Brain Structure and Circuitry

in Body Dysmorphic Disorder (BDD) Patients.

A Multimodal Neuroimaging Study

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Submitted in fulfilment of the requirements for the degree of

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Monash University

PART A: General Declaration

Monash University

Declaration for thesis partially based on conjointly published or unpublished work

General Declaration

In accordance with Monash University Doctorate Regulation 17.2 Doctor of Philosophy and Research Master's regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes two original papers published in peer reviewed journals and two as yet unpublished manuscripts, submitted for peer review. The core theme of the thesis is a neurobiological exploration of body dysmorphic disorder. The ideas, development and writing of the papers in the thesis were the principal responsibility of myself, the candidate, working within Monash University under the supervision of Professor Susan Rossell.

In the case of the following chapters my contribution to the work was the following:

Thesis chapter	Publication title	Publication status*	Extent of candidate's contribution
Chapter 2	Body Dysmorphic Disorder: A Review of Nosology, Cognition and Neurobiology	Published	85%
Chapter 6	Regional Brain Volumes in Body Dysmorphic Disorder Compared to Controls	Submitted	75%
Chapter 8	Brain Connectivity in Body Dysmorphic Disorder Compared with Controls: A Diffusion Tensor Imaging Study	Published	75%
Chapter 9	Altered Fronto-Limbic Functional Connectivity in Body Dysmorphic Disorder: A Resting-State fMRI Study.	Submitted	50%

A more detailed account of my contribution to these chapters can be found at the start of the above chapters. All other chapters were wholly my work. I have renumbered sections of published and submitted papers in order to generate a consistent presentation within the thesis.

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Notice 1

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I would like to take this opportunity to express my deep appreciation to people without whom I would not have been able to complete this thesis.

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To Jerome Maller, thank you for your contribution to this research project, particularly for introducing me to neuroimaging analysis, something I knew nothing about before you taught me! It's been great learning from you and sharing your enthusiasm for this area.

I would also like to express my sincere gratitude to all the participants who took part in this study. Thank you for sharing your stories with me and taking time out of your busy lives to contribute to scientific research. It is my hope that this research will contribute to the scientific exploration of body dysmorphic disorder and one day help people recover from the disorder. So thank you for your help.

I would also like to acknowledge the staff at Monash University's School of Psychology and Psychiatry and Monash Alfred Psychiatry Research Centre. Further acknowledgement goes to all the staff and students involved in the DPsych program at Monash who have always been supportive.

To my wife and parents, thank you for everything.

Publications and Presentations during Doctoral Candidature

Peer reviewed publications

Buchanan, B. G., Rossell, S. L., & Castle, D. J. (2011). Body dysmorphic disorder: a review of nosology, cognition and neurobiology. *Neuropsychiatry, 1*(1), 71-80.

Buchanan, B., Rossell, S., Maller, J., Toh, W., Brennan, S., & Castle, D. (2013). Brain connectivity in body dysmorphic disorder compared with controls: a diffusion tensor imaging study. *Psychological Medicine*, 1-9.

Poster Presentations

Buchanan, B., Rossell, S., Maller, J., Toh, W., Brennan, S., & Castle, D. (May, 2013). Brain Connectivity in Body Dysmorphic Disorder Compared with Controls: A Diffusion Tensor Imaging Study. Poster session at the Monash University School of Psychology and Psychiatry, Australia

Rossell, S., Buchanan, B., Volziker, A., Nibbs, R., Toh, W. L., Maller, J. & Castle, D. J. (May 2013). Altered fronto-limbic functional connectivity in Body Dysmorphic Disorder: A resting-state fMRI study. Poster session at the Conference of Biological Psychiatry, San Francisco

Buchanan, B., Rossell, S., Maller, J., Toh, W., Brennan, S., & Castle, D. (May, 2013). Regional brain volumes in body dysmorphic disorder. Poster session at the Monash University School of Psychology and Psychiatry, Australia, (May, 2013)

Conference Presentations

Brain connectivity in body dysmorphic disorder compared with controls: a diffusion tensor imaging study, *Society of Biological Psychiatry 68th Annual Scientific Convention*, San Francisco May 16-18, 2013

Amygdala volumes in schizophrenia, body dysmorphic disorder and controls. *The Australasian Society of Psychiatric Research Conference*, Bondi Beach, Sydney, December 5 - 8, 2010

Other Publication

Buchanan, B. G. (2013, June 13). Body dysmorphic disorder puts ugly in the brain of the beholder. Retrieved June 13, 2013, from https://theconversation.com/body-dysmorphic-disorder-puts-ugly-in-the-brain-of-the-beholder-12609

I am waiting for a research participant to arrive in the foyer of the Royal Children's Hospital. She is late and I start feeling a bit nervous because I only have a limited time booked for the MRI scanner before another researcher has to use it. My phone is ringing; she is asking for directions and finally finds her way to the entrance. As she walks in I'm holding a sign saying "BDD research"; she looks at it, then me, then looks the other way, pretending not to see me. She is wearing sunglasses and a hat. Although we have never met, I assume it is her and I take a few steps forward and introduce myself. We walk upstairs together and sit down. I am explaining the MRI procedure and saying that she will need to take out any hair clips or other metallic articles.... I am interrupted. She says, "I don't take my hat or sunglasses off in public, people look at me". I am looking down at my papers, I know it, she is perfect for this study, but finishing the MRI protocol in time will be a challenge.

Abstract

Body dysmorphic disorder (BDD) is a mental disorder with five times the prevalence of anorexia, affecting up to 2.4% of the general population. The main symptom is a fixation on a feature of appearance that they attest looks ugly and they may engage in repetitive and ritualistic behaviour, including picking of their skin or checking their appearance in the mirror very frequently. The concern with appearance and associated behaviours are analogous to the obsessions and compulsions experienced in obsessive compulsive disorder (OCD).

This thesis aimed to characterise the brain structure and circuitry of BDD to understand the mechanism that underlie the disorder's onset and maintenance. We acquired the largest BDD neuroimaging sample to date, scanning 20 BDD participants and compared them to 20 healthy controls. Three imaging techniques were reported; structural magnetic resonance imaging (MRI), diffusion tensor imaging (DTI) and resting state functional MRI.

The structural data showed reduced volumes in the orbitofrontal and anterior cingulate cortex, while the DTI data revealed for the first time that BDD patients have compromised integrity of most major white matter tracts throughout the brain. Resting state functional MRI showed abnormalities in fronto-amygdala and occipital lobe connectivity.

Collectively, our evidence contributed rich data showing widespread abnormalities in the brains of BDD participants. These abnormalities may be the foundation for BDD symptoms, including increased fearful threat perception, and dysfunction in self-reflection, executive function and visual processing. It was concluded that the frontal and fronto-amygdala deficits found in BDD are important to the disorder, and suggest it lies on a spectrum of anxiety disorders characterized by emotional dysregulation.

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List of Abbreviations

ACC	Anterior Cingulate Cortex
AN	Anorexia Nervosa
BA	Brodmann Area
BDD	Body Dysmorphic Disorder
BDD-DM	Body Dysmorphic Disorder Diagnostic Module
BDD-YBOCS	Yale Brown Obsessive Compulsive Scale Modified For Body Dysmorphic Disorder
BOLD	Blood Oxygen Level-Dependent
CBT	Cognitive Behaviour Therapy
CC	Corpus Callosum
CSTC	Cortico-Striatal-Thalamo-Cortical
DLPFC	Dorsolateral Prefrontal Cortex
DSM	Diagnostic And Statistical Manual Of Mental Disorders
FA	Fractional Anisotropy
fcMRI	Functional Connectivity Magnetic Resonance Imaging
fMRI	Functional Magnetic Resonance Imaging
GM	Grey Matter
ILF	Inferior Longitudinal Fasciculus
IPL	Inferior Parietal Lobe
MD	Mean Diffusivity
mPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
OCD	Obsessive Compulsive Disorder
OFC	Orbitofrontal Cortex
PCC	Posterior Cingulate Cortex
PFC	Prefrontal Cortex
PTSD	Post-Traumatic Stress Disorder
ROI	Region Of Interest
SD	Standard Deviation
SAD	Social Anxiety Disorder
SIAS	Social Interaction Anxiety Scale
SLF	Superior Longitudinal Fasciculus
SPECT	Single Photon Emission Computed Tomography
SRI	Serotonin Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
UF	Uncinate Fasciculus
VBM	Voxel-Based Morphometry
WM	White Matter
WTAR	Wechsler Test Of Adult Reading
ZUNG	Zung Self-Rating Of Depression Scale

Chapter 1

Introduction to Body Dysmorphic Disorder

Body dysmorphic disorder (BDD) is a mental disorder characterised by a preoccupation with an imagined defect in physical appearance, or excessive concern for a slight physical abnormality. Individuals with BDD often engage in repetitive and ritualistic behaviour, including picking their skin, camouflaging their supposed defect with makeup, or checking their appearance in the mirror very frequently. Such behaviours are persistent and pervasive and often lead to significant levels of distress.

Body dysmorphic disorder was first documented in 1886 by an Italian psychopathologist named Enrique Morselli. At the time, he named the condition "Dysmorphophobia" to reflect its phobic-like nature. Since then, it has been recognised using different names and/or conceptualisations. A popular and descriptive term was “Beauty Hypochondria”, which encapsulated the “imagined ugliness” as well as the hypochondriacal conceptualisation of the disorder (Ladee, 1966). In European literature, it was termed "monosymptomatic hypochondriacal psychosis". Freud, (1959, as cited in Veale, 2003) described perhaps the most famous early case of BDD in a patient known as the "Wolf Man" who was preoccupied with an imagined defect of his nose.

"He neglected his daily life and work because he was engrossed, to the exclusion of all else to the state of his nose. On the street he looked at himself in every shop window; he carried a pocket mirror, which he took out at every few minutes. First he would powder his nose; a moment later he would inspect it and remove the powder. He would then examine the pores, to

see if they were enlarging. Then he would again powder his nose, put away the mirror, and a moment later begin the process anew".

Diagnostic and Statistical Manual of Mental Disorder (DSM) Classification

The official diagnosis of BDD was introduced in the *Diagnostic and Statistical Manual of Mental Disorders (DSM) Third Edition* (American Psychiatric Association, 1980), which conceptualised it as an atypical paranoid disorder or atypical psychosis.

In the *DSM-IV-TR* (APA, 2000) it was classified as a somatoform disorder, because its main symptom is a physical complaint with no organic cause; however, it does not strongly resemble any other disorder under this category (Castle, Rossell, & Kyrios, 2006). In fact, the whole category of somatoform disorders has been criticised and there has been some debate over its abandonment (Mayou, Kirmayer, Simon, Kroenke, & Sharpe, 2005). Accordingly, in the most recent edition of the manual, the DSM-5, the disorder has been categorised under the newly formed obsessive-compulsive spectrum category.

The development of this new obsessive-compulsive spectrum category reflects the increasing body of evidence that these disorders are related to one another in terms of symptomatology, aetiology, and treatment response (Phillips, Stein, et al., 2010). There have been a number of other changes to BDD diagnosis and conceptualisation in DSM-5. There is now a diagnostic criterion describing repetitive behaviours or mental acts in response to preoccupations with perceived defects or flaws in physical appearance. A specifier, "with muscle dysmorphia", has been included, which reflects a growing body of literature on the diagnostic validity and clinical utility of making this distinction. The delusional variant of body

dysmorphic disorder (which identifies individuals who are completely convinced that their perceived defects or flaws are truly abnormal-looking) was coded as two separate disorders in the DSM-IV-TR; delusional disorder, somatic type, and body dysmorphic disorder. In the DSM-5 the level of insight/delusionality is specified *within* the BDD diagnosis instead. Table 1 presents the diagnostic criteria for the two most recent versions of the DSM.

Table 1. DSM-IV and DSM-5 Diagnostic Criteria for BDD

DSM-IV-TR	DSM-5
A. Preoccupation with an imagined defect in appearance. If a slight physical anomaly is present, the person's concern is markedly excessive.	**A.** Preoccupation with one or more perceived defects or flaws in physical appearance that are not observable or appear slight to others.
B. The preoccupation causes clinically significant distress or impairment in social, occupational or other important areas of functioning.	**B.** At some point during the course of the disorder, the individual has performed repetitive behaviours (e.g., comparing his or her appearance with that of others) in response to the appearance concerns.
C. The preoccupation is not better accounted for by another mental disorder (e.g. dissatisfaction with body shape and size in anorexia nervosa).	**C**. The preoccupation causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
	D. The appearance preoccupation is not better explained by concerns with body fat or weight in an individual whose symptoms meet diagnostic criteria for an eating disorder.
	Specify if: With muscle dysmorphia Specify if: With good or fair insight With poor insight With absent insight/delusional beliefs

As mentioned, before the publication of the DSM-5 it was widely acknowledged that the nosology of BDD was in need of substantial review (e.g. Castle, et al., 2006; Phillips, Stein, et al., 2010). There exists two main lines of discussion: The first is related to the classification of BDD as a somatoform disorder, with some authors suggesting that it should be re-classified and re-conceptualised as an obsessive-compulsive (OC) spectrum disorder (e.g. Phillips et al., 1997; Phillips, Stein, et al., 2010). The second area of debate relates to the delusional subtype of BDD and how this can best be conceptualised within the BDD classification framework. This debate will be briefly discussed in Chapter 2, a review article that was published in 2011 and is included as part of this thesis. Other intuitive links between BDD and body-image related disorders exist, and these will now be briefly discussed.

BDD as a body image disorder

On the surface, BDD is closely related to other body image disorders like anorexia nervosa, thus there has been debate on whether or not it should be subsumed under a "body-image disorder" diagnostic category (e.g. Ruffolo, Phillips, Menard, Fay, & Weisberg, 2006). Proponents of this view emphasise that anorexia nervosa (AN) and BDD are both disorders that are characterised by a chronic and obsessive shame about the body, poor insight, as well as the tendency for onset in childhood or adolescence (Rosen & Ramirez, 1998). Furthermore, individuals with AN may not only be preoccupied by their body weight, but like BDD, can also be fixated on other aspects of their physical appearance (Ruffolo, et al., 2006). Likewise, 29% of people with BDD are discontented with their body weight (Kittler, Menard, & Phillips, 2007), although only 9% of people with BDD have a lifetime AN diagnosis (Ruffolo, et al., 2006).

Despite the relationship between these two disorders, there are several important differences that preclude them from being classified as variants of each other, or categorised within the same class of body image disorders. The central component of AN diagnosis is maladaptive eating habits that cause a number of physical health problems; this feature is not present in BDD. Additionally, individuals with BDD are significantly more distressed and handicapped than other individuals with other body image disorders (Phillips, 2000b). Substantial gender differences also suggest these disorders are aetiologically distinct, with BDD having a roughly equal gender balance, and AN mainly affecting women (Ruffolo, et al., 2006).

Thus, while there are superficial similarities between BDD and AN, the general consensus, and research data, suggest that OCD and BDD are conceptually closer than BDD is to other body image related disorders.

Demographic information

When most people think of a mental disorder related to body image, anorexia is generally the first disorder that comes to mind, as it has received a large amount of public and research attention. Despite this, BDD is actually five times more prevalent than anorexia, and has received little public attention.

Reported prevalence rates of BDD vary widely from study to study, from between 0.7% (Otto, Wilhelm, Cohen, & Harlow, 2001) to 5% (Bohne et al., 2002). The most comprehensive estimate comes from a German community sample of 2552 which reported a prevalence rate of 1.7% (Rief, Buhlmann, Wilhelm, Borkenhagen, & Brahler, 2006). An Australian study showed a similar rate of 2.3% with a sample of 619 university students (Bartsch, 2007).

The lack of public recognition is perhaps understandable given the nature of the disorder, which is often secretive and thus generally underdiagnosed, as individuals are not likely to reveal their symptoms unless they are directly questioned about their body image concerns. The private nature of BDD sufferers, as well as the strongly held belief that they possess a physical defect rather than a psychological one, means that few individuals with BDD will seek or receive appropriate treatment.

The onset of BDD is usually during adolescence (mean age of 16.4 years), with patients recounting a hypersensitivity about their physical appearance for all, or much, of their lives (Phillips, Menard, Fay, & Weisberg, 2005). In contrast to other disorders relating to body image (such as anorexia nervosa), the prevalence of BDD has been shown to be similar between men and women. However, there are consistent gender differences in the body parts of concern (Phillips, Menard, & Fay, 2006; Rief, et al., 2006). Women tend to focus on skin, legs, and breast size while men are concerned with baldness, body hair, build, and genitals. Similarly, the prevalence of BDD seems to be consistent across cultures, with different cultures being dissatisfied with different body parts (Bohne, Keuthen, Wilhelm, Deckersbach, & Jenike, 2002; Rief, et al., 2006). The similarity in gender and the culture prevalence rates suggest that the onset of BDD is separate from culture, while the differences in body part manifestations of BDD reflect different societal values.

Aetiology

The literature related to the aetiology of BDD is slowly developing, with the most compelling evidence coming from neuropsychological and neurobiological studies. Before examining this evidence, it is important to look broadly at the psychological and sociocultural

factors that have been theorised to contribute to the development and maintenance of the disorder.

Sociocultural factors

Sociocultural models of BDD tend to focus on the constant exposure to unrealistic standards of physical beauty through the media (Rivera & Borda, 2001). In this model, positive reactions to beauty and negative reactions to ugliness are culturally exaggerated, and individuals may learn to have overstated psychological reactions to body parts culturally endorsed as unattractive. While some evidence has cited that the cultural exposure to unrealistic ideals of beauty increases the risk of BDD (Phillips, 1998), this explanation is largely unsubstantiated. For instance, the onset of BDD has been shown to be largely independent of culture (Rief, et al., 2006). Moreover, some cultures value physical attractiveness more than others, and while this has been shown to affect the prevalence rate of milder body concerns, this has not been found to affect the prevalence rate of BDD (Bohne, Keuthen, et al., 2002). Furthermore, most individuals with BDD have no physical defect to which to have a negative reaction. Thus, this model does not take into account the delusion of ugliness, but focuses on the exaggerated nature of the adverse reactions instead.

Psychological and situational factors

Individuals with BDD often have exaggerated personality traits, which may include obsessional, schizoid, narcissistic, and/or hyochondriacal personalities (Munro & Stewart, 1991). Additionally, they tend to be introverted, perfectionists, and sensitive to criticism (Phillips, 1998). Individuals with BDD report a higher rate of criticism from peers and family in relation to

body image than individuals without BDD, and the psychological model emphasises that the higher reporting rate is due to their hypersensitivity towards such criticisms, rather than a higher rate of actual occurrence (Buhlmann, Cook, Fama, & Wilhelm, 2007; Rivera & Borda, 2001).

Nevertheless, the majority of BDD patients report particular instances of teasing during their adolescence, when they "realized" that they were ugly and they attach considerable self-meaning to these memories. In fact, the therapeutic use of "imagery rescripting" allowing imaginary exposure to this event is often used in treatment of BDD (Veale & Neziroglu, 2010). Revisiting this traumatic memory provides an opportunity to reflect on unhelpful and perpetual thought processes that resulted from it.

Cognitive-behavioural model

Cognitive-behavioural models of BDD represent an interaction between psychological and sociocultural aetiological theories. According to this theory developed by Veale (2004), a combination of personality factors such as negative affect, introversion, and self-consciousness together with early childhood experiences and social learning culminate in BDD. Personality factors are seen as contributing to an individual's predisposition towards BDD, while a series of critical events may trigger its development. For example, individuals with BDD report a significantly greater incidence of emotional and sexual abuse (Didie et al., 2006), indicating either more attendance to these experiences or actual increased abuse, or both. According to this theory, adversarial experiences can condition individuals to have negative feelings when observing body parts later in life (Veale, 2004). This model targets the mechanisms that maintain the preoccupation with appearance: the patient's rehearsal of negative and distorted self-statements about physical appearance, avoidance behaviours that prevent the patient from

habituating to the sight of his or her appearance, and checking behaviour that may provide immediate relief, but in the long run keeps the person's attention focused on aspects of appearance that elicit anxiety (Rosen, Reiter, & Orosan, 1995).

The cognitive-behavioural model for BDD is now well developed and treatment manuals have been specifically formulated based on this conceptualisation (Veale & Neziroglu, 2010), as discussed shortly . However, this model fails to fully differentiate between factors that contribute to milder body images related concerns and the onset of BDD, and incorporates many elements of general cognitive-behavioural models of OCD and body image disturbance (e.g. Cash, 2008). This model, therefore, does not give a full explanation of the underlying cause of BDD.

Neurobiological factors

The neurobiological model of BDD is concerned with the psychobiology of the disorder, and may explain why some people develop BDD and others do not. Such biological factors tend to be genetically transmitted, and evidence for this lies in familial prevalence rate. Two studies have shown that prevalence rates of BDD are higher among first degree relatives, with between 5.8% to 8% of relatives being diagnosed with the disorder (Bienvenu et al., 2000; Phillips, Menard, et al., 2005).

