual stream when viewing HSF faces using a novel, integrated functional and structural connectivity technique, but abnormalities were not apparent in either modality alone. Thus, studies combining modalities may have better sensitivity to detect these differences.

Our findings support our working model of visual dysfunction in AN and BDD, with electrophysiological and hemodynamic evidence of deficiencies in configural processing in the dorsal stream. The extent of the reduced activity along dorsal stream are more widespread for BDD, while perhaps more localized to early visual areas for AN. However, our results also suggest an enhancement of detailed processing in the ventral stream, which, in tandem with abnormal configural processing could create an imbalance in local vs. global processing that could result in the subjective experience of body image distortions. It is possible that this enhanced detailed processing (which could be either a primary disturbance or compensatory) could be present to a greater degree in BDD than AN, and result in a more severe phenotype of distorted visual processing, as evidenced by previous studies suggesting more severe impairment from body image disturbance in BDD than AN (3).

These studies represent a significant contribution to the AN and BDD literature. Not only are these the first neuroimaging studies to compare these two related body

image disorders, they are the first studies to directly compare their neurobiology in any way. Our results extend the existing, separate AN (4–6) and BDD (7–9) neuroimaging literature to provide valuable information about abnormalities in temporal and spatial domains, using EEG and fMRI data. Finally, our DTI study is the first to investigate white matter abnormalities in BDD, and link fiber integrity with clinical symptom measures.

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CHAPTER 6

Future Research and Directions

The work presented is of a preliminary nature, being the first neuroimaging studies to directly compare AN and BDD, and consisting of relatively small sample sizes. Additional research is required to better characterize the pathophysiological and etiological roots of these disorders, which can then be used to develop discriminating biomarkers and more targeted therapies. With the advances in neuroimaging techniques, much of the neural spatiotemporal dynamics in these disorders involving body image can be defined in the near future.

6.1. Simultaneous EEG/fMRI

A limitation of both fMRI and EEG is the indirect nature of the brain signals acquired through either modality, requiring caution in interpretation of results. The sluggishness of the hemodynamic response in fMRI and the spatial blurring through volume conduction in EEG results in ambiguity in time and space of our signals. However, with the advance of simultaneous EEG and fMRI, increases in precision and accuracy to EEG source space solutions are possible through integration with MRI volume spaces and constraining of the source voxels. In addition, this technological leap allows study of the same brain at the same time as the cognitive task, removing adaptation or other temporal effects from non-simultaneous experiments. The use of simultaneous EEG-fMRI in our task would further enhance our data to give more precise and accurate measurements of visual processing.

6.2 Extend investigation to other/later EEG components

Because we discovered such striking general deficits in P100 and N170 amplitudes for AN subjects, we would like to investigate whether this is a general abnormality that affects other sensory systems such as auditory processing. Examining auditory components such as the N1 or the mismatch negativity can better elucidate whether AN abnormalities are vision-specific or broader in scope and extent.

Later components such as the P300 or event related negativity (ERN) are important markers that index attention, salience, or conflict monitoring. ERP studies that investigate these later components may discover abnormalities in conscious perception, emotion regulation, or executive functioning that are not indexed by the P100 or N170. These components may represent further dimensions along which we can characterize and profile AN and BDD.

6.3. Frequency analysis

Changes in the frequency spectrum of EEG appear to index brain mechanisms involved in sensory processing (1), arousal (2), and attention (3), especially in the alpha, beta, and theta ranges. ERPs, although reliably robust and easily observable, miss much of the background EEG activity not phase-locked to the stimulus. Use of time frequency analyses including phase locking and event related spectral perturbances (ERSP) will allow us to investigate abnormal oscillatory components between AN and BDD groups and controls. Furthermore, these analyses can be done on resting state data, especially in underweight and normal weight AN subjects, to understand if abnormalities in resting EEG may relate to deficits in subjects' ERP components. These can then be used to complement our ERP and Fusion ICA results.

6.4. Endophenotype Research

With better understanding of the underlying biological mechanisms behind these body image disorders, we may be able to identify heritable endophenotypes that can help index an individual's likelihood of developing the disorder. ERPs are promising as a potential endophenotype in that they are robust, straightforward to measure, and are largely automatic. Further studies can measure ERP amplitudes and latencies in unaffected first-degree relatives or monozygotic, discordant twins to quantify risk of disease development. These can be supplemented by other neuroimaging techniques such as fMRI and structural MRI to give a more complete neural profile.

6.5 Translational Research

In addition, these results may inform the development of novel perceptual remediation therapies targeting impairment in early dorsal versus ventral visual streams. Strategies that have been proposed include mirror retraining that directs individuals to avoid focusing on negative labeling, refraining from engaging in rituals, or describing their entire bodies while standing a normal distance away (4). However, these have not been tested in isolation from a whole CBT module, so their efficacy is unknown. Informed by the current research, possible alternative strategies could include visual retraining tasks that specifically limit scan paths (e.g. by increasing visual fixation), which may limit the piecemeal and detailed acquisition of information, or enhancing holistic processing by showing images very rapidly, at a distance, and/or that are low-pass spatial frequency filtered – all strategies that should engage dorsal visual stream. These, in conjunction with existing therapies such as CBT or medication, may enhance treatment outcomes beyond the existing options. In particular, correction of perceptual distortions might protect against relapse after treatment, as persistent abnormalities of

perception of appearance is a significant predictor of relapse in disorders of body image such as anorexia nervosa and bulimia (5; 6). Finally, further investigation on how and if these markers change pre- and post- treatment could provide an objective measure of their clinical relevance and efficacy.

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