Recently, particular brain structures have been implicated in the development of BDD. For instance, right temporal lobe damage has been linked to the spontaneous onset of BDD (Gabbay et al., 2003; Naga, Devinsky, & Barr, 2004). This is an area of the brain that has been previously implicated in the self-perception of body image (Trimble, 1988). Treatment studies have implicated serotonergic systems in the aetiology of the disorder (Barr, Goodman, & Price,

1992; Hollander et al., 1999; Marazziti et al., 1999), although underlying mechanisms remain largely unknown. A promising line of research related to the basis of BDD symptoms also comes from neuropsychological and brain imaging studies, which will be examined in a published review in Chapter 2 and further explored throughout this thesis.

Treatment

Two comprehensive reviews of treatment efficacy for BDD have been conducted: a Cochrane Review (Ipser, Sander, & Stein, 2009), and a Treatment Practice Guideline for OCD and BDD from the United Kingdom's National Institute for Health and Clinical Excellence (2006). Both the reviews recommended cognitive behavioural therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) as first line treatments, though acknowledge that more research is needed.

Cognitive behavioral therapy (CBT)

Most published studies of CBT for BDD have included cognitive restructuring, exposure (e.g. to avoided social situations), and response (ritual) prevention (e.g. not seeking reassurance) that is tailored specifically to BDD symptoms (Veale & Neziroglu, 2010). Additional strategies used in combination with the above approaches include perceptual retraining with mirrors, habit reversal for BDD-related skin picking or hair plucking, cognitive approaches that target core beliefs, incorporation of behavioural experiments into exposure exercises, motivational interviewing tailored to BDD, and other approaches (Phillips & Rogers, 2011). The low levels of insight means maintenance of long term treatment can be challenging; however, research data suggests a low dropout rate once someone enters treatment (Rosen, et al., 1995).

A review of three eligible randomized control trials included three separate psychotherapy studies (83 participants) (Ipser, et al., 2009). They compared 12-week CBT against a waiting list comparison group and found significant improvements, with 81.5% of participants receiving CBT no longer meeting diagnostic criteria post treatment.

The relapse rate for one of the studies was also low, with three-quarters of patients having recovered 4.5 months after treatment had ended, which is lower than the relapse rate for patients treated with medication. In addition, a meta-analysis showed that CBT treatment was significantly more effective than medication after 16 weeks of treatment (Williams, Hadjistavropoulos, & Sharpe, 2006).

Pharmacotherapy

Selective serotonin reuptake inhibitor (SSRI) medication is the most commonly used psychopharmacological treatment for BDD, and although there is apparent widespread use of antipsychotics to treat BDD (Saxena et al., 2001), the only placebo controlled study of the efficacy of this medication class in treating 28 patients with BDD was not able to detect any significant differences (Phillips, 2005).

Evaluation of SSRI medication in randomized, double-blind, controlled studies in adults demonstrated that fluoxetine was more efficacious than placebo (Ipser, et al., 2009; Phillips & Hollander, 2008). One study found a combination of comipramine and SSRIs was more beneficial than SSRIs alone (Phillips & Hollander, 2008). The authors of that research note that this combined approach is similar to pharmacotherapy treatments of OCD, further strengthening the conceptual links.

Overall, both medication and CBT are effective in the treatment of BDD. Unfortunately most patients are usually not diagnosed and treated until 10-15 years after the onset of BDD (Phillips, 1991; Veale, 2009). The course of the disorder is generally chronic if untreated, with one study showing that the mean duration of the disorder is 16 years (Phillips & Stout, 2006). If treated, the outlook is more positive, with nearly 60% of patients achieving full remission after four years of treatment with psychotherapy and medication (Phillips, Grant, Siniscalchi, Stout, & Price, 2005).

Chapter 2

Body Dysmorphic Disorder: A Review of Nosology, Cognition and Neurobiology

Published literature review

Reference:

Buchanan, B. G., Rossell, S. L., & Castle, D. J. (2011). Body dysmorphic disorder: a review of nosology, cognition and neurobiology. *Neuropsychiatry*, 1(1), 71-80.

The published article is included in Appendix A

Introductory note.

This literature review was written as a stand-alone manuscript so there may be a degree of repetition. In addition, given that it was published in 2011 it does not have all of the up-to-date literature. Updated literature is included in the following chapters. A "practice points" section is included as per the journals format.

Monash University

Declaration of Authorship for Thesis Chapter 2

Body dysmorphic disorder: a review of nosology, cognition and neurobiology
Buchanan, Ben G., Rossell, Susan L. & Castle, David J.

Declaration by candidate

In the case of this chapter, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
I researched and wrote the entire chapter intended for publication with feedback from co-authors.	85%

The following co-authors contributed to the work.

Name	Nature of contribution	Extent of contribution (%)
Susan Rossell	Helped in formulating structure of review, hypotheses and gave feedback on final report.	10%
David Castle	Feedback on finished manuscript	5%

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date 13/8/2013**
Main Supervisor's Signature	[redacted]	**Date 13/8/2013**

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

Executive Summary

Background: An understanding of the neurocognitive and neurobiological underpinnings of body dysmorphic disorder (BDD) is important in differentiating BDD from related disorders, namely obsessive compulsive disorder and psychotic disorders.

Neurocognition: Similar cognitive anomalies in executive function, spatial visual processing and memory (bias to process detailed visual information) have been found in BDD and OCD samples, while schizophrenia patients display more pervasive cognitive deficits. Emotional hyperactivity and misinterpretation of emotion in others have been found in BDD, with similar results to OCD samples.

Neuroimaging : Neuroimaging has shown abnormalities in the prefrontal cortex, visual cortex, caudate nucleus and right amygdala in BDD patients. These findings are consistent with the neurocognitive profile.

Concluding remarks: This field of research is in its infancy. However, the bias towards detailed visual analysis may be an important clue when investigating the neurobiological basis of BDD, and could explain why individuals exhibit focussed attention on one aspect of their own appearance. Emotional hyper-arousal caused by amygdala pathology may reinforce a perception of negative physical appearance.

Practice points

- Body dysmorphic disorder is underdiagnosed, as individuals with BDD are unlikely to reveal their body image concerns unless directly asked. They may, however, seek cosmetic procedures for their perceived defect or psychological treatment for a comorbid condition.
- Common comorbid conditions include depression, social phobia, anorexia nervosa and obsessive compulsive disorder (OCD).
- OCD and BDD have similar symptoms and research is beginning to show that they also have similar underlying cognitive dysfunctions.
- The delusional subtype of BDD is best considered as a more severe case of BDD with lower levels of insight, rather than a separate subtype.
- Individuals with BDD have visual processing abnormalities including a tendency to process visual information in a piecemeal manner rather than holistically. This indicates that they see things differently and may explain their fixations on slight anomalies in their own appearance.
- Hyperactivity in the limbic system may explain why individuals with BDD feel that they are constantly being negatively judged by others.
- BDD can be successfully treated with cognitive behavioural therapy and medication.

A degree of concern about physical appearance is culturally accepted and even expected; however, for some individuals concern about their appearance is excessive and causes them considerable distress. These people may be identified as having body dysmorphic disorder (BDD), which is a mental disorder that includes obsessive compulsive phenomena and overvalued ideas that may become delusional. This review will discuss the phenomenological similarities between BDD, obsessive compulsive disorder and psychotic disorders; and review neuropsychological and brain imaging studies and their possible implications for a neurobiological model of BDD.

Characteristics of Body Dysmorphic Disorder

Individuals with BDD frequently describe themselves as unattractive, disfigured, deformed or ugly, and are preoccupied with one or more aspect of their appearance that they attest to looking abnormal. The disorder's essential feature, as defined by the *DSM, Fourth Edition, Text Revised* (*DSM-IV-TR*) is a preoccupation with some imagined defect in appearance, or, if a slight physical abnormality is present, that the person has a disproportionate concern about the anomaly. Furthermore, individuals with BDD often demonstrate little insight into the fact that their self-perception of repulsiveness is unrealistic, and these beliefs may thus reach delusional proportions.

BDD patients are usually preoccupied with their face or head, and most commonly their skin, hair, or nose (Neziroglu, 2008); they can spend between three to eight hours per day thinking about their perceived defects; in fact some individuals report that these thoughts are present continuously (Veale et al., 1996). Beliefs about their defects usually carry strong personal meaning, and are often cited as the main reason for personal problems (Veale, 2003),

for example, “I cannot get a job because of my nose”. Many individuals with BDD give almost exclusive attention to their perceived flaws while ignoring other aspects of their appearance.

Individuals with BDD have impaired psychosocial functioning and quality of life (Phillips, Menard, et al., 2005). They may experience prolonged unemployment, severe social isolation and suicidal ideation, with approximately 25% of individuals with BDD attempting suicide (Phillips et al., 2005).

Prevalence rates of BDD are reportedly between 0.7% (Otto, et al., 2001) and 2.4% (Koran, Aboujaoude, Large, & Serpe, 2008) and have similar levels in males and females. It is generally under diagnosed, as individuals are not likely to reveal their symptoms unless directly questioned about their body image concerns. The secretive nature of BDD, as well as the strongly held belief that they possess a physical defect rather than a psychological problem, means that few individuals with BDD will seek appropriate treatment. They may, however, opt for cosmetic procedures to “cure” their problem. For example, Veale et al. (Veale, et al., 1996) found in their BDD samples that 26% had had one or more cosmetic operation. Furthermore, the vast majority (83% in the study by Phillips et al. (Phillips, Grant, Siniscalchi, & Albertini, 2001)) of BDD patients experience either no improvement or a worsening of BDD symptoms after surgery. In cosmetic settings, rates of BDD are high: 7% in a sample of cosmetic surgery patients (Sarwer, Wadden, Pertschuk, & Whitaker, 1998), and between 8.8%-14% in dermatology patients(Conrado et al., 2010; Phillips, Dufresne Jr, Wilkel, & Vittorio, 2000).

If individuals with BDD do present for psychological treatment it is often for a secondary or associated condition, such as depression, obsessive compulsive disorder, anorexia nervosa or social anxiety (Nierenberg et al., 2002; Simeon, Hollander, Stein, Cohen, & et al.,

1995; Wilhelm, Otto, Zucker, & Pollack, 1997). Patients are commonly not diagnosed with BDD until 10-15 years after the onset, which usually occurs in adolescence (Veale, 2009). The course of the disorder is generally chronic if untreated. If treated with psychological therapy and medication (Phillips, Grant, et al., 2005) , however, the outlook is more optimistic, with nearly 60% achieving remission after 4 years.

Nosology

At present BDD is classified as a somatoform disorder in the *DSM-IV-TR.* However, it is widely acknowledged that the nosological status of BDD is in need of review (Castle, et al., 2006; Phillips, Wilhelm, et al., 2010), with the DSM-V working group recommending that BDD be reclassified as either an Anxiety Disorder or an Obsessive Compulsive Spectrum Disorder (Diagnostic and Statistical Manual of Mental Disorders 5; Phillips, Wilhelm, et al., 2010). There is also debate relating to the delusional subtype of BDD, and how this can best be conceptualised within the BDD classification framework. Currently the delusional 'variant' requires a separate, additional, classification with the delusional disorders.

There is also debate over how BDD relates to other mental disorders. For example, social phobia shares many characteristics with BDD, such as the tendency to feel socially anxious and chronic fear of embarrassment or rejection (Stark et al., 2003). In fact 39% of individuals with BDD have had comorbid lifetime social phobia (Stark, et al., 2003). While BDD has been compared with many disorders, this review will focus on the issues most salient in the context of the possible reclassification of the disorder within the DSM-V, namely BDD as an obsessive compulsive spectrum disorder and BDD's delusional variant.

Body Dysmorphic Disorder as an Obsessive Compulsive Spectrum Disorder

BDD shows several similarities to OCD, including: (a) preoccupations that are often described as obsessional, anxiety producing, and difficult to control (Hollander & Phillips, 1992); (b) engagement in repetitive and ritualistic behaviours, such as skin picking and checking behaviours, which may take up many hours of the day (Eisen, Phillips, Coles, & Rasmussen, 2004); (c) a concern with aesthetics such as symmetry (Stewart, Stack, & Wilhelm, 2008); (d) a tendency to engage in reassurance seeking from others (Stewart, et al., 2008); and (e) social withdrawal (Frare, Perugi, Ruffolo, & Toni, 2004).

A number of studies have directly compared BDD to OCD on a broad range of demographic and clinical features, with relatively consistent findings (Frare, et al., 2004; Phillips, Gunderson, Mallya, McElroy, & Carter, 1998; Phillips et al., 2007; Simeon, et al., 1995). Comorbidity studies have tended to focus on the prevalence of BDD in OCD samples. They have shown that 7.7% to 15.3% of those with OCD meet diagnostic criteria for concurrent BDD (Stewart, et al., 2008; Wilhelm, et al., 1997). The high comorbidity rate may represent a diagnostic overlap or an aetiological link. In clinical BDD samples, OCD is a frequent comorbid disorder (41%) (Perugi et al., 1997). Furthermore, familial studies have demonstrated a familial link between OCD and BDD. Hollander, Cohen and Simeon (1993) found that OCD was the most common disorder found in the relatives of 50 BDD participants, with 17% of them having first degree relatives with OCD.

As well as the phenomenological and familial links between OCD and BDD, both disorders have similar treatment responses to serotonergic reuptake inhibitor (SRI) medications (Ipser, et al., 2009; Landeros-Weisenberger et al., 2010). Given these similarities there seems to

be a general consensus towards conceptualising BDD as an OC spectrum disorder (Phillips, 2000a), and some neuropsychological studies have set out to measure BDD against OCD to test this conceptualisation; this is addressed below.

Delusional and non-delusional subtype

A key difference between OCD and BDD, and a topic of debate regarding subtypes of BDD, is the delusional and non-delusional typology. In BDD, obsessions tend to be held with more conviction and less insight than those of OCD (Vitiello & De Leon, 1990). Thus, whilst only 2% of OCD patients were 'delusional', 27% of BDD participants were currently delusional according to the Brown Assessment of Beliefs Scale (BABS). Other studies have found a higher rate of delusions in BDD, of between 34% and 60% (Labuschagne, Castle, Dunai, Kyrios, & Rossell, 2010; Mancuso, Knoesen, & Castle, 2010). In contrast to delusions in psychotic disorders such as schizophrenia, delusional beliefs in BDD tend to be non-bizarre and monothematic and generally linked to their perceived flaw. BDD patients also often experience delusions of reference, such as the belief that other people take special notice of the supposed defect, for example, talk about it and mock it (Phillips, McElroy, Keck, Pope, & Hudson, 1993).

Under the present diagnostic system for BDD in the *DSM-IV-TR* there is the provision of a secondary diagnosis of a delusional disorder within the delusional disorder group, somatic subtype. This diagnosis is given if beliefs reach delusional intensity, or strong ideas of reference are present. The current psychotic/nonpsychotic dichotomy has been under scrutiny because the separate classification of the types implies that they are, in fact, distinct disorders. However, available evidence suggests that the delusions present in BDD should not be represented as a categorical difference in classification but rather reflect a dimensional intensity of belief

(Labuschagne, et al., 2010; Phillips, McElroy, Keck, Hudson, & et al., 1994). To this end, there has been considerable speculation regarding a dimensional approach to the delusional aspect of BDD in development of the *DSM-V* (Castle & Rossell, 2006; Castle, et al., 2006; Labuschagne, et al., 2010).

Nevertheless, there are several differences between the subtypes: Individuals with delusional BDD experience more impairment in social functioning, more suicide attempts and rate of hospitalisation, and have more severe BDD symptoms compared to their non-delusional counterparts (Mancuso, et al., 2010; Phillips, Menard, Pagano, Fay, & Stout, 2006). Delusional subjects also have lower scores on nearly all functioning and quality of life variables. However, there are more similarities than differences between the two subtypes, including age, comorbidity, and most importantly, the core symptomatology of BDD. Moreover, both delusional and non-delusional variants respond similarly to serotonin reuptake inhibitor (SRI) pharmacotherapy (Hollander, et al., 1999). Thus, the delusional subtype patients could merely have a more severe form of the same core disorder.

Neurocognition

The severe body image distortions that individuals with BDD experience suggest that fundamental cognitive and perceptual abnormalities are involved. Cognitive research has revealed a range of deficits in BDD, including executive function (Dunai, Labuschagne, Castle, Kyrios, & Rossell, 2009; Hanes, 1998), selective attention (Buhlmann, McNally, Wilhelm, & Florin, 2002), information processing (Deckersbach et al., 2000; Dunai, et al., 2009), recognition of emotion in others (Buhlmann, McNally, Etcoff, Tuschen-Caffier, & Wilhelm,

2004) and visual processing (Feusner, Moller, Altstein, Sugar, et al., 2010; Feusner, Townsend, Bystritsky, & Bookheimer, 2007).

In the context of the nosological debate surrounding BDD, studies that have directly compared cognition in BDD, OCD and schizophrenia are of particular interest. Hanes (Hanes, 1998) compared a BDD group with OCD and schizophrenia groups on executive function tasks. Parallel deficits in BDD and OCD were found, while the schizophrenia group showed more severe and widespread deficits. The author concluded that the cognitive similarities between OCD and BDD imply that the neuroanatomical underpinnings may be similar. In OCD, impairment on one of the same executive function tasks (Stroop colour naming) has shown to be associated with abnormal frontal-striatal and limbic activation (van den Heuvel, Veltman, Groenewegen, Witter, et al., 2005), although this has not to our knowledge been directly investigated in BDD.

Dunai et al. (2009) demonstrated executive function impairments in BDD patients compared to non-clinical controls, with the BDD group making more errors on a Spatial Working Memory task, and performing more slowly on the Stocking of Cambridge task that required organisation, planning and on-line manipulation of visual information. Such deficits, on the same tasks, have previously been observed in OCD (Veale, Sahakian, Owen, & Marks, 2009) and schizophrenia (Pantelis et al., 1997). Executive function deficits in BDD, however, were not pervasive, and the BDD group scored similarly to controls on a pattern recognition task and another test of spatial short term memory, suggesting that spatial memory capacity, motor speed and visual memory are intact.

One of the most cited neuropsychological findings in BDD has been that individuals with BDD process images in a detailed fashion rather than in a more holistic way (Deckersbach, et al., 2000; Feusner, Moller, Altstein, Suger, et al., 2010). Deckerbach et al. (2000) showed disruptions in visual learning when holistic organisation of visual information is required rather than detailed analysis; this is also characteristic of OCD (Boone, Ananth, Philpott, Kaur, & Djenderedjian, 1991; Savage et al., 2000). Interestingly, holistic visual processing disruption with facial stimuli was shown in schizophrenia by Joshua and Rossell (2009), suggesting that BDD, OCD and schizophrenia all have a bias towards detailed visual processing. However, no published studies have directly compared BDD to OCD or schizophrenia in this regard, so any conclusions are only tentative.

In a recent study examining detail bias in BDD (Feusner, Moller, Altstein, Suger, et al., 2010), participants viewed images of faces that were either upright or inverted. Inverted faces slowed the recognition response time in both BDD and control groups, but individuals with BDD slowed significantly less than controls. Gestalt recognition is disrupted when images are inverted, and the smaller response delay for the BDD group suggests they rely on detailed visual analysis, causing less disruption when images are inverted. This detailed analysis bias has also been demonstrated in a study that showed that individuals with BDD were more accurate than controls with dermatological conditions at noticing small differences between facial images (Stangier, Adam-Schwebe, Muller, & Wolter, 2008). However, there has been some variation in results, with BDD participants in another study showing no difference to OCD and control subjects in their ability to detect slight asymmetry in faces (Reese, McNally, & Wilhelm, 2010).

Other studies of BDD patients have focused on facial emotional recognition. One study compared BDD with OCD on a facial emotion identification task (Buhlmann, et al., 2004) and

found that both disorders were associated with difficulties interpreting the emotional facial expressions compared to controls. The BDD group more often misidentified emotional expressions as angry compared with OCD and control subjects. Such emotional misinterpretation has also been shown for non-face general social scenarios (Buhlmann et al., 2002; Clerkin & Teachman, 2008), suggesting a more generalised emotional hyper-arousal. In another study (Feusner, Bystritsky, Hellemann, & Bookheimer, 2010) requiring matching of faces, BDD participants performed similarly to non-clinical controls when the stimulus facial expression was neutral. However, when the stimulus faces where showing emotion (e.g. sad, happy, angry), BDD participants reacted more slowly and made twice as many mistakes as controls, indicating a tendency to be distracted by emotional cues and a possible hyper-sensitivity to emotion.

Identification of these emotional biases, coupled with fundamental cognitive abnormalities and deficits in information processing can inform our understanding of the neurobiologcal abnormalities underpinning BDD. Thus, this review of neurocognition illustrates that individuals with BDD have abnormal ways of processing information, and that these may be linked to specific brain regions. For example, poor executive functioning is surmised to be a result of abnormalities in the prefrontal cortex (Dunai, et al., 2009; Hanes, 1998), while memory deficits are thought to involve abnormalities of the medial temporal cortex (Deckersbach, et al., 2000); and poor facial expression recognition implicates underlying networks involved in facial recognition, including the superior temporal sulcus (Haxby, Hoffman, & Gobbini, 2000). More specifically, interpretation biases may implicate emotional regulation system in the brain, particularly the limbic system (Stein, Goldin, Sareen, Zorrilla, & Brown, 2002). Specific functional neuroimaging experiments will need to be conducted to confirm these interpretations, but there is a coherent emerging ‘story’ that can now be told. We now turn to neuroimaging

studies that have investigated the pathophysiology of BDD. None of these studies have directly compared BDD to other disorders.

Neuroimaging

Both functional and structural imaging has been conducted with BDD patients. Functional imaging has tended to focus on activation levels while the participants engage in visual processing tasks, as their symptomatology is closely related to these systems.

Feusner et al. (2007) conducted an fMRI study to explore brain activation in 13 BDD and 12 control participants. The participants were presented with faces that had been digitally manipulated to either have low, normal or high levels of detail. The low spatial frequency was blurred, while the high spatial frequency had exaggerated contour details. Previous research has shown that visual processing of detailed stimuli produces different brain activation to global processing in healthy participants (Iidaka, Yamashita, Kashikura, & Yonekura, 2004; Vuilleumier, Armony, Driver, & Dolan, 2003). Given that individuals with BDD tend to have a bias toward detail in visual analysis (Deckersbach, et al., 2000; Feusner, Moller, Altstein, Suger, et al., 2010), patterns of brain activation in response to the three different spatial frequency stimuli were expected to be different to controls.

The researchers found two major group differences. First, right amygdala activation was significantly greater in the BDD group for high spatial frequency and low spatial frequency facial pictures, but there were similar levels of activation for the normal resolution pictures. Second, there was more left hemispheric activation in the lateral aspects of the middle and inferior prefrontal cortex in the high and low spatial frequency face presentation for the BDD

group, while controls had more right activation. Studies (e.g. Van Kleeck, 1989) with healthy individuals have demonstrated that left prefrontal cortex activation is associated with local or analytical processing while the right prefrontal cortex has increased activation for holistic or global processing. The results from this study showing greater activation in the BDD group for brain regions associated with detailed analysis, taken together with the Deckersbach et al. (Deckersbach, et al., 2000) study showing a bias for detailed visual information organisation, suggest that BDD participants engage in a more piecemeal and detailed analysis of faces compared to healthy individuals.

A subsequent study (Feusner, Moody, Hembacher, Townsend, et al., 2010) with similar design aimed to examine brain function particular to visual presentation of BDD participants' own face or a familiar face. The BDD patients (n=17) demonstrated lower levels of activation in primary and secondary visual cortical areas for low-detail images for the own faces and faces of familiar people, compared to 16 healthy controls. Since the low-detail images require holistic processing, abnormal brain activation may indicate difficulties in processing such information. Additionally, this study demonstrated hyperactivity in the left orbitofrontal cortex and bilateral caudate when shown a picture of their unaltered face, compared to the familiar face condition. OCD samples have also demonstrated hyperactivity in these areas (Rauch, 2000), supporting their conceptual association. The study also found that frontostriatal activation was correlated with higher levels of obsessive thoughts and compulsive behaviours in the BDD group. These two studies are particularly interesting because the face is the most common area of fixation in BDD. Future research should consider comparing BDD groups based on area of fixation (facial versus body), as cortical differences may be present.

Abnormal cortical activation in BDD patients has also been found for visual stimuli which are unrelated to BDD symptoms. Feusner et al. (2010) found that, when presented with manipulated images of houses, individuals with BDD showed similar abnormalities in brain activation as when shown faces; this suggests general abnormalities in visual processing rather than symptom-specific deficits.

Another brain imaging study (Carey, Seedat, Warwick, van Heerden, & Stein, 2004) used single photon emission computed tomography (SPECT) with six BDD participants. SPECT imaging uses injected radioactive material to measures blood flow (perfusion) in different areas of the brain. There was no control group in this study, thus the results from brain regions of interest were compared to previously acquired and standardised region-of-interest templates. The study found widespread neurocircuitry abnormalities, including perfusion deficits in bilateral anterior-medial temporal, occipital regions and frontal areas and asymmetrical perfusion in parietal lobes. Of particular note were the blood flow deficits in the temporal regions, as these regions are associated with body image perception (Trimble, 1988). Ventral areas of the temporal region are known to be involved in face perception, while anterior areas are involved in visual processing (Haxby, et al., 2000; Kanwisher, McDermott, & Chun, 1997); both functions have been shown to be abnormal in BDD (Buhlmann, Etcoff, & Wilhelm, 2006; Deckersbach, et al., 2000). However, due to the small sample size and no control group replications of these findings are needed.

Neuroanatomical differences in BDD were studied by Rauch and colleagues (Rauch et al., 2003). They conducted a brain structure study using morphometric magnetic resonance imaging (MRI) with eight female BDD participants and the same number of sex matched controls. They reasoned that studying brain structure could establish a basis for comparison of

BDD to other OC spectrum disorders. Their results showed that there was greater total white matter volume and a left-shifted caudate asymmetry in BDD. These results may explain the selective attentional biases towards detail found in the cognitive studies reviewed above (Deckersbach, et al., 2000; Feusner, Bystritsky, et al., 2010; Feusner, Moller, Altstein, Suger, et al., 2010), as the caudate region is involved in the filtering of new sensory information, learning and memory. The caudate nucleus is also consistently abnormal in OCD samples (Whiteside, Port, & Abramowitz, 2004). Volumetric differences between all other measured brain regions, including the amygdala, thalamas, globus pallidus, hippocampus and putamen were not significant. However, due to the female gender bias in the sample and the small sample size, these results should viewed with caution, as non-significant findings may be due to lack of power and significant findings may be due to sampling error.

In contrast to the all female sample in the above study, Atmaca et al. (2010) compared 12 male BDD subjects who were unmedicated, to 12 male controls. Greater total white matter volumes were found, confirming results found by Rauch et al. (2003). Consistent with fMRI data showing hyperactivity in the orbitofrontal cortex (Feusner, Moody, Hembacher, Townsend, et al., 2010), this structural study found that the BDD group had significantly smaller orbitofrontal cortices compares with controls. Moreover, the study found that the longer the duration of illness the smaller the orbitofrontal cortex volumes, suggesting hypoatrophy caused by hyperactivation. These results may explain the executive function and emotional regulation deficits in BDD. Additionally, these results give further support for the conceptual link between OCD and BDD, as similar reductions in volumes has been demonstrated in the orbitofrontal cortex in OCD (Rotge, 2010; Saxena, Bota, & Brody, 2001).

Feusner and colleagues (2009) also undertook a structural imaging study with 12 BDD participants and 12 controls. This study measured specific regions of interest using a manual tracing technique, limiting the brain regions measured to the amygdale, caudate and inferior frontal gyri. This technique is in contrast to the Rauch et al. (1997) study that measured more regions with a more automated although less accurate process, making comparison between their studies difficult. Feusner et al. (Feusner, et al., 2009) found no significant differences between the groups in terms of volumetric differences in white and grey matter or their regions of interest. However, symptom severity within the BDD group was significantly positively correlated with right amygdala volumes, supporting previous fMRI data of abnormal right amygdala activation (Feusner, et al., 2007). This finding is consistent with current knowledge on amygdala function, as the amygdalae have consistently been shown to be involved with emotional arousal (Phelps, 2004) and affective facial recognition (Stein, et al., 2002). The right amygdala is particularly active in tasks that require the processing of emotional visual information (Iidaka, et al., 2004). As individuals with BDD have been shown to be have high emotional arousal, biases in affective facial recognition tasks (Buhlmann, et al., 2006) and their primary symptoms involve visual emotional disturbances, the finding of right amygdala structural and functional abnormalities suggests that hyperactive amygdalae might be important in BDD symptomatology. However, further evidence of amygdala pathology is needed, especially as the Fuesner et al. (2009) structural study again had a small sample size. In fact the reported significant correlation between amygdala size and symptom severity may be explained by two outliers among the twelve data points.

Figure 1 shows brain areas that have been shown to be abnormal in BDD. Additionally, in terms of general differences between BDD and control brains, increased white matter volumes and leftward shift in hemispheric activation have been consistent findings.

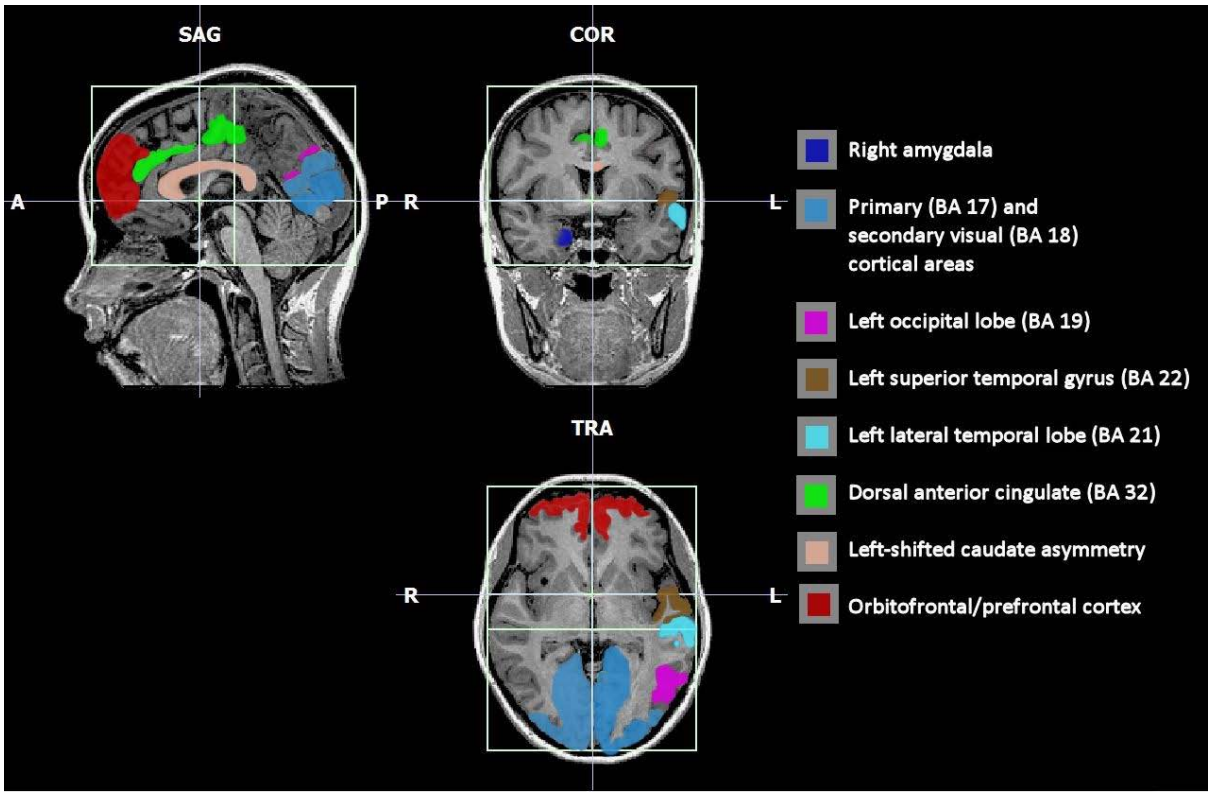

Figure 1. Implicated brain regions in body dysmorphic disorder

Aetiology of BDD

This review has focussed on neurocognitive and neurobiological underpinnings of BDD, but these can by no means comprehensively explain the mechanisms by which BDD evolves within certain individuals. For example, certain psychological and sociocultural factors have been shown to be related to the onset of BDD (Buhlmann, et al., 2007; Neziroglu, Khemlani-Patel, & Veale, 2008): the causal interaction of these factors has been conceptualised well in the

cognitive behavioural model of BDD (Neziroglu, et al., 2008; Veale, 2004). Nevertheless, neurobiological pathology as discussed here represent the most direct factors underlying BDD symptomatology. Such pathology is perhaps influenced by genetic factors and early environmental experiences. Indeed, genetic influences have been shown to be important, with prevalence studies showing higher BDD rates of 5.8% to 8% among first degree relatives of those with BDD (Bienvenu, et al., 2000; Phillips, Menard, et al., 2005); there is also a genetic link to OCD (Hollander, et al., 1993). Thus, any holistic model of BDD must encompass all of these parameters.

Conclusion

While much is known about the phenomenology of BDD, further research is needed into the fundamental cognitive and neurophysiological underpinnings of the disorder. Neuropsychological studies have indirectly implicated certain regions of the brain and contributed to the formulation of a neurobiological paradigm of BDD. Based on this evidence, it is possible that the perceptual distortions experienced by individuals with BDD are caused by a tendency to process detailed visual information rather than configural arrangement. Neuroimaging research to date supports this, showing hyperactivity in the left hemisphere associated with detailed analysis, rather than right-hemisphere-mediated holistic appraisal. The tendency for individuals with BDD to mirror gaze and focus on one aspect of their appearance can be explained through this mechanism. The emotional hyper-activity and misinterpretations experienced in BDD may make individuals with the disorder more likely to interpret slight physical anomalies in a negative manner, exaggerated by the perceived negative evaluation by others. This may involve abnormal functioning of the limbic system including the amygdalae.

In terms of the nosological debate around BDD as an obsessive compulsive disorder or a delusional disorder, the available data have produced more support for BDD's conceptualisation as an obsessive compulsive spectrum disorder. Similarities to OCD in executive function, visual processing, facial emotion recognition and abnormal patterns of activation in the oritofrontal cortex have been found. These similarities, however, are largely based on comparison of separate study's findings. Beyond neurocognitive similarities, OCD and BDD still have important difference in terms of insight, and the delusions present in BDD make classification within an obsessive compulsive spectrum disorder category problematic. Thus, more data directly comparing BDD to OCD and schizophrenia is needed. Neurocognitive similarities between BDD and schizophrenia should also be directly examined, as comparative neuroimaging studies would help inform the nosological debate.

Future perspective

Over the next decade it is predicted that there will be greater emphasis on untangling the aetiological factors important for understanding BDD. This will include an influx of neuroimaging studies examining the integrity of both the structure and function of the brain using MRI and other techniques. There is also scope to employ other technologies, including advanced modern eyetracking. Eye movement abnormalities have frequently been reported in other mental illnesses including schizophrenia and other anxiety disorders. There is a particular dearth of such investigation in BDD, which is surprising given the extensive literature on visual processing problems.

In addition, the publication of the DSM-5 may see BDD placed as an obsessive compulsive spectrum disorder. However, there will be ongoing debate as to the significance of delusions in BDD and the nosological implications thereof.

Chapter 3

Regions of Interest and Neurobiological Models of BDD

In the last two decades, magnetic resonance imaging (MRI) has allowed unprecedented access to the function and physiology of the brain. Since its introduction, thousands of brain MRI scans from healthy participants and those with mental illness have been acquired and analysed, often in respect to diagnosis and/or psychological variables. An account of these methods will be explored in Chapter 5, but let us first discuss the knowledge about the brain and mental illness that these methods have given us. First, this chapter will focus on specific regions of interest and extend the review presented in Chapter 2 with updated literature in BDD. Then, neurobiological models for BDD and their associated hypotheses will be provided.

Regions of potential interest

There are two major traditions to approach an analysis of the brain's cognitive function. The first relates to theories of modularity, which emphasise functional specialisation and suggests the brain has different modules that are domain specific in function. The second type, distributive processing theories, emphasise that the brain is highly interactive, and brain function is better understood in terms of functionally interconnected dynamics rather than specialised brain regions. Both approaches are important, with a more sophisticated understanding of brain functioning transpiring from an integration of the modular and distributive theories.

One way to approach understanding the whole is to first understand the parts that make up the whole, so the following section will focus on specific regions of the brain that are likely to be related to BDD pathophysiology. These regions are the temporal lobe, amygdalae,

hippocampus, occipital lobe, parietal lobe, precuneus, prefrontal cortex, orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC). After these are examined, the next section of this thesis will emphasise the interconnected nature of these regions and propose overarching neurobiological models of BDD.

Temporal lobe

The first area of interest in BDD is the temporal lobe, a region of the cerebral cortex that is located beneath the lateral fissures of both cerebral hemispheres. Within the temporal lobe is the amygdala and hippocampus, which will be discussed separately given their importance to BDD. Also within the temporal lobes are the primary auditory cortex and, importantly to BDD, the fusiform gyrus, which is fundamental to face perception (Kanwisher, et al., 1997). In general, the temporal lobe is involved in retaining visual memories, processing sensory input, comprehending language, storing new memories, emotional processing, and deriving meaning from stimuli.

The temporal lobes have been implicated in BDD via neuropsychological research, as well as neuroimaging data. The memory deficits demonstrated in BDD implicate the medial temporal cortex (Deckersbach, et al., 2000); and poor facial expression recognition implicates the superior temporal sulcus (Haxby, et al., 2000). A preliminary neuroimaging study in BDD used single photon emission computed tomography (SPECT) imaging, and found widespread neurocircuitry abnormalities (Carey, et al., 2004). Of particular note were the blood flow deficits in the temporal regions associated with body image perception and ventral areas of the temporal region known to be involved in face perception (Kanwisher, et al., 1997). However, due to the small sample size and lack of a control group, replications of these findings are needed for

further verification. Nevertheless, the data showing facial processing deficits in BDD coupled with temporal lobe differences suggests the disruption of face processing circuitry may be important to BDD onset and maintenance. In fact, face perception is hypothesised to be of such importance to BDD that it will be proposed on page 57 as a core cognitive disruption that underpins BDD symptoms.

Amygdalae

Within the medial temporal lobes reside two almond-shaped groups of nuclei which are among the most studied brain areas in affective disorders: the amygdalae. In general, they has been shown to play a primary role in the processing of memory and emotional reactions, and is a core area implicated in social (dys)function. In fact, it could be considered as the most important region in the limbic system, and is often thought of as a central structure in the "social brain" because of its importance in processing and modulating socially relevant stimuli (Kleinhans et al., 2007). Thus, the amygdalae may be important for disorders such as BDD that involve emotional dysregulation and social dysfunction.

The traditional view of the amygdalae emphasises its involvement in threatening stimuli, particularly in processing facial expressions that depict fear or anger. It responds to emotional stimuli before conscious awareness, generally irrespective of attentional focus, and enhances perception of emotional stimuli (Kleinhans, et al., 2007; Phelps, 2004). Additionally, the amygdala's response to emotional stimuli is generally related to the intensity, positive or negative, of the stimulus (Kleinhans, et al., 2007). Furthermore, the amygdala is important in terms of facilitation of memory, an effect mediated by the basolateral amygdala (Paz, Pelletier, Bauer, & Paré, 2006). Taken together, these findings suggest that amygdala activation might

cause affective experience more by influencing perception and memory than being the actual root of the negative affect experience (Barrett, Bliss-Moreau, Dunca, Rauch, & Wright, 2007). Indeed, evidence from lesion studies shows that the amygdala is not necessary for the experience of affect (Anderson and Phelps, 2001, 2002, as cited in Barrett, et al., 2007). Thus, the amygdala serves to enhance perceptual sensitivity for negative experiences, influencing how the negative sensory information is processed in the brain.

In healthy individuals, evidence indicates that those who report high levels of negative affect show a perceptual sensitivity to negative stimuli, mediated by amygdala response (Barrett, et al., 2007). For example, individuals with high trait anxiety (either with or without a diagnosed anxiety disorder) are biased to shift their attention to negative stimuli and have great amygdala activation (Whalen, 1998). A number of experimental paradigms have been used to measure this bias, including the emotional Stroop task (Myers & McKenna, 1996). This same task has been used with BDD samples with results that are typical of disorders with amygdala hyperactivity (Buhlmann, McNally, et al., 2002). That is, when performing the Stroop task individuals with BDD are vulnerable to distraction by emotional cues in general, and by words related to their current concerns in particular.

In the context of BDD, the amygdalae's influence over emotional salience and memory may help explain why this patient group has far greater recollection of childhood body-related teasing instances compared to controls (Buhlmann, et al., 2007). Indeed, their recollection of such incidences are far more vivid than controls (Osman, Cooper, Hackmann, & Veale, 2004), and evidence suggests that these memories might represent more vigilance to teasing experiences rather than more actual teasing experiences. A predisposition to increased activation of the

amygdala (and hippocampus) may increase the memory and meaning of the event, contributing to BDD onset.

In clinical samples, the amygdala has received a large amount of attention compared with other brain regions due to its well documented role in emotion. Studies have documented reduced amygdala volumes in depression (Sheline, Gado, & Price, 1998), obsessive-compulsive disorder (OCD) (Szeszko et al., 1999), schizophrenia (Rajarethinam et al., 2001), bipolar disorder (Blumberg et al., 2003), and borderline personality disorder (Schmahl, Vermetten, Elzinga, & Douglas Bremner, 2003). However, other reports have found the opposite. For example, in major depression, there have been results of volumetric increases of the amygdala (Frodl et al., 2003) and a meta-analysis finding no difference in amygdala volumes between patients with major depression and controls (Koolschijn, van Haren, Lensvelt Mulders, Hulshoff Pol, & Kahn, 2009). In general, studies of disorders conceptualised as "fear circuitry" and "threat perception" disorders have reported relatively heightened amygdalae activation in response to disorder-relevant stimuli, including in post-traumatic stress disorder, social phobia, and specific phobia (Marek, Strobel, Bredy, & Sah, 2013; Whalen, 1998). Therefore, fear circuitry will be proposed as promising neurobiological model for BDD on page 60.

Amygdala volumes have been far more reliably studied in OCD than BDD. The three volumetric studies in BDD have not found group differences (Atmaca, et al., 2010; Feusner, et al., 2009; Rauch, et al., 2003), though differences in activation have been reported during visual tasks (Feusner, et al., 2007). The lack of volumetric finding probably represents a lack of statistical power due to small sample sizes and the reliability problems in volumetric measurement of the area (as examined in Chapter 5). However, the overwhelming parallels

between anxiety disorders, OCD, and BDD strongly suggest amygdala differences are likely to be found with further investigation.

Despite the established role of the amygdala in affective disorders, there is still contention around the mechanisms by which amygdala volumes change. Some posit that reduced amygdala volume in OCD is a result of a generalized neurodegenerative process that predisposed individuals to OCD onset (Szeszko, et al., 1999). On the other hand, in the light of inconsistent volume results, amygdala enlargements could be a result of hypertrophy caused by chronic activation. Such enlargement of the amygdala after stress has been documented in animal studies (Vyas, Mitra, Shankaranarayana Rao, & Chattarji, 2002). However, such causal relationships remain speculative in humans. In fact, reverse causation is also likely, where a larger amygdala causes hyperactivity.

The amygdala is not the sole region responsible for emotional hyperarousal; rather, the connections between the amygdala and other brain regions are now understood to be of central importance. For example, the connections between the amygdala and prefrontal cortex are more highly predictive of anxiety than the amygdala itself (Kim & Whalen, 2009; Marek, et al., 2013). These connections will be discussed in detail on page 60, as they are of central importance to the proposed fear circuitry hypothesis of BDD neurobiology. In addition, subsequent analysis of face perception (page 57) and emotional deregulation in BDD will all include the amygdala as a site that could mediate symptoms.

Hippocampus

Like the amygdala, the hippocampus has been implicated in a large number of mental disorders including OCD, schizophrenia (Kwon, Shin, et al., 2003) and depression (Campbell, Marriott, Nahmias, & MacQueen, 2004), but has not been examined in BDD. The hippocampus belongs to the limbic system and plays important roles in the consolidation of information from short-term to long-term memory (Phelps, 2004). The hippocampus is particularly vulnerable to degenerative changes caused by chronic stress, a process that is mediated by mechanisms involving high levels of glucocorticoid secretion and activation of excitatory amino acid release (Vyas, et al., 2002).

Developmental factors are also known to influence the hippocampus. One study, for example, found that in healthy eight to seventeen-year-olds, smaller hippocampal volumes were associated with higher levels of anxiety symptoms (Bakermans-Kranenburg & Crone, 2013). More specifically, higher scores on the withdrawal and anxiety/depression syndrome scales were strongly correlated with smaller volume in the left hippocampus. In fact, the authors demonstrated that a smaller hippocampus is a predictive risk factor for the development of internalising symptoms, and possibly, in the long run, anxiety disorders.

The role the hippocampus plays in affective disorders is not well-understood. Despite this, its reduced volumes in OCD (Kwon, Shin, et al., 2003); and the developmental findings that the hippocampus is susceptible to chronic stress make it a region that would likely show differences in patients with BDD when compared to controls.

Thalamus

Recent brain imaging findings in OCD have been compelling in suggesting that specific circuits that include the thalamus are responsible for the mediation of OCD symptoms (Atmaca, Yildirim, Ozdemir, Tezcan, & Kursad Poyraz, 2007). The cortico-striatal-thalamo-cortical (CSTC) circuitry will be discussed in detail in a later in this chapter (page 67), but the following section will focus on the findings specifically related to the thalamus.

The thalamus is part of the limbic system, and one of its roles is to receive sensory information from every sense system (with the exception of the olfactory system) and send them to the associated primary cortical area. In addition, it relays information between a variety of subcortical areas and the cerebral cortex. The majority of research in mental illness has been devoted to the CSTC loop, however in the context of BDD, where patients have an integration of details and holistic visual information, the thalamus's role as a sensory relay centre could also be important.

Anatomically, the thalamus is situated between the cerebral cortex and midbrain, both in terms of location and neurological connections. Its location serves to send nerve fibres in all directions to relay information between subcortical areas and the cerebral cortex. The thalamus is closely connected to the hippocampus via the mammillo-thalamic tract, and this connection has been reported to contribute to spatial memory and episodic memory (Briggs & Usrey, 2008).

Neuroimaging data in BDD has shown that the thalamus is the only area with increased volume relative to controls (Atmaca, et al., 2010; Atmaca, et al., 2007). This parallels findings in OCD, where there is a general reduction in grey matter volume (but not white matter volume) in the OFC, ACC, anterior cingulate gyrus and caudate nucleus, but a general increase in bilateral

thalamus volumes (Atmaca, et al., 2007; Gilbert et al., 2000; Hoexter et al., 2011; Venkatasubramanian et al., 2012). Several studies have directly implicated the thalamus in OCD, and findings that partial thalamotomy could reduce symptom severity in treatment-refractory OCD patients provided further evidence of its role in the pathophysiology of OCD (Chiocca & Martuza, 1990 as cited in Atmaca, et al., 2007). Furthermore, increased thalamus volumes have been found among medicated and medication-free OCD patients (Atmaca, et al., 2007; Gilbert, et al., 2000). Particularly compelling for the thalamus's role in OCD are treatment studies that have revealed that patients with OCD showed reduced thalamic volumes after selective serotonin reuptake inhibitor (SSRI) treatment (Gilbert, et al., 2000; Rosenberg, Benazon, Gilbert, Sullivan, & Moore, 2000) and normalized activation after cognitive behavioural therapy (CBT) (Saxena et al., 2008). In fact, reduction of thalamic activity may be fundamental to the improvement in OCD.

Although the dynamics involved between the thalamus and OCD are not completely understood yet, emerging evidence suggests overactivity in the thalamus may mediate OCD behaviours in both humans and animal models (Briggs & Usrey, 2008). Importantly, these studies demonstrate that the thalamus cannot be viewed in isolation, but must be considered as an integral part of a thalamo-cortico-thalamic-cortical circuit which interconnects the thalamus and cortex for sensory processing, with both excitatory and inhibitory roles (Briggs & Usrey, 2008), as discussed shortly.

In terms of findings related specifically to the thalamus, if parallel volumetric and activation findings in BDD can be confirmed, then it would lend some support to the neurobiological similarities of BDD to OCD. In particular, given that the thalamus shows increased volumes among a multitude of reduced grey matter volumes in OCD, it has some value

to specify a phenotypical neurobiological signature. If the same signature was present in BDD, it would provide compelling evidence of similarities between OCD and BDD, and provide further support for categorisation of BDD in the DSM-5 under "obsessive compulsive and related disorders".

Occipital lobe

One of the main clinical symptoms in BDD is distorted perception of a person's own appearance. Indeed, in laboratory settings, BDD participants have been shown to have differences in the way they process visual information, having a detailed processing bias in both faces and other objects (Feusner, Hembacher, Moller, & Moody, 2011; Feusner, Moller, Altstein, Suger, et al., 2010; Feusner, et al., 2007). Therefore, BDD can be conceptualised as a disorder of visual perception, making the occipital lobe of some interest.

On an anatomical level, the eyes convey stimuli through the optic tracts to the thalamus, where optic radiations continue to the visual cortex within the occipital lobe. The occipital lobes receive raw sensory information, and through a series of circuits within different areas of the lobe and feedback from the frontal and temporal lobes "perception" is created. The occipital lobe can be broken into five regions, V1 to V5, with V4 being the most relevant to BDD.

Compared to other occipital regions, V4 specialises in somewhat more complex perception of specific objects, including faces. The so-called "occipital face area" within V4 is tuned to recognise faces, as is the fusiform face area in the temporal lobe. Dynamic interactions between these two areas are important to face recognition (Kanwisher, et al., 1997). Thus, a

problem in either area or a problem with the connection between the areas is likely to cause abnormalities in perception.

One study in BDD has demonstrated that when patients viewed photographs of houses, those who had more severe BDD symptoms were more likely to have lower activity in the dorsal occipital cortex and ventrolateral prefrontal cortex (Feusner, et al., 2011). These results lend support to fundamental differences in visual perception (not just differences in face perception), mediated by the occipital lobe. In fact, visual perception differences may represent a key underlying deficit in BDD, a hypothesis that will be discussed further on page 57.

Parietal lobe

The excessive concern that individuals with BDD possess over their appearance could have a visual basis, but another possibility is that they have difficulties in proprioception and kinaesthetic awareness, which are mediated by the parietal lobes. The parietal lobes integrate sensory information from different modalities to facilitate the body's spatial sense. The parietal lobes also comprise the somatosensory cortex, which is involved with body awareness and the dorsal stream of the visual system. This enables regions of the parietal cortex to map objects perceived visually into body coordinate positions (Kaplan, Rossell, Enticott, & Castle, 2013).

The superior parietal lobule is involved in maintaining internal representations, kinaesthetic attention (Stoeckel et al., 2004) and visual tasks that require spatial shifts of attention (Corbetta, Shulman, Miezin, & Petersen, 1995). Thus, problems with either sensory interaction or kinaesthetic awareness could play an important role in BDD.

Some authors have suggested that the right parietal lobe has specific functions that may make it more important than the left parietal lobe for BDD (Kaplan, et al., 2013). Indeed, lesions in the right parietal lobe have been associated with the onset of body image disorders (Roth, 1949). On top of this, a complex network involving right parietal areas has been implicated in different aspects of self-perception, including body and facial recognition of self. This network appears to be central to awareness of, and identification with, one's own body.

Precuneus

The precuneus is the posteromedial portion of the parietal lobe. A body of literature has been emerging regarding the precuneus's importance in self-perception, making this region an area of interest in BDD. Two studies in BDD have reported incidental findings in the area during visual tasks (Feusner, et al., 2011; Feusner, et al., 2007). The first study found that BDD participants had activation in the right precuneus while viewing detailed facial stimuli, while control participants had activation bilaterally (Feusner, et al., 2007). The second study used houses as visual stimuli and found that there were differences in precuneus activation when participants were viewing low detail images (Feusner, et al., 2011). These studies, however, did not robustly demonstrate the precuneus's role and the findings remain unclear. Nevertheless, the precuneus's role in self-perception and visual perception, as outlined below, suggests that it may be of theoretical importance to BDD. Therefore, the precuneus will be discussed here in some detail.

Anatomically, the precuneus is connected with other parietal areas but also has a strong connection to the frontal lobe and anterior cingulate cortex (Joshi et al., 2010). Other reciprocal cortical connections involve the parietooccipital visual area and the caudomedial lobule, and the

temporo-parieto-occipital cortex (which is buried in the superior temporal sulcus). The association cortices of the temporo-parieto-occipital form a cortical network, which is involved in the integration of somatosensory and visual information (Cavanna & Trimble, 2006). The interconnected posteromedial parietal cortex and medial prefrontal regions have been proposed to represent a network through which personal identity and past personal experiences are interlinked with one another, culminating in self-awareness (Cavanna & Trimble, 2006). Given the BDD is a disorder of fixated self awareness such findings are of particular interest.

Over and above the precuneus's role in self-perception, the anatomical and connectivity data suggests its role in the implementation of a wide range of higher-order cognitive functions. Indeed, it has been specifically implicated in visuo-spatial imagery and body perception as well as self-referential thinking, insight and first-person perspective taking (Cavanna & Trimble, 2006). Its role in integration of visual information could play an important part in BDD given the piecemeal way individuals with BDD process visual information. Additionally, its role in body perception and self-referential thinking seems important given that these are two of the main features of BDD symptoms.

Functional MRI (fMRI) studies have found a high level of activation in the precuneus in tasks associated with self-relevant information processing, reflective self-awareness and representations of the mental self (Kircher et al., 2002; Kircher et al., 2000; Vogeley et al., 2004). The activation wasn't limited to the precuneus, however, with the left prefrontal cortex and left anterior cingulate cortex also showing high levels of activation, suggesting they are all important in self-processing. In a transcranial magnetic stimulation study, the precuneus was again shown to be important in self-perception. Lue et al. (2004) found that disturbing the precuneus and associated neural circuits disrupted the subject’s ability to retrieve judgments

about oneself. They concluded that this area is fundamental to self-monitoring and self-awareness.

Individuals with BDD seem to have deficits in evaluating emotions to a higher degree in self-referential conditions (when they imagine a face is looking at them rather than looking at someone else) (Buhlmann, et al., 2006), perhaps implicating problems in the precuneus. In BDD, perspective taking is of particular importance given their well-documented low levels of insight and frequent presence of ideas of reference (e.g., that other people stare at them). In fact, the level of insight (or level of delusions) is a key difference between BDD and OCD (Eisen, et al., 2004). Thus, the deficits in theory of mind and insight that individuals with BDD experience may be due to differences in the precuneus structure/function, though this theory is yet to be tested.

To date, neuroimaging studies have not focussed on the parietal lobe's role in BDD, with only incidental findings, with studies tending to focus on the differences in fronto-limbic system. Nevertheless, an important question of how BDD's neuropathology is different from OCD and other related disorders remains. For example, the current neuroimaging findings in BDD regarding the frontostiatal system are consistent with OCD and other psychiatric disorders, but there has been no key evidence to set BDD and other disorders apart. Pathology in the parietal lobe, particularly the precuneus, could be a key neurobiological difference.

Prefrontal cortex (PFC)

In contrast to the above discussion, the prefrontal cortex (PFC) has received much attention in BDD through neuropsychological research (Dunai, et al., 2009; Hanes, 1998;

Labuschagne, Rossell, Dunai, Castle, & Kyrios, 2013) and neuroimaging studies (Feusner, et al., 2007). Additionally, anatomical abnormities have been shown in related disorders namely: OCD (Atmaca, et al., 2007), anxiety (Davidson, 2002) and schizophrenia (Lawrie, Whalley, Job, & Johnstone, 2003).

Anatomically, the PFC is the anterior part of the frontal lobes of the brain, lying in front of the motor and premotor areas (Fuster, 2001). The PFC is subdivided in three major regions: orbital, medial, and lateral. The medial PFC is a neocortical structure and is cytoarchitectonically divided into four distinct regions from dorsal to ventral: the medial precentral cortex, the anterior cingulate cortex (ACC), the prelimbic, and the infralimbic prefrontal cortex (Heidbreder & Groenewegen, 2003). The orbital and medial areas are involved in emotional behaviour. The lateral regions provide cognitive support to the temporal organization of behaviour, speech, and reasoning.

Functionally, the PFC has been implicated in planning complex cognitive behaviours, personality expression, decision making and moderating appropriate social behaviour (Miller, Freedman, & Wallis, 2002). The PFC is also important in executive function, which is the ability for an individual to maintain control, consciously or unconsciously, over other lower order cognitive processes. Moreover, the PFC is central for someone's ability to maintain control and inhibit automatic emotional reactions. Disturbances in these functions in BDD have been demonstrated by multiple modalities (neuropsychological and neuroimging) (Atmaca, et al., 2010; Dunai, et al., 2009; Hanes, 1998). In fact, deficits in the PFC are perhaps the area most well demonstrated to be of importance in BDD pathophysiology.

Of particular interest are the connections between the PFC and the amygdalae. The skill to inhibit automatic and emotional reactions to stimuli is not simply a result of the strength of the PFC but more specifically the connections between the PFC and other regions (Kim & Whalen, 2009). Especially important for the current research is the connection of the ventral and medial aspects of the PFC to the amygdalae (Ray & Price, 1993). These connections represent a key neurobiological model and will be discussed in detail in terms of the "fear circuitry" hypothesis (pages 60 to 64).

Orbital frontal cortex (OFC)

A region within the prefrontal cortex which is considered central to OCD is the orbital frontal cortex (OFC) (Remijnse et al., 2006). Given the similarities of cognitive and symptom profiles between OCD and BDD, the OFC is naturally of interest in BDD as well. Functionally, the OFC is important in reward and punishment, motivation and response to learnt and unlearnt reinforcers, as well as general decision making (Kringelbach & Rolls, 2004). The OFC also learns and readily reverses association between secondary and primary reinforcers. It has strong reciprocal connections to the amygdalae, and evidence suggests that they are both important to emotion, although the orbitofrontal cortex appears to be more important for rapid emotion-related learning, while the amygdala is more important for reactions to emotion (Kringelbach & Rolls, 2004).

The OFC has, of course, been implicated in BDD in neuropsychological studies (e.g. Labuschagne, et al., 2013) and previous neuroimaging studies have shown that the OFC in BDD has exhibited volume reduction as well as abnormal activation (Atmaca, et al., 2010; Feusner, Moody, Hembacher, Townsend, et al., 2010). The BDD literature in this area is in its infancy,

but similar and extended findings in OCD give grounds for the area's importance in mediating symptom expression. For example, OFC activation during resting states is greater in OCD patients than in normal control subjects (Kwon, Kim, et al., 2003) and after successful psychological treatments OFC activation decreases in OCD patients (Saxena, et al., 2008).

Indeed, the majority of morphometric MRI studies have indicated that grey matter volumes of the OFC are reduced in patients with OCD (e.g. Togao et al., 2010). The implication of these findings is that increased metabolism may underlie the persistence of obsessive thoughts in the maintenance of the disorder. Thus, these findings suggest that this area may be involved in mediating the expression of obsessive–compulsive symptoms and, therefore, may also play a key role in BDD.

Anterior cingulate cortex (ACC)

Another area of considerable importance to BDD is the anterior cingulate cortex (ACC). In fact, over the past decade this area of the brain has been shown to be of key importance to many mental illnesses and only a few cortical areas have been ascribed such a broad set of functions. The ACC is connected to motor systems and is involved in executive functions, response selection, emotional processes, volition generation, self-awareness, cognitive processing of affective states and even conscious experience (Devinsky, Morrell, & Vogt, 1995).

Anatomically, the ACC lies rostral to the corpus callosum. In general, the ACC can be divided anatomically based on cognitive (dorsal) and emotional (ventral) components. The dorsal part of the ACC is connected to the prefrontal cortex and parietal cortex as well as the motor system, making it a central station for processing top-down and bottom-up stimuli and an

important component in attention and cognitive control (Sotres-Bayon, Bush, & LeDoux, 2004). By contrast, the ventral part of the ACC is connected with amygdala, nucleus accumbens, hypothalamus, and anterior insula, and is involved in assessing the salience of emotion, regulating emotion and motivational processing. Of particular importance are the functional connections between the ACC and amygdala.

ACC volumes and activation have been shown to be related to symptom severity in OCD patients. Studies implicate this region early in the disease's course, and successful treatment has been shown to reduce its activation (Rosenberg & Keshavan, 1998). For example, in an OCD treatment study using CBT, significant increases in right dorsal ACC activity that correlated strongly with the degree of improvement in OCD symptoms (Saxena, et al., 2008).

Though involvement of the ACC in OCD is now well documented (Menzies, Chamberlain, et al., 2008; Togao, et al., 2010), the exact role of this region in the pathophysiology of the disorder remains unclear. In BDD, the evidence of ACC involvement is in its early stages, but seem to parallel the findings in OCD. For example, Atmaca (2010) found significantly reduced ACC volumes and highlighted the trend towards the right ACC being larger in both BDD and OCD. An fMRI study found that BDD participants had greater dorsal ACC activation than control participants during face recognition tasks with low levels of detail (Feusner, et al., 2009).

There has been an extensive literature on ACC differences in OCD during the Stroop task. No such work has been completed in BDD, to date. Numerous studies have revealed longer colour-naming latencies for disorder-related words in OCD and across other anxiety disorder patient groups such as social phobia (Amir et al., 1996; Buhlmann, McNally, et al., 2002; Kühn

et al., 2012; Whalen et al., 1998). In particular, the emotional Stroop task has been employed to measure the interference experience triggered by emotionally-salient words. Performance on this task is closely related to the volume and functional activation of the ACC in OCD (Whalen, et al., 1998). The Stroop task has been conducted in BDD patients without neuroimaging correlates, finding that BDD patients are similarly more susceptible to information-processing biases when compared to controls (Buhlmann, McNally, et al., 2002). This demonstrates that BDD patients, like OCD patients, have information processing biases and problems with top-down regulation of automatic responses, possibly mediated by the ACC (though the same results could be explained through other mechanisms in the frontal-striatal loop).

Another important role of the ACC is in error detection, with data showing a higher level of activation in the ACC in OCD participants than in control participants when detecting mistakes or faults (Remijnse, et al., 2006). Given that both BDD and OCD are concerned with (false) detection of errors (such as imperfections), the ACC may play an important role in the neurocognitive model of the disorders. Indeed, a recent volumetric neuroimaging study in BDD (Atmaca, et al., 2010) showing reduced volumes in the ACC supports the idea that these cognitive deficits are mediated by the ACC. The error detection hypothesis, possibly mediated by the ACC, will be discussed further on page 64.

Region of interest summary

In this section, the anatomy and role of specific brain regions in BDD has been examined. Available neuroimaging and neuropsychological data in BDD, and related disorders, has been used to implicate the following regions in the pathophysiology of BDD; the temporal lobe, amygdala, hippocampus, and thalamus were discussed in terms of face perception and emotional

processing. The occipital lobe and parietal lobes (specifically the precuneus) were examined in terms of visual and body perception. The prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex were examined in light of executive functioning data and regulation of emotion.

Even if more neuroimaging data was available in BDD none of these individual areas are able to fully explain BDD symptomatology. What has hopefully become clear, however, is that the pathophysiology of the disorder is likely best represented by examining neural networks and dynamic relationships between these areas.

Neurobiological models of body dysmorphic disorder

The following section will move away from specific brain areas and move towards understanding BDD symptoms in terms of theoretical models. Such a discussion will focus on fundamental mechanisms that may explain BDD symptomatology and cognitive profile. In particular, established neurobiological models in OCD will be used to springboard our understanding of BDD. Alternative and complementary theories will be discussed in the context of current data within BDD. In the interest of advancing the understanding of BDD, the possible acquisition of new data that could support or refute these models will be identified.

First, the disconnection hypothesis, which emphasises difficulty in integration of separate brain modules, will be discussed. Disrupted face processing and dysregulated fear circuitry will be examined as possible roots of BDD. Based on the OCD literature, the error detection hypothesis will also be introduced. Finally, the frontostiatal and cortico-striatal-thalamo-cortical hypotheses will also be canvassed as possible neurobiological models of BDD.

Disconnection hypothesis

Any neurobiological model of BDD is likely to integrate two principles: functional specialisation and functional integration. The former posits that brain systems are specialised for various perceptual and cognitive functions, and the latter emphasises interactions among these specialised systems. The disconnection hypothesis is an overarching theory asserting that cognitive dysfunction and psychiatric symptoms are a function of impaired integration among neuronal systems.

The most notable use of the disconnection hypothesis has been within schizophrenia research to try and explain disrupted cognitive functions. Many of the symptoms of schizophrenia have been conceptualised in terms of defective cognitive integration (Friston, 1999; Joshua & Rossell, 2009). For example, hallucinations can be construed as a misattribution of internally generated speech to an outside agency. This speaks to a failure to integrate the attribution of agency and inner speech. Likewise, BDD patients' insistence that others are looking at them and judging them may have similar roots. Another example of failure to integrate information, possibly mediated by brain disconnectivity, is the difficulty of integrating detailed visual information with configural information, which both schizophrenia and BDD seem to share (Feusner, Moody, Hembacher, Townsend, et al., 2010; Joshua & Rossell, 2009).

A neuroimaging technique that has recently been used to investigate the physical connections between brain regions is diffusion tensor imaging (DTI), which will be discussed in Chapter 7. In OCD, there have been at least 18 studies that have used DTI to investigate the physical connections within the brain. Within OCD samples, DTI has found abnormalities in the frontostiatal neural pathway, the corpus callosum, and the superior longitudinal fasciculus, as

well as a generalized disorganization among neural tracts (Bora et al., 2011; Garibotto et al., 2010). Indeed, a study in another disorder related to BDD, social phobia, has found reduced strength of the uncinate fasciculus (Phan et al., 2009), the major white matter tract connecting the frontal cortex to the amygdala and other limbic temporal regions. This reduction in its strength could underlie the aberrant amygdala-prefrontal interactions, resulting in dysfunctional threat processing.

While there has been growing neurobiological evidence of compromised brain connectivity in many mental disorders, there is limited neuroimaging research supporting the hypothesis in BDD. To date, there has only been one DTI study in BDD. The results of this study, published in two separate articles, revealed a general trend towards reduction in white matter pathway strength (Arienzo et al., 2013; Feusner et al., 2013), giving preliminary support to the disconnection hypothesis. This study also found that the clinical measure of poor insight correlated negatively with white matter strength in the inferior longitudinal fasciculus, which connects visual with emotional processing systems. Furthermore, the forceps major, which connects the right and left visual processing systems, had reduced integrity, which is consistent with the disconnection hypothesis in relationship to visual stimuli. Indeed, this could explain the tendency for individuals with BDD to focus on detail without the ability to integrate it into a holistic picture (Feusner, et al., 2007), a tendency that has also been documented in schizophrenia (Joshua & Rossell, 2009). To investigate the disconnection hypothesis this thesis will use DTI (as presented in Chapter 8) and functional connectivity measures from fMRI (as presented in Chapter 9) to determine the physical and functional connectivity between regions.

Visual and face processing hypothesis

Visual perception is a function with significant complexity, as reflected in cognitive models that propose a hierarchy of parallel and serial processing stages. Thus, disconnection between any of these stages may result in disrupted perception. BDD could very well be conceptualised as a disorder of vision, given that individuals focus on a flaw in appearance. Indeed, individuals with BDD seem to be particularly sensitive to visual stimuli, with 20% of BDD patients having education or occupation related to art and design (Veale, Ennis, & Lambrou, 2002), as compared to 3% in OCD.

Preliminary results suggest there could be fundamental differences in the way their brains are processing stimuli, as previously discussed (page 44). The problems with visual perception in BDD can be summarized into two main difficulties: first, they have deficits in face perception, demonstrated through their difficulties in recognising nonverbal emotional information communicated through facial expressions (Buhlmann, Wilhelm, et al., 2002); and second, they have a tendency to process stimuli in a detailed fashion rather than a holistic way (Feusner, et al., 2007). These will be addressed in turn, as they implicate different brain mechanisms.

Individuals with BDD tend to (but not always) focus on a defective facial feature (Buhlmann, et al., 2006). The perceived "defect" is often the nose, eyes or lips, and individuals with BDD frequently check their facial appearance in mirrors and often scrutinize others' faces (Phillips, 1998). Face perception is a psychologically unique class of visual stimuli, given that faces convey important social and emotional information. A study showed that individuals with BDD misidentify emotional expressions as angry more often than individuals with OCD or control participants (Buhlmann, et al., 2004). The authors speculate that perceiving others as

angry and rejecting might reinforce concerns about one's personal ugliness. Furthermore, BDD patients' strong fear of negative evaluation and frequent presence of ideas of reference (e.g., that other people stare at them) could be mediated by a sensitivity and bias in face perception.

The extended system for face perception includes the amygdalae, which plays a central role in processing the social relevance of information gleaned from faces, particularly when that information may signal a potential threat (as previously discussed). Activation of the amygdalae during emotional face tasks has been investigated in BDD, and the results showed relatively heightened right amygdala activation in individuals with BDD when compared to controls (Feusner, et al., 2007). These results are similar to those shown in related disorders such as social phobia (M. Stein, et al., 2002). Pathogenic development or activation in at least one of the face perception structures, therefore, could be a core neurobiological characteristic of BDD, explain their concern with social judgement, and even be a key difference between the neurobiology of BDD and OCD.

Fundamental visual processing difficulties have been investigated using both cognitive and neurobiological techniques. A neuropsychological study demonstrated disrupted visual learning when holistic organization of visual information was required, though learning was intact for detailed information (Deckersbach, et al., 2000). Indeed, the detailed bias has been shown in BDD to both pictures of objects (houses) and faces (Feusner, Moody, Hembacher, Hoffman, et al., 2010), suggesting that there are more widespread cognitive differences than just face perception. Studies using fMRI during these tasks have shown a greater left side activation in the lateral prefrontal cortex, lateral temporal lobe and dorsal anterior cingulate regions for face tasks (Feusner, et al., 2011; Feusner, et al., 2007). Interestingly, no differences in the occipital lobe were documented, suggested higher order perceptual differences rather than fundamental

vision processing problems. In general, the greater leftward activation in BDD is consistent with the behavioural data, which shows bias to process the visual information in a detailed rather than configural way, with the left hemisphere generally considered to process detailed features.

Relevant for both general visual perception and face perception, preliminary evidence in BDD shows compromised structural integrity in the inferior longitudinal fasciculus, the white matter connection between the occipital and temporal areas (Feusner, et al., 2013). Long fibres in this tract connect the anterior temporal lobe with posterior occipital regions (Catani & Thiebaut de Schotten, 2008). The occipital branches of the inferior longitudinal fasciculus extend to the extrastriate cortical regions in the dorso-lateral occipital lobe, the lingual and fusiform gyri, and the cuneus, while temporal branches extend medially near the amygdala, hippocampus, and uncus/parahippocampal gyrus. Thus, differences in face perception shown in BDD (Feusner, Bystritsky, et al., 2010; Feusner, Moller, Altstein, Suger, et al., 2010; Feusner, et al., 2007; Stangier, et al., 2008) may not be a result of pathology within the occipital lobe, but may result from compromised connections between areas of the face processing network.

In summary, a detailed visual processing and an emotion recognition bias have been demonstrated in BDD, though different mechanisms seem to be responsible for these two abnormalities. Indeed, the emotion recognition bias may have little to do with face perception; it may be a result of hyperactive emotional responses in general, mediated by the amygdalae. More neuroimaging data is needed. This thesis will investigate visual systems further by measuring the integrity of relevant white matter tracts (Chapter 8), volumes of visual areas (Chapter 6), and the functional connectivity within the occipital lobes (Chapter 9).

Fear circuitry hypothesis

Anxiety disorders, including BDD, can be conceptualised in terms of heightened fear responses. This excessive fear could have an evolutionary basis in terms of heightened ability for threat perception and precautionary responses (Stein & Nesse, 2011). For example, in OCD, patients often present with the fear of contamination or the fear of hurting others, which are evolutionarily important to maintain health and social ties. The fear experienced in BDD is well-demonstrated through their fear of social judgement about their perceived defect. For example, the intense fear of going bald which is common among male BDD patients. Theoretically, their fixation on appearance may be evolutionary important in terms of attracting a mate. The behavioural and neurobiological mechanisms underlying the fear response and treat perception may have substantial power in the explanation of BDD aetiology, maintenance and remission.

Fear is defined behaviourally and physiologically. Behaviourally, there is a spectrum of defensive behaviours that are engaged when someone is threatened - from vigilance and checking, to attempted suppression of fearful thoughts. Physiologically, fear is associated with activation of the autonomic nervous system: release of adrenaline and cortisol, and activation of the amygdala and other limbic structures (Sotres-Bayon, et al., 2004).

Fear can be innate. For example, most people have some level of amygdalae activation and fear response to an angry face, though some people have a heightened reaction to such stimuli. It seems likely that BDD, like other anxiety disorders, have heightened levels of innate (genetic predisposed) fear, mediated by the amygdalae, as discussed on pages 36-44. On the other hand, fear can be learned, and much of what is known about the neurobiology of fear learning comes from research based on Pavlovian conditioning. In Pavlovian conditioning, an

initially neutral conditioned stimulus is paired with an aversive unconditioned stimulus. This basic behavioural science has been used to conceptualise a range of mental disorders. Phobias, social anxiety disorder, post-traumatic stress disorder (PTSD) and OCD can all be thought of in terms of an exaggerated fear response (Marek, et al., 2013; Sotres-Bayon, et al., 2004; Stein & Nesse, 2011; M. Stein, et al., 2002).

According to the fear conditioning model, BDD sufferers' concern with specific body parts could be due to the process of conditioning, mediated by a predisposition to hyperactive amygdala responses. For example, the conditioned stimulus is the body part of concern while the unconditioned stimulus might be an angry face or a thought or memory of judgement, which innately elicits negative emotions. BDD patients, perhaps, (mis)perceive an angry face or experience teasing related to the body part. Over time, or perhaps through only one instance, they learn to pair these adverse feelings with the body part (conditioned stimulus). This one trial learning is also consistent with the influence the amygdala has over memory as discussed on pages 36 to 44.

Of course, once a fear is learned, it can become unlearned through the process of fear extinction, where a gradual reduction in fear is experienced through repeated exposure to the conditioned stimulus (the body part) without the presence of the unconditioned stimulus (angry face or teasing). This process is generally considered to involve the establishment of inhibitory control of the medial prefrontal cortex over the amygdala-based fear process (Marek, et al., 2013; Sotres-Bayon, et al., 2004).

The prefrontal cortex and the amygdalae have extensive bidirectional connections that mediate fear learning, maintenance and fear extinction. The amygdala is extensively

interconnected with cortical and subcortical regions and while structures such as the hippocampus can modulate aspects of fear learning, connections between the amygdala and medial prefrontal cortex (mPFC) are crucial for both fear conditioning and extinction (Sotres-Bayon & Quirk, 2010).

Animal models have been used to support the hypothesis that fear extinction involves a process by which neural activity in the mPFC comes to regulate the amygdala-mediated expression of conditioned fear responses (Sotres-Bayon & Quirk, 2010). For example, ablation of the mPFC in animal models results in a deficit in extinction memory, suggesting that the mPFC is required for consolidation of extinction (Sotres-Bayon, et al., 2004). Thus, damage to the amygdala or mPFC, or reduced connectivity between these regions through white matter pathways could reduce fear extinction in humans. In terms of BDD, the disruption to this system might mean that an otherwise transient and normal body image concern develops into BDD.

As discussed above, the amygdala, taken alone, has been assigned a crucial role in emotional learning, whereas the prefrontal cortex has been implicated in a variety of cognitive functions involving the strategic use of information in memory. However, it is the connection between these areas that is thought to be important for extinction of the fear response. Indeed, in healthy individuals, several studies have shown that functional activity in the mPFC is inversely related to amygdala activity (Marek, et al., 2013), and this circuit is seen to be compromised in many emotional disorders (Steele & Lawrie, 2004; M. Stein, et al., 2002).

This is important when viewed in the context of the cognitive behavioural model of BDD, where BDD is thought to be a result of an uncontrolled conditioned negative emotional response to body stimuli. Perhaps CBT partially works by activating the mPFC to down regulate

hyperactive amygdala responses, causing fear conditioning extinction. Indeed, the therapeutic technique of exposure and response prevention is explicitly designed to unlearn maladaptive compensatory behaviours.

Research involving individuals with mental disorders conceptualised as having heightened fear responses seem to support the mPFC-amygdala mediated hypothesis, and can be extended onto BDD. In an fMRI study, Rauch et al. (1994) showed that those with PTSD had an exaggerated amygdala response to the presentation of fearful faces. In addition, social phobic patients have been shown to exhibit greater left-sided amygdala activation compared with controls when viewing angry or contemptuous faces (M. Stein, et al., 2002). Extending these results, during symptom provocation, OCD patients have increased activation specifically in the left anterior cingulate cortex and bilateral orbitofrontal cortex (Rauch et al., 1994; Rauch, et al., 1997). Such fear response fMRI research has not yet been completed in BDD, though may have been inadvertently tested in a study with emotionally neutral faces (in high and low detail) (Feusner, et al., 2007). BDD participant had heightened amygdala response during non-emotional face presentation, which may have simply occurred because the BDD participants misperceived natural expressions as angry or contemptuous expressions, as demonstrated outside the MRI scanner (Buhlmann, et al., 2006).

However, more research is needed in BDD to lend support for pathology in fear circuitry. In particular, resting state fMRI could be used to investigate the inhibitory and inverse correlation between the mPFC and amygdala activation in BDD. Empirical data to this effect is presented in Chapter 9. Additionally, the strength of the physical connection between these areas could be investigated directly using DTI, presented in chapter Chapter 7. Reduced white matter integrity in the uncinate fasciculus would demonstrate compromised fronto-amygdala structural

connectivity. Finally, structural MRI could investigate the volumes of these areas, thereby determining if there are any localized pathologies within one or more components of the fear circuits, as presented in Chapter 5.

Error detection hypothesis

In OCD, the error detection hypothesis posits that symptoms may be a result of the brain's tendency for inappropriate or hyperactive error detection signals, manifesting phenomenologically as a feeling that "something is wrong", and thus giving rise to the urge for correction typically observed in OCD (Nieuwenhuis, Nielen, Mol, Hajcak, & Veltman, 2005). Indeed, the feeling that "something is wrong" is similar in BDD with only the focus of attention differing: BDD focuses on visually self-referential stimuli while OCD has a broader range of concerns.

These error detection signals are thought to be generated by an internal monitoring system that resides in the anterior cingulate cortex (ACC). Indeed, during tasks designed to elicit a high degree of performance monitoring and error-detection, neuroimaging studies have found that OCD patients exhibit excessive activity in the ACC, orbitofrontal cortex and structures of the basal ganglia (Fitzgerald et al., 2005; Nieuwenhuis, et al., 2005). In general, patients with OCD engage in excessive action monitoring even when an action has been performed correctly, while control participants only receive negative neural feedback when they actually make a mistake.

On an anatomical level, reward-prediction and error signals are computed by the basal ganglia and conveyed by the midbrain dopamine system to the ACC, where they are used to

reinforce behaviours (Nieuwenhuis, et al., 2005). The error-related negativity reflects the dopaminergic modulation of anterior cingulate activity. Thus, an imbalance between the excitatory and inhibitory circuits may underlie the excessive error signals in OCD, and perhaps, BDD as well. Indeed, the constant signals that "something is wrong" could also underlie BDD patients' reduced tendency for behavioural extinction and their basis for misperceiving neutral faces as angry. The error detection hypothesis, therefore, could explain a broad array of BDD phenomenology and symptomatology. The volumetric dataset presented in Chapter 5, and in particular measurement of ACC volumes, will be useful in examining this hypothesis.

Frontostriatal circuits hypothesis

A neurobiological model of OCD that has received considerable research attention focused on the dysfunction of the frontostriatal circuit, particularly orbitofrontal-striatal circuitry (Harrison et al., 2009; van den Heuvel, Veltman, Groenewegen, Cath, et al., 2005). The hypothesis of pathology within this circuit was first based on evidence showing OCD onset after lesions to the basal ganglia (Laplane et al., 1989) and through knowledge of the interaction of the frontostiatal loop. Unlike the previous hypotheses based on dysfunctional behaviour and a top down understanding of OCD, the frontostriatal hypothesis represents a bottom up understanding with the theory based largely on neurobiological grounds.

Indeed, the frontostriatal dysfunction hypothesis is consistent with many of the preceding hypotheses, including fear circuitry and error detection, and incorporates many of the areas detailed in the region of interest section (pages 35-53). Additionally, neuropsychological studies have shown cognitive impairments in OCD and BDD related to these brain regions, particularly with regard to visuospatial processing, executive functioning, and motor speed (Greisberg &

McKay, 2003; Labuschagne, et al., 2013). Other cognitive domains appear to remain more intact, indicating specific cognitive deficit related to the frontostriatal circuit rather than a general degradation as proposed by the disconnection hypothesis (page 55). In particular, neuropsychological data has shown parallels between BDD and OCD in executive functioning using the Tower of London task (Hanes, 1998) and a similar cognitive profile in general (Labuschagne, et al., 2013).

Since the establishment of core cognitive deficits in OCD, various neuroimaging modalities have been employed to provide evidence for their neurobiological underpinnings, with most confirming frontostriatal involvement. For example, an fMRI study during the Tower of London task confirmed the planning deficits in OCD and suggested that this may be mediated by decreased frontal-striatal responsiveness, mainly in the dorsolateral prefrontal cortex and caudate nucleus (van den Heuvel, Veltman, Groenewegen, Cath, et al., 2005). Resting state fMRI comparing OCD and control participants found clear differences in functional connectivity between ventral cortico-striatal regions, consistent with the notion of frontostriatal dysfunction (Harrison, et al., 2009). In other anxiety related disorders such as panic disorder and hypochondriasis, similar executive functioning deficits mediated by frontostriatal abnormalities have been demonstrated (van den Heuvel, Veltman, Groenewegen, Witter, et al., 2005).

Although there has been no direct investigation using functional neuroimaging during executive function tasks in BDD, the frontostriatal model remains a promising hypothesis. Indirect support has also been provided for this hypothesis in BDD by structural imaging showing reduced OFC volumes (Atmaca, et al., 2010). In addition, an fMRI study showed group differences in OFC and caudate activity suggest frontostriatal hyperactivity in BDD (Feusner, Moody, Hembacher, Townsend, et al., 2010). The only study to investigate white matter

connectivity did not indicate compromised frontostriatal circuits (Feusner, et al., 2013). Due to inconsistent findings and small sample sizes, more investigations of grey and white matter are needed. In particular, resting state fMRI could be effectively employed to determine the functional connectivity between frontal and striatal regions, as presented in Chapter 9.

Cortico-striatal-thalamo-cortical (CSTC) circuitry hypothesis

In what could be considered as a development of the frontostriatal hypothesis, the cortico-striatal-thalamo-cortical model (CSTC) emphasises the dynamic relationship between cortical, striatal, and thalamic regions. It has become a well-established theoretical model of OCD neurobiology and therefore, could also underpin BDD pathophysiology. This model focuses on the imbalance between the proposed opposing functions of the 'direct' versus 'indirect' projection pathways of the basal ganglia. One supported hypothesis posits that hyperactivity of the orbitofrontal–subcortical loops caused by a disruption in the balance of activity through these opposing basal ganglia pathways (specifically, excessive direct pathway activation) underlies the manifestation of OCD symptoms (Ting & Feng, 2011). In particular, OCD symptoms are considered to be mediated by hyperactivity in orbitofrontal–subcortical circuits, involving projections from the orbitofrontal cortex to the head of the caudate and ventral striatum, then to the mediodorsal thalamus via the internal globus pallidus and finally, returning from the thalamus to the orbitofrontal cortex (Togao, et al., 2010).

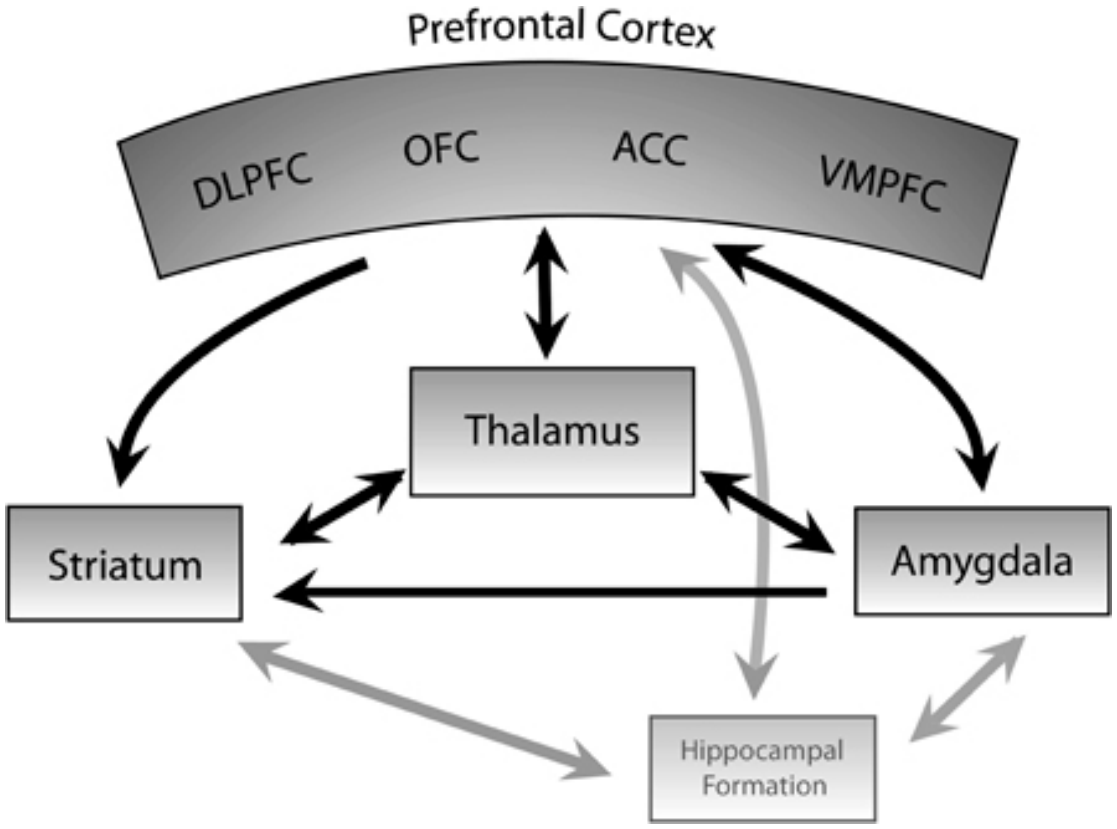

Figure 2. Cortico-striatal-thalamo-cortical (CSTC) circuitry

On the basis of this imaging research, a theoretical model has been proposed. This theory posits that there are a series of dynamic and feedback loops that serve to perpetuate OCD symptoms (Baxter Jr et al., 1992). First, inappropriately increased activity in the head of the caudate nucleus inhibits globus pallidus fibres that ordinarily dampen thalamic activity. The resulting increase in thalamic activity produces increased activity in the orbitofrontal cortex, which, via the cingulate gyrus, completes the circuit to the caudate and produces increased activity in the head of the caudate. Hypothetically, symptomatic cleaning and checking behaviours are "hard-wired" in the thalamus. Alternatively, it could be that the hyperactivity observed in this neuronal loop arises because of impaired caudate nucleus function. The

impairment allows "worry inputs" from the orbitofrontal cortex to inhibit excessively the inhibitory output from the globus pallidus to the thalamus. This model also incorporates the proposed opposing functions of the ‘direct’ versus ‘indirect’ projection pathways of the basal ganglia (Ting & Feng, 2011). The resulting excess in thalamic output then impinges on various brain regions involved in the experience of OCD symptoms, including the orbital frontal region, thus reinforcing hyperactivity in the neuronal loop.

While the CSTC hypothesis probably represents an approximation of the neural circuitry that gates obsessions and compulsive behaviour, it provides a useful theoretical framework for devising hypotheses on the mechanisms of circuitry dysfunction. Unfortunately, current neuroimaging techniques cannot robustly test every aspect of the model, but can provide convergent supporting data. Animal models, however, have been more successfully used to test core hypotheses with more complete results (Ting & Feng, 2011).

In a recent study, optogenetics was used to induce neural activation in rats that mimicked CSTC activation found in OCD (Ahmari et al., 2013). The researchers found that short-term inducement of activation in the OFC and ventromedial striatum did not produce OCD-like behaviours. However, hyper-activation repeated over multiple days generated a progressive increase in grooming, a mouse behaviour related to OCD. Increased grooming persisted for two weeks after stimulation stopped. Both increased grooming and hyperactivity were reversed by fluoxetine treatment. This is consistent with OCD treatment data in humans, both for fluoxetine (Saxena et al., 2002) and cognitive behaviour therapy (Saxena, et al., 2008). This compelling evidence implicates CSTC circuitry in OCD, and tentatively suggests that CSTC hyperactivity causes OCD onset rather than the other way around.

To date, human neuroimaging studies have tentatively confirmed the CSTC hypothesis in OCD; however, some data suggests that more extensive regions are likely to be impaired (Menzies, Chamberlain, et al., 2008). Supporting evidence for a multi-circuit pathophysiology of OCD was summarized by Togao et al. (2010). They suggest that their own, and others', results showing volume increase of the anterior limb of internal capsule as well as the frontal white matter strongly suggest a positive and excitatory feedback loop from the OFC to the thalamus via the internal capsule. Additionally, the volumes reductions in the prefrontal regions support the hyper-activation of this loop as described above. In terms of white matter connectivity, the abnormalities in the medial prefrontal cortex and anterior cingulate white matter may be related to the affective loop linking the limbic system to the ACC or medial prefrontal cortex. In addition, volume changes in the dorsolateral PFC and the posterior parts of the brain suggest the involvement of the dorsolateral prefronto-stiatal loop that is associated with visuospatial attention and working memory processing.

Existing neuroimaging data in BDD is not inconsistent with the CSTC hypothesis yet does not confirm it either. This data included reduced OFC and ACC volumes, increased thalamus volumes (Atmaca, et al., 2010), and similar planning deficits in BDD and OCD associated with activation to OFC (van den Heuvel, Veltman, Groenewegen, Cath, et al., 2005). However, more data is needed. If similar findings to those described above in OCD can be robustly demonstrated in BDD, it would be supportive of the CSTC hypothesis. Multiple modalities including structural imaging, DTI and resting state fMRI can all be used to help determine if CSTC circuitry is disrupted in BDD.

Summary of hypotheses

This chapter described various alternative models of BDD dysfunction in the context of current literature in BDD and OCD. The neurobiological research into BDD is in its early stages, and the current data suggests that it has a similar neurobiology to OCD. The disconnection hypothesis was proposed as an overarching hypothesis in BDD, based on the relatively widespread neuropsychological deficits (Hanes, 1998). The role of the amygdala in emotional face processing and fear circuitry was examined, with an emphasis on functional connection between the amygdalae and frontal regions. The heightened error detection mediated by the ACC was hypothesised, possibly explaining the feeling of "wrongness" in BDD about how they look.

Finally, the impact of a dysfunctional cortico-striatal-thalamo-cortical (CSTC) circuitry was examined, with compelling OCD and animal models suggesting it may be the neurobiological basis for OCD, and therefore BDD. Indeed, this model also partially encapsulated other models described (frontostriatal and error detection). Although the pathophysiology underlying OCD is unclear, multiple lines of evidence implicate deregulation within CSTC circuits. Specifically, functional imaging studies suggest that hyperactivity in the orbitofrontal cortex (OFC), thalamus and ventromedial striatum may be important.

There are many different ways to test these hypotheses, yet no method provides a "silver bullet". The three imaging modalities presented in this thesis, the volumetric study (Chapter 6), diffusion tensor imaging study (Chapter 8), and resting state fMRI study (Chapter 9) are three methods that will provide data to further discuss and perhaps confirm or refute such neurobiological models. High quality imaging data in studies of adequate sample sizes are lacking in BDD research, so this thesis aimed to contribute such data.

Chapter 4

Procedure and Participants

This chapter describes the two groups of participants, a sample of 20 individuals with BDD and 20 controls. These participants were involved in the series of three neuroimaging studies completed for the current thesis. After documenting general recruitment and assessment procedures a short description of each of the measures used will be provided. Then, participant information is presented, both general demographics and symptom specific for the BDD group. The participant characteristic will be discussed in relation to the relevant demographic literature.

As shown in Appendix B, the research protocol was granted ethics approval by the Human Research Ethics Committee at The Alfred Hospital. Appendix C shows the comprehensive informed consent forms that were presented to our research participants. The research protocol conformed to the provisions of the Declaration of Helsinki.

Recruitment procedure

Recruitment and protocol are covered in this section. Participants with BDD were recruited from patients attending the St. Vincent's Body Image Service, Melbourne, Australia. These patients had been diagnosed as experiencing BDD with varying degrees of severity, and all had received some form of mental health care. Twelve of the twenty BDD participants had, prior to being involved in this research, taken part in visual scanpath research (Toh, 2011), and had expressed interest in being involved with future research. The other eight had not completed any research with our team previously. Our MRI acquisition occurred between July 2009 to April 2011.

Potential BDD participants from the St. Vincent's Body Image Service were approached by their primary clinician (D. Castle), who provided a brief introduction of the study and its aims. For new research participants and those involved with prior research, permission was sought from interested parties to have their contact details passed on to the researcher, who established telephone contact in a timely manner. At this point, the researcher explained the requirements of the study in detail, and administered a series of brief screening questions to ensure that relevant inclusion criteria were met. The informed consent form (Appendix C) was mailed to the participant and a week later the researcher recontacted potential participants to answer any queries. If they were agreeable to proceed, a research appointment was scheduled.

Healthy control (HC) participants were sourced from a voluntary healthy research database, comprising members of public, the research community and their affiliates. If their demographic variables matched those of BDD they were telephoned and asked if they would be interested in participating. If they were interested and eligible an informed consent was mailed to the participant and a session was scheduled.

All participants were reimbursed $20 per hour. The MRI data collection took one hour while the clinical and demographic data was collected in one to two hours. In addition to the MRI and clinical session there was also a neurocognitive session (not presented in this thesis).

Volunteers were invited to attend a magnetic resonance imaging session at the Murdoch Research Institute, Medical Imaging Department, Royal Children's Hospital, Flemington Road, Parkville. During the MRI session they also completed a range of clinical interviews and self-report questionnaires (as detailed below).

Inclusion criteria

All participants were to be between the ages of 18 and 65, with no neurological disturbance, major medical condition, head injury, metal implants, current alcohol or substance abuse or history of intellectual/cognitive impairment, with all participants having a Wechsler Test of Adult Reading (WTAR) premorbid IQ score of >80. Further, all participants had English as their preferred language. After inclusion, one control participant was excluded due to incidental brain pathology and is not presented in any of the data.

Control participants

The control group had no personal or family history of a mental disorder, and were assessed as subclinical on depression (ZUNG) (Biggs, Wylie, & Ziegler, 1978; Zung, 1965) and anxiety (SIAS) (Osman, 1998) self-report scales, as detailed below. Control participants were screened using the MINI (Sheehan et al., 1998) to ensure no mental disorder was present. Control participants were recruited based on them matching the age, gender, handedness and education characteristics of the BDD sample.

BDD participants

All BDD participants had been independently assessed as having the disorder by their treating clinicians, and upon referral to the research program the diagnosis was confirmed by a clinical interview screening questions (Body Dysmorphic Disorder Diagnostic Module: BDD-DM as discussed below).

In addition to meeting the general inclusion criteria for all participants, BDD patients were excluded if they had a past or current psychotic disorder, obsessive compulsive disorder, bulimia nervosa or anorexia nervosa. Furthermore, BDD participants were excluded if they had a comorbid mental disorder that was considered to be their primary diagnosis, ensuring that all individuals in the patient sample had BDD as their primary concern. Because primary diagnosis can be difficult to delineate when there is comorbid OCD, individuals with OCD were excluded, whereas individuals who also fulfilled the criteria of social phobia or major depression were allowed if BDD was clearly assessed as their primary diagnosis. As BDD shows very high rates of psychiatric comorbidity (Phillips, Pinto, et al., 2007) our exclusion criteria was calibrated to obtain a highly representative sample.

Measures

A clinical demographic record was completed by all participants, including medical history, medication, educational and employment details. Participants were screened with the Mini-International Neuropsychiatric Interview (Sheehan, et al., 1998). Handedness was assessed with the Edinburgh Inventory (Oldfield, 1971), and depression and social anxiety were measured by the Zung Self-Rating of Depression Scale (Zung, 1965) and the Social Interaction Anxiety Scale (SIAS) (Brown et al., 1997). Estimated IQ was assessed by the Wechsler Test of Adult Reading (WTAR) (Holdnack, 2001). All participants were screened for BDD with the Body Dysmorphic Disorder Diagnostic Module (BDD-DM) (Phillips, 1998). In addition, BDD participants were assessed with the, the Yale Brown Obsessive Compulsive Scale Modified for Body Dysmorphic Disorder (BDD-YBOCS) (Phillips, et al., 1997).

(Complete measures can be found in Appendix D)

Education and estimated IQ

The Wechsler Test of Adult Reading (WTAR) IQ score is designed to provide a measure of premorbid intelligence, the degree of intellectual function prior to the onset of illness (Holdnack, 2001). It relies on vocabulary level as a correlate to IQ, is normed across the age range (Mathias, 2007), and has shown to reliable (Mathias, 2007). During administration of the WTAR, participants are presented with irregularly spelled words and prompted to pronounce each; the irregular grapheme-to-phoneme translations (such as the "gh" in the word tough) in the prompts make it difficult pronounce without having previously learned the word. The number of correctly pronounced words is summed and converted into an age related estimated IQ score. An analysis of the psychometric properties revealed that there was a correlation of .71 between WTAR IQ scores and the verbal intelligence quotient assessed via the WAIS-III (Mathias, 2007).

Handedness

Handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971) where a participant nominates which hand they used for a list of ten activities (i.e. writing, use of toothbrush). The inventory has items that were developed to accurately discriminate between ambidextrous, left and right handedness. Scores range from +100 (totally right-handed) to -100 (totally left-handed).

An analysis of the distributions produce the intuitive bimodal distribution of handedness (Oldfield, 1971). There are a number of scoring methods and for the purposes of this study we coded individuals with score of 40 or higher as right handed and those with a negative 40 or lower score as left handed.

Depressive symptoms

The Zung Self-Rating Depression Scale is a short self-administered survey to quantify the current depressed status of adult patients (Zung, 1965). There are 20 items on the scale that rate the four common characteristics of depression over the "past several days"; the core depressive factor; cognitive factor; an anxiety factor; and a somatic factor. The psychometric properties were evaluated in a large community sample (n= 2,120) of New Zealanders between 16 and 89 years of age. High estimates of reliability based on internal consistency statistics were found (Knight, Waal-Manning, & Spears, 1983). Cronbach's alpha was satisfactory at 0.79. Split-half reliability studies in a psychiatric population found a correlation (r) of 0.73 (Zung, 1972). This data indicates the scale is a reliable measure of depression symptoms in psychiatric populations and community samples.

Social anxiety symptoms

The SIAS is a 20 item self-report scale designed to measure social interaction anxiety defined as "distress when meeting and talking with other people" and is helpful in tracking social anxiety, particularly as part of an assessment for social phobia or other anxiety related disorders. The SIAS has been compared to other scales that measure social anxiety, including the Social Phobia and Anxiety Inventory (Peters, 2000). Convergent validity was established with a highly significantly correlation between the scales ($r = 0.86$, $P<0.001$) and via clinician rated severity rating. Peters (2000) defined the cut off score as 36 for probable social phobia, though with less than ideal specificity of 0.60, and a sensitivity of 0.93. The scale was administered to both groups to help characterise and compare general levels of social functioning.

Clinical data

In addition to the data collected in both groups, the BDD group completed a clinical interview, which included a number of measures listed below. In addition, the control group was also screened for a diagnosis of Body Dysmorphic Disorder using the Diagnostic Module (BDD-DM).

Body Dysmorphic Disorder Diagnostic Module

Diagnosis was confirmed with the Body Dysmorphic Disorder Diagnostic Module (BDD-DM) (Phillips, 1998). The BDD-DM is a semi-structured clinical interview utilising a SCID-like format; the DSM-IV-TR diagnostic criteria are listed on one side, with corresponding questions addressing the presence of each criterion on the opposite side. Initial screening questions directly probed the existence of appearance-related concerns over one's lifetime. If answered in the affirmative, respondents were invited to describe their specific concerns and associated degrees of preoccupation as well as the nature of any clinically significant distress and/or functional impairment. This was followed by exclusion questions related to body size and weight concerns to rule out eating disorders. Responses are scored on a categorical basic, where 1 - absent; 2 - subthreshold; and 3=threshold or true. All questions must receive a score of 3 to quality for BDD diagnosis. The BDD-DM has shown excellent inter-rater reliability (.96) (Phillips, 1998).

Body Dysmorphic Disorder Modification of the YBOCS (BDD-YBOCS).

This instrument is a 12-item semi-structured clinician-rated interview designed to provide a quantitative measure of BDD severity over the past week. The BDD-YBOCS is included in Appendix D. This instrument taps into five domains; time spent, interference, distress, resistance and degree of control. Items 1 to 5 centre on obsession and items 6 to 10 focus on compulsions. In addition, items 11 and 12 target the constructs of insight and avoidance. The BDD-YBOCS was constructed from the original YBOCS designed to measure OCD symptoms, with some modifications to make it suitable for appearance-related concerns (Phillips, et al., 1997).

Each item is rated on a 5-point likert scale, ranging from 0=absent or minimal symptoms to 4=extreme symptoms, with the final rating depending on a combination of patient report and clinician judgement. The total score is attained by summing all of the items, to score between 0 and 48. Normative data has been collected and suitable cut-off scores have been suggested (Phillips, et al., 1997). Scores below 15 indicate “mild” BDD symptoms, from 16 to 30 are "moderate" symptoms while scores from 31 to 48 are defined as “severe” symptoms.

The reliability and validity of the measure was assessed using 125 participants with BDD (Phillips, et al., 1997). Intraclass correlation coefficients demonstrated excellent interrater reliability across four raters (.99) and test-retest reliability over an interval of one week was also acceptable (r=88). The scales homogeneity was shown to be high, with a Cronbach's alpha of .80. The study also found that BDD-YBOCS scores were significantly negatively correlated to Global Assessment of Functioning scores (r = -51, $p<.001$) but it was independent to the Brief Psychiatric Rating Scale, indicating it had discriminant validity and was not overly influenced by general functioning.

Participant characteristics

To confirm that the BDD and control groups were well matched, both matching criteria and other key demographic variables were compared using independent sample t-tests at $p = .05$. Demographic and clinical data are displayed in Table 2.

Table 2. Demographic and Clinical Variables

	BDD (mean ± SD)	**Controls (mean ± SD)**	**Group Comparison (df = 38)**
Demographic Characteristics			
- Age (Years)	34.6 ± 11.5	31.9 ± 11.4	$p = 0.45$
- Years of Education	14.9 ± 2.4	16.3 ± 3.0	$p = 0.11$
- WTAR IQ estimate	106 ± 10.7	110 ± 6.5	$p = 0.13$
- Handedness (L/R)	3/17	3/17	
- Gender (M/F)	6/14	6/14	
Clinical variables			
- Depression (Zung)	46.0 ± 11.3	23.3 ± 8.7	$p < 0.05$
- Social Anxiety (SIAS)	41.7 ± 18.0	17.1 ± 4.2	$p < 0.05$

The two participant groups were well matched on age, gender, education, estimated IQ and handedness, with no statistically significant differences between the groups. As expected, the control group had a low level of depression and social anxiety, while the BDD group experienced significant levels of these symptoms.

Education and Estimated IQ

In the current BDD and control samples the mean IQ scores were above the population average (which is 100). The variability within the BDD group was higher than in the control group, and the control group had slightly and non-significantly higher estimated IQ.

Likewise, our BDD group had lower levels of educational attainment compared to controls, although this difference was not statistically significant. Lower levels of educational attainment are typical in BDD samples (Phillips, Pinto, et al., 2007), so the fact the control and participant groups had slight differences in years of education and IQ indicates that the BDD group was of a typical nature. In particular, BDD patients typically derive significantly less satisfaction from school life and 32% reported substantial interference in their academic work owing to BDD symptoms (Phillips, Menard, et al., 2005). Given that the WTAR scores are influenced by education (Mathias, 2007), and BDD diagnosis is known to influence educational attainment, this is thought to be a representative and well matched sample.

Handedness

The control participants were selected to give an exact match for handedness, with three participants in each group being left handed. No participants were scored as being ambidextrous.

Although the participants were exactly matched on handedness it is acknowledged that having left handed people is a source of heterogeneity within groups (in relation to brain imaging data), and thus may reduce the power of our neuroimaging analysis. In the general population there is a robust-but-imperfect correlation between handedness and brain lateralization, and among psychiatric samples left handed individuals are over represented (Good et al., 2001).

Therefore, hemispheric dominance differences in the neuroimaging analysis should be interpreted cautiously.

Gender

The exact match of gender distributions across groups was also achieved, with four male participants per group. However, population data shows that the prevalence rate of BDD in men and woman are roughly equal, with only slight higher rates for females. Woman have a reported prevalence rate of 2% while for men it is 1.5% (Buhlmann et al., 2010). Therefore, the current sample is slightly overrepresented by females, which may reflect the higher degree of access to mental health services typically shown by females. Nevertheless, evidence suggest that there are more similarities than differences among male and female BDD patients (Phillips, Menard, & Fay, 2006). Differences between the genders, however, include data showing that women generally have earlier onset of subclinical BDD symptoms (Phillips, Menard, & Fay, 2006). However, men had more severe BDD, lower general levels of functioning, are less likely to be working because of psychopathology, and were more likely to be receiving disability payments.

Depressive symptoms

The Zung depression scores presented in Table 2 indicated that the BDD sample had a higher level of depressive symptoms compared to controls. All control participants rated in the subclinical range of depression for the Zung.

Twelve of the BDD participants rated as having subclinical levels of depression, defined as scores below 50 (Zung, 1965). Seven participants were defines as having "mild" depression

symptoms, defined as a score between 51 and 59, and one BDD participant was defined as having "moderate" depression symptoms, defined as scores between 60 and 69. No BDD participants were defined as have "severe" symptoms, defined as scores above 70. On average the BDD group fell in the subclinical range of depressive symptoms (below 50).

BDD samples typically show high rates of depression (Phillips, Siniscalchi, & McElroy, 2004). In fact, in some samples depression is the most common comorbid disorder, with Phillips (2000b) finding that in a sample of 62 BDD consecutive outpatients, 51% had major depression. Therefore, the depression rates in our sample, if anything, were under those typically seen. As discussed below, our formal assessment of comorbidity with the MINI showed that only four BDD participants fulfilled the diagnostic criteria for current major depressive disorder or dysthymia. The underrepresented depression is likely because our inclusion criteria specified that BDD be the primary diagnosis. Therefore, individual presenting for treatment that were considered by their treatment team as having depression as their primary concern were not referred to this research project. In summary, our BDD sample showed significantly higher levels of depression than our control group, and depression levels of our BDD sample were consistent with the overall characterisation of the disorder.

Social anxiety

In the control sample no participant scored as having significant levels of social anxiety symptoms. In the BDD sample, however, the SIAS scores showed that on average the BDD sample had a moderate level of social anxiety symptoms; less than people diagnosed with social phobia but higher than other anxiety disorders (Peters, 2000), which is typical of BDD samples (Coles et al., 2006). Thirteen BDD participants scored above the cut-off of 36, indicating that

social interaction was a significant difficulty for many. It is not considered, however, that this cut-off score accurately indicated the presence of social phobia given the scales low specificity, and the fact the social interaction difficulties can be conceptualised as a core symptom of BDD rather than a separate problem. Rather than being useful for a separate diagnosis, the SIAS is useful at measuring the severity of the social aspect of BDD symptoms, and can be used as a clinical correlate to brain measures. Actual diagnosis of social phobia was also assessed by the MINI, showing that five had current agoraphobia or social phobia, as discussed below.

Employment

An assessment of employment was included as it gives some insight into the overall level of functioning of our groups. Employment status for both groups is presented in *Figure 3,* and shows that each group has similar proportions of currently employed participants. Of note is the higher proportion of students in the control group and higher levels of unemployed participants in the BDD group. Fifteen percent of our BDD participants were currently unemployed which is similar to the proportion reported in a comprehensive prevalence survey, that reported unemployed of 13.3% (Buhlmann, et al., 2010).

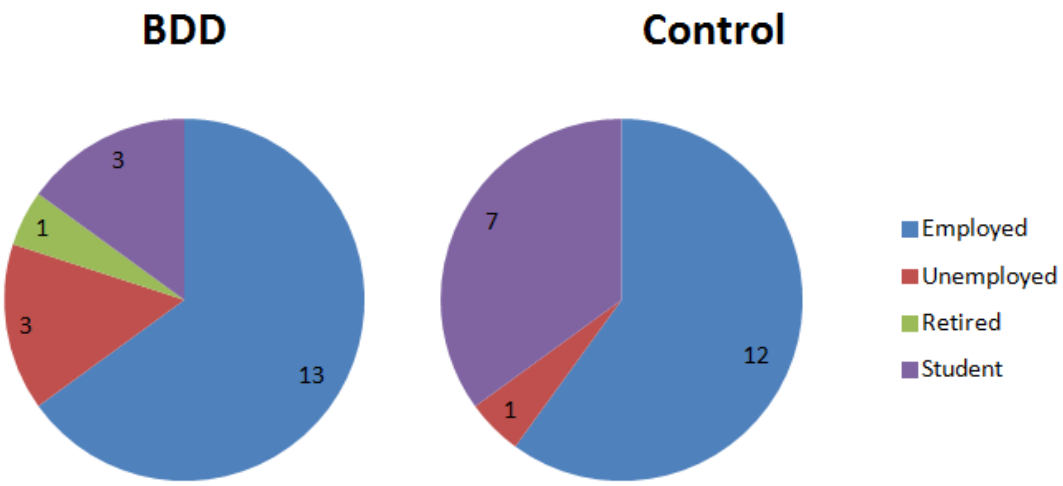

Figure 3. Current employment status across groups

Relationship status

Relationship status was also assessed, which can give insights into the social and relational functioning of the two groups. Relationship status is shown in *Figure 4*, indicating that BDD and control participants had similar patterns of relationships. The largest relationship status in the two groups was "single", which was coded if a participant was not in a romantic relationship or was in a romantic relationship but was not living with their partner, i.e. individuals in non-cohabitating relationships were coded as single. In a population based survey, Buhlamnn et al. (2010) found that individuals with BDD were significantly less likely to be married or in a de facto relationship compared to those without BDD (42% versus 52%). Thus, our sample is reprehensive of general relationship characteristics of BDD and control participants.

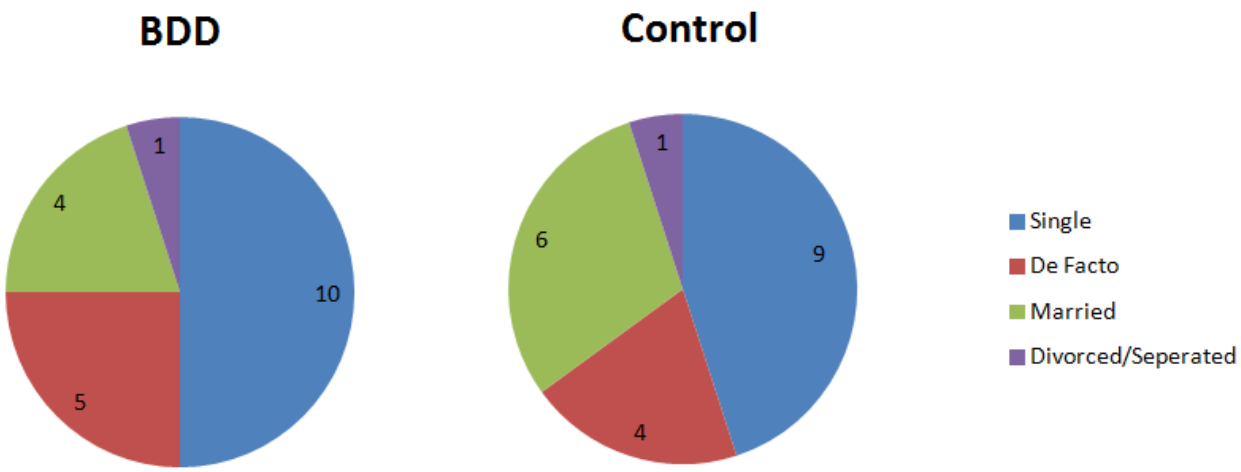

Figure 4. Current romantic relationship status for BDD and control samples.

Body Dysmorphic Disorder Diagnostic Module

In this sample, the BDD-DM confirmed that all BDD participants qualified for diagnosis and that none of the control participants had BDD.

In addition to a yes/no diagnosis, the area of aesthetic concern was also recorded using the BDD-DM. All but three BDD participants had more than one area of concern. The skin on the face was the most common concern, followed by the shape of the face. *Figure 5* shows the spread of concerns among the BDD participants. Indeed, this data is consistent with frequent areas of concern assessed in other samples, where the skin, face and hair are the top three areas of concern, followed by nose, weight and teeth (Kittler, et al., 2007).

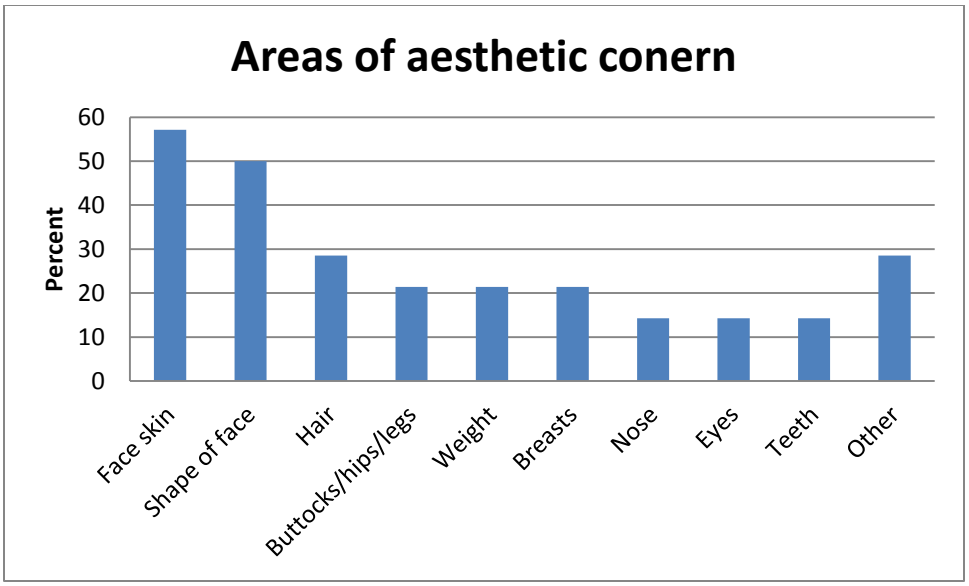

Figure 5. Percentage of BDD participants concerned with appearance by area.

Body Dysmorphic Disorder Modification of the YBOCS (BDD-YBOCS)

Once diagnosis of BDD was determined using the BDD-DM, the BDD participant's symptom severity was assessed using the BDD-YBOCS.

The BDD-YBOCS scores indicate that mean BDD severity was in the "moderate" range. At the time of MRI acquisition our sample comprised two participants in the mild range, thirteen with moderate symptoms and five in the severe range. *Figure 6* shows the distribution of BDD-YBOC scores. The mean score was 24.9 with a standard deviation of 9.6.

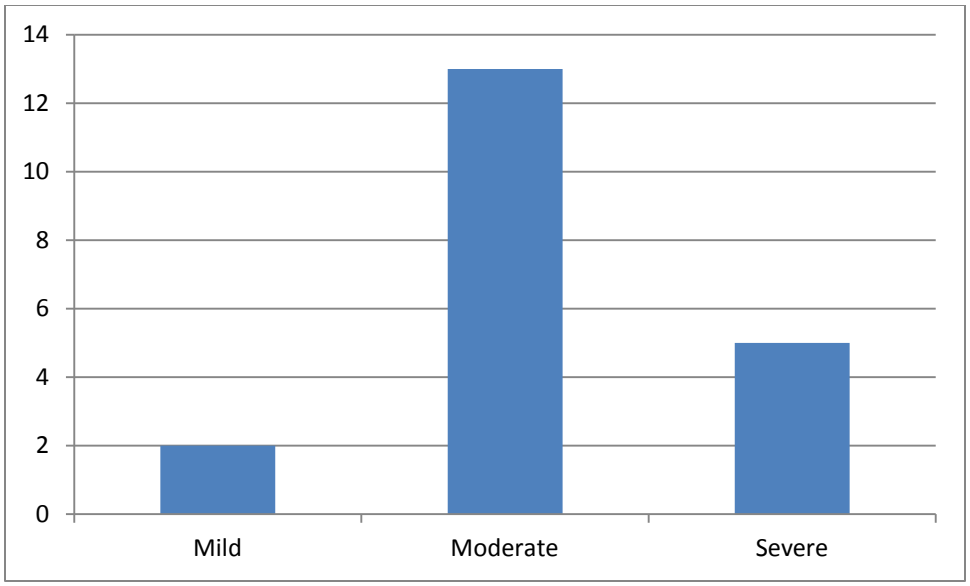

Figure 6. BDD-YBOCS severity ratings

Table 3 gives a more detailed account of responses to BDD-YBOCS items. For the majority of items the median severity was rated as moderate. The two exceptions of this were (1) item 7, where the interference caused by behaviours related to the body part of concern were rated as mild, and (2) item 11, where BDD participants were rated as having poor insight, maintaining that their concern about their defect was not excessive.

Table 3. Median Score for BDD-YBOCS Items

BDD-YBOCS Item	Median	Description of median response
1. Time occupied by thoughts about body defect	2	Moderate (1-3 hrs/day)
2. Interference due to thoughts about body defect	2	Moderate, definite interference with social or occupational performance, but still manageable
3. Distress associated with thoughts about body defect	2	Moderate, disturbing, but still manageable
4. Resistance against thoughts of body defect	2	Makes some effort to resist
5. Degree of control over thoughts about body defect	2	Moderate control, sometimes able to stop or divert obsessions
6. Time spent in activities related to body defect	2	Moderate (spends from 1 to 3 hrs/day performing compulsions), or frequent performance of compulsive behaviours
7. Interference due to activities related to body defect	1	Mild, slight interference with social or occupational activities, but overall performance not impaired
8. Distress associated with activities related to body defect	2	Moderate, reports that anxiety would mount but remain manageable if compulsions prevented, or that anxiety increases but remains manageable during performance of compulsions
9. Resistance against compulsions	2	Makes some effort to resist
10. Degree of control over compulsive behaviour	2	Moderate control, strong pressure to perform behaviour, can control it only with difficulty
11. Insight	3	Poor insight - maintains that thoughts or behaviours are not unreasonable or excessive, but acknowledges validity of contrary evidence (i.e. Overvalued ideas)
12. Avoidance	2	Moderate, some avoidance; clearly present

As part of the BDD-YBOCS assessment the participants were asked specify how many hours a day they spent on specific activities related to their appearance. On average this group of participants spent a total of 4 hours a day preoccupied with their perceived defect. The mean time spent on each activity is shown in Table 4.

Table 4. Mean Time Spent per Day on Behaviours Related to Perceived Defect.

Behaviour	**Average hours spent**
Checking mirrors/other surfaces	0.8
Grooming activities	0.5
Applying makeup	0.5
Time spent camouflaging with clothing/other cover	0.5
Scrutinising others' appearance (comparing)	0.85
Questioning others about/discussing your appearance	0.55
Picking at skin	0.4
Total Hours	**4.1 (SD = 0.50)**

In addition to rating how much time was spent on each of the above activities, BDD participants were asked about additional behaviours that they engage in on a daily basis. Seven participants reported they did not engage in any additional behaviour. The additional behaviours of the thirteen other participants reported included, muscle clenching, plucking facial hair, mirror avoidance, avoiding heaters, breaking hair, social avoidance, trying on other people's accessories, social avoidance, mirror avoidance, avoidance of people, cutting hair, squeezing scalp and purging.

Illness duration

The mean age of the BDD sample, 34.6, was similar to typical samples of BDD reported elsewhere (Phillips, Menard, & Fay, 2006). BDD participant's ages ranged from 19 to 64. The average duration of illness was assessed via clinical interview and could be determined for 17 of the 20 participants. The mean duration of illness was 10.8 years with a standard deviation of 6.9 years. The range of duration of illness was between 2 and 26 years, and current age was significantly correlated with duration of illness (r= 41, $p < .05$). Average age of onset was 23.5 years of age, which is significantly above the mean age of onset reported elsewhere. Typically the onset has been reported to be around 17 years of age (Altamura, Paluello, Mundo, Medda, & Mannu, 2001). This difference is likely a result from differing assessment methods, and it is acknowledged that the way age of onset may have been interpreted by some authors, including this study, is when they first sought treatment for the disorder or when they received the diagnosis. Our duration of illness data and therefore age of onset data, therefore, may be an overestimate the age of onset.

Comorbidity

Assessment with the MINI showed that four BDD participants fulfilled the diagnostic criteria for current major depressive disorder or dysthymia, and five had current agoraphobia or social phobia. High levels of co-morbidity of Axis 1 conditions is typical of BDD samples. For example, in one study 40% of those with primary BDD also had at a point in their lives fulfilled the criteria for a diagnosis of social phobia (Coles, et al., 2006).

There were some notable differences in our data compared to typical comorbid rates in naturalistic samples, mostly owing to our strict inclusion criteria. For example, one study found that around 32% of BDD subjects had a co-morbid lifetime eating disorder. None of our participants had current eating disorder given our exclusion criteria, although it is noted that two of our participants reported purging. Another difference between our sample and typical co-morbidity rates is the absence of OCD. High lifetime OCD rates (34–78%) have been found in several samples of BDD patients (Altamura, et al., 2001; Frare, et al., 2004; Hollander & Phillips, 1992). We excluded BDD participants with OCD because it can difficult to differentiate the disorders, and we wanted to ensure that our sample all had BDD as their primary diagnosis. This method also leaves open the possibility of future comparisons to OCD groups, to determine if there are district brain mechanisms at play in the two disorders. In general, our BDD group had lower levels of comorbidity than other samples, probably due to our "primary diagnosis" inclusion criteria. Nevertheless, our sample is considered to strike the balance between representativeness and within group homogeneity.

Psychopharmacology

Given that all participants came into contact with this research project through a mental health care facility, all had received or were receiving some level of treatment. All but two members of the BDD sample were taking at least one psychoactive medication: five where taking seroquel, four escitalopram, two duloxetine, two desvenlafaxine, two diazepam, and one each paroxetine, mirtazapine, lorazepam, methylphenidate, sodium valproate or clomipramine.

The fact that our participants were receiving treatment at the time of MRI is likely to have reduced the severity of BDD symptoms, thereby possibly influencing brain measurement.

For example, in OCD citalopram has been shown to influence diffusion tensor imaging measurements (Yoo et al., 2007), and CBT and SSRI treatment has been shown to influence structural and functional brain measures (Gilbert, et al., 2000; Rosenberg, et al., 2000; Saxena, et al., 2008). These brain differences are thought to be a result of changes in OCD symptom severity rather than a direct result of medication. Given that our sample, on average, rated as having "moderate" BDD symptoms despite treatment, the brain measurement will likely sufficiently reflect a typical BDD group.

Magnetic Resonance Imaging Procedure

On the day of the scan participants were met in the foyer of the Royal Children's Hospital and lead to the Murdock Children's Research Institute. Participants were asked to arrive one hour before the scheduled scan time in order to complete assessments. Firstly, the client filled out MRI safety sheet as required by the hospital in the waiting room and it was handed to the radiographer. Then participants were accompanied into an interview room to complete the clinical assessments before the scan started. The MRI procedure was explained.

The scanning sequence was an hour long and data was acquired using the following modalities; structural T1 scan, diffusion tensor imaging scan (DTI) and resting state fMRI scran. After each scanning sequence the participant was briefly talked to by the researcher through a microphone. During the scanning sequence two BDD participants become distressed and asked for the scan to be suspended. One of these participants, after a short break, was able to complete the full scanning sequence, while the other participant was excused from the resting state fMRI because they become too distressed to complete the full scan. There was also a face task

presented during the scanning sequence however data for that task is not presented in this thesis, and will be presented elsewhere in a subsequent publication.

Below is a short description of each scanning sequence, and details for the each will be presented in their respective sections in Chapter 6, Chapter 8 and Chapter 9.

Structural - T1

The structural data was acquired using a AC-PC high-resolution structural T1-weighted MPRAGE sequence (512 slices per slab; slice thickness = 1 mm; TE = 2.15 ms; TR = 1900 ms; field of view = 256 mm; in plane resolution 0.5 x 0.5 mm2)

Diffusion tensor imaging -DTI

The scanner acquired an isotropic diffusion tensor imaging sequence for FA estimations (Number of directions = 60, b-value = 2000s/m^2, slice thickness = 2.5mm).

Resting state fMRI

The resting state scan consisted of T2*-weighted, gradient echo, echo-planar images, acquired to encompass the whole brain (TR = 2400ms, TE= 5190ms (short), 7650ms (long); flip angle 35^0, 256x64x64 acquisition matrix); consisting of 36 (157 time points) contiguous interleaved 3mm thick slices, with an in-plane field of view of 240mm.

Chapter 5

Volumetric Measurement Method

The first in the sequence of three empirical studies included in this thesis is a comprehensive examination of brain volumes between our BDD and control groups. Much of the rationale and method is discussed within the empirical paper itself (Chapter 6), however given the short nature of publications it could not all be included. Therefore, this chapter examines the methodology by which volume data was acquired. In particular, a description of the FreeSurfer software will be given, along with empirical evidence demonstrating the validity of this measurement modality.

The increased accessibility in MRI technology to researchers during the last two decades has resulted in an explosion of empirical studies seeking to evaluate brain volume differences. Many of the research programs rely upon accurate segmentation and quantification of brain regions from high-resolution MR images. Until recently, manual tracing of brain regions by experts in neuroanatomy has been the accepted gold standard (Morey et al., 2009). However, as the size of the MRI datasets has increased, the time and cost required for the labour intensive process of manual tracing has become prohibitive. For example, an experienced researcher may require two hours to trace a single structure such as the amygdala, and more than a week to trace all of the major structures of the brain (Morey, et al., 2009). Moreover, differences in the way experts define particular regions can be problematic, leading to a lack of consistency. Thus, FreeSurfer was created to automate this process for increased efficiency and consistency, and therefore, reliability.

FreeSurfer

FreeSurfer software package (Version 4.5) [http://www.martinos.org/freesurfer] is a suite of tools used for the analysis of neuroimaging data that utilizes an array of algorithms to quantify structural properties of the human brain. It evolved from a package primarily aimed at generating surface representations of the cerebral cortex into one that automatically creates models of most the commonly measures structures in the human brain (Fischl, 2012). It relies on any reasonable high contrast T1-weighted input image, of which the data used in the current study exceeds the minimum required quality considerably. The software is freely available, open source and in this project was run on a dedicated linux computer workstation.

For the current volumetric study the following procedure was used, based on an established method used in similar research (i.e. Venkatasubramanian, et al., 2012). The processing included transferring the 40 T1-weighted scans onto a linux computer with FreeSurfer 4.5 allowing the 'recon-all' function (for cortical reconstruction and brain segmentation; http://surfer.nmr.mgh.harvard.edu/fswiki/recon-all). The automated processing of the images took approximately 18 hours per scan.

This automated process included motion correction, removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, segmentation of the sub-cortical white matter and deep grey matter volumetric structures, intensity normalization, tessellation of the grey matter - white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the grey/white and grey/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Desikan et al., 2006; Fischl, 2012;

Ségonne, Pacheco, & Fischl, 2007; Venkatasubramanian, et al., 2012). Subsequent to completion of cortical modelling, a number of deformable procedures were performed for further data processing and analysis: these included surface inflation, registration to a spherical atlas which utilized individual cortical folding patterns to match cortical geometry across subjects, parcellation of the cerebral cortex into units based on gyral and sulcal structure, and creation of surface-based data. Neuroanatomical labels are assigned to each voxel in the image based on the probabilistic information automatically estimated from a manually labelled training set (Desikan, et al., 2006). *Figure 7* and *Figure 8* show the anatomical labels as defined by Desikan et al. (2006).

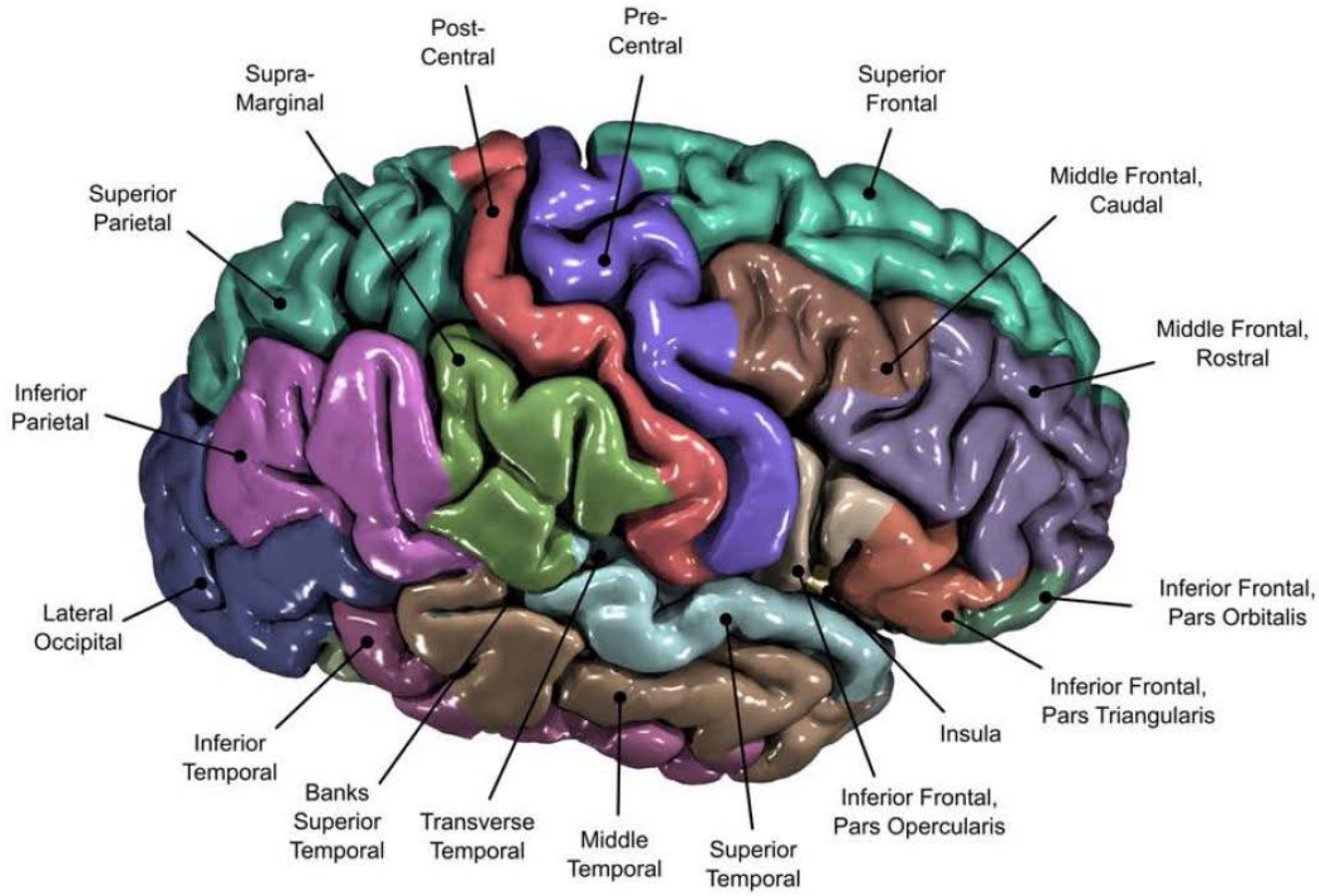

Figure 7. Lateral view of right hemisphere FreeSurfer segmentation. Anatomical labels as defined by Desikan et al. (2006). Image from Winkler et al. (2009).

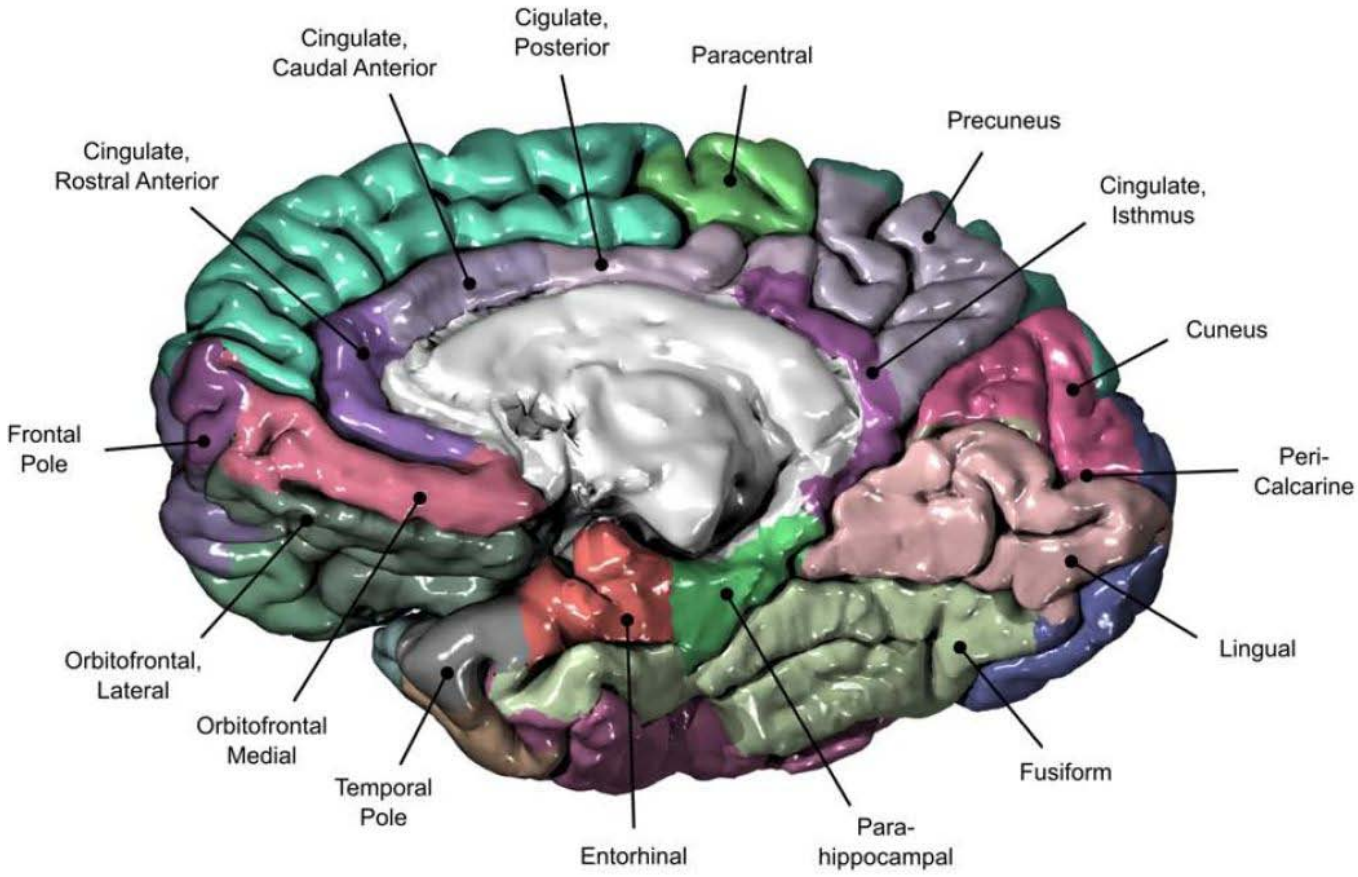

Figure 8. Medial surface of the right hemisphere. Anatomical labels as defined by Desikan et al. (2006). Some regions are buried inside sulci and cannot be fully observed. Image from Winkler et al. (2009).

Analysis of our data

In the current study, after the 'recon-all' function was complete, volumetric data composed 139 brain regions for each participant, outputted as mm^3. In addition to this numerical value, each participant's brain scan was represented by a 3D model with colour coded segmentations, allowing for visual inspections of the neuroanatomical models. *Figure 9* shows an example of an accurate anatomical segmentation for one of our research participants.

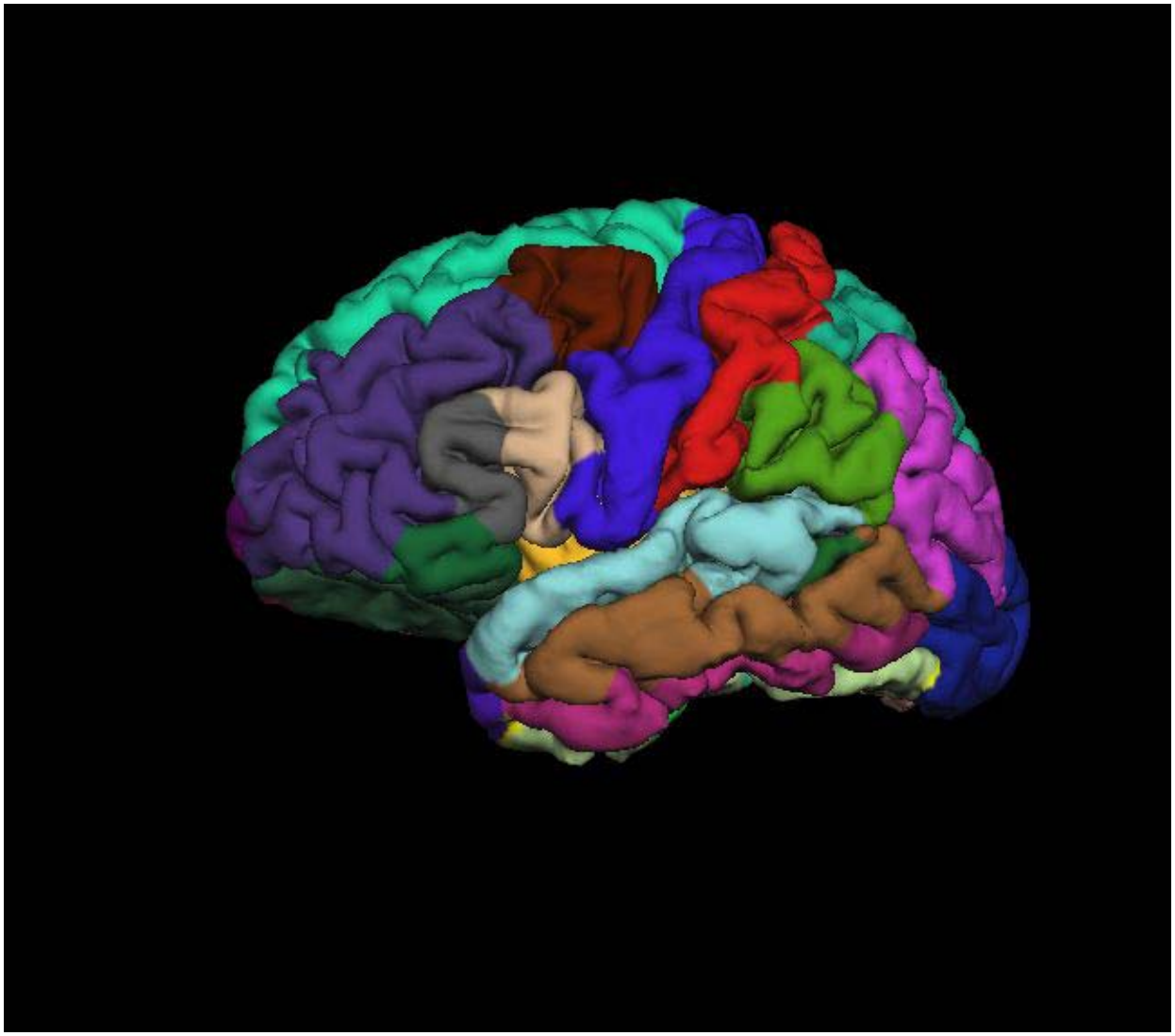

Figure 9. Example of anatomical segmentation control participant's brain scan, using Desikan et al. (2006) labels.

Measurement error

Each of the 40 brain scans in our study was visually inspected, with particular attention paid to regional volumes that fell outside two standard deviations from the group mean. If upon visual inspection the automated segmentation appeared accurate, the value was not changed. There were ten regions in total among four participants where it was apparent that there was

measurement error due to problems with the automated skull strip, white matter identification or segmentation. These 10 values were replaced with group mean values.

For example, *Figure 10* shows a participant who had measurement error of bilateral amygdalae and hippocampal volumes. This participant was specifically screened because these volumes fell outside two standard deviations from the mean. In *Figure 10* the amygdale volume segmentations are blue and the hippocampal segmentations are yellow, in transverse, sagittal and coronal views. The figure shows that the inferior horn of the lateral ventricle had been mislabelled as hippocampus and amygdalae. This participant was the only one to have an error in these regions, which are the most difficult areas to measure to measure, as discussed below.

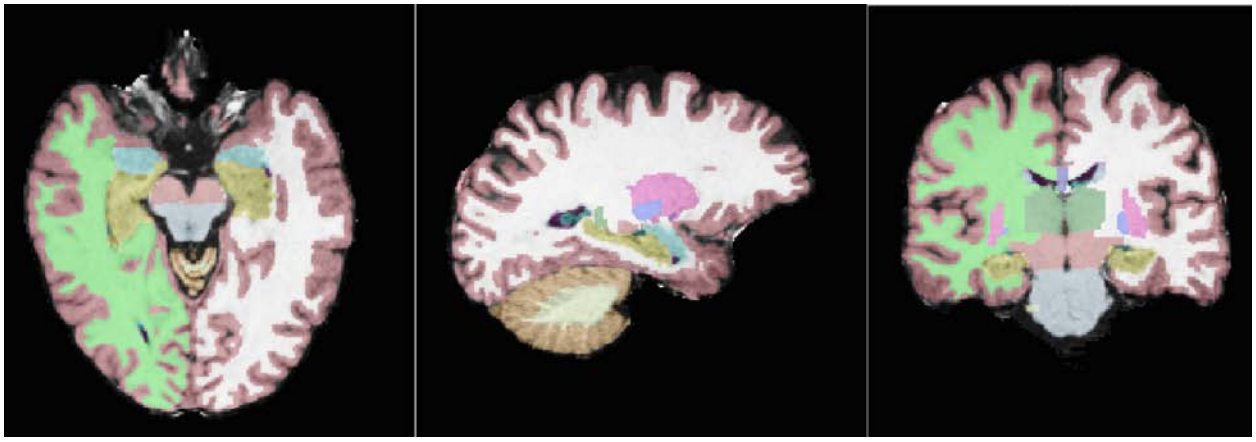

Figure 10. Incorrect amygdalae volume (blue) and hippocampal segmentation (yellow), in transverse, sagittal and coronal views.

Another error occurred in one participant's scan which had an abnormally large measure post central gyrus volume, and upon visual inspection it was apparent that there was a skull strip error, as shown in *Figure 11*. This participant's scan was subsequently re-analyzed after

adjusting skull strip tolerances. The skull strip error was likely due to motion artefact caused by movement during the scanning procedure.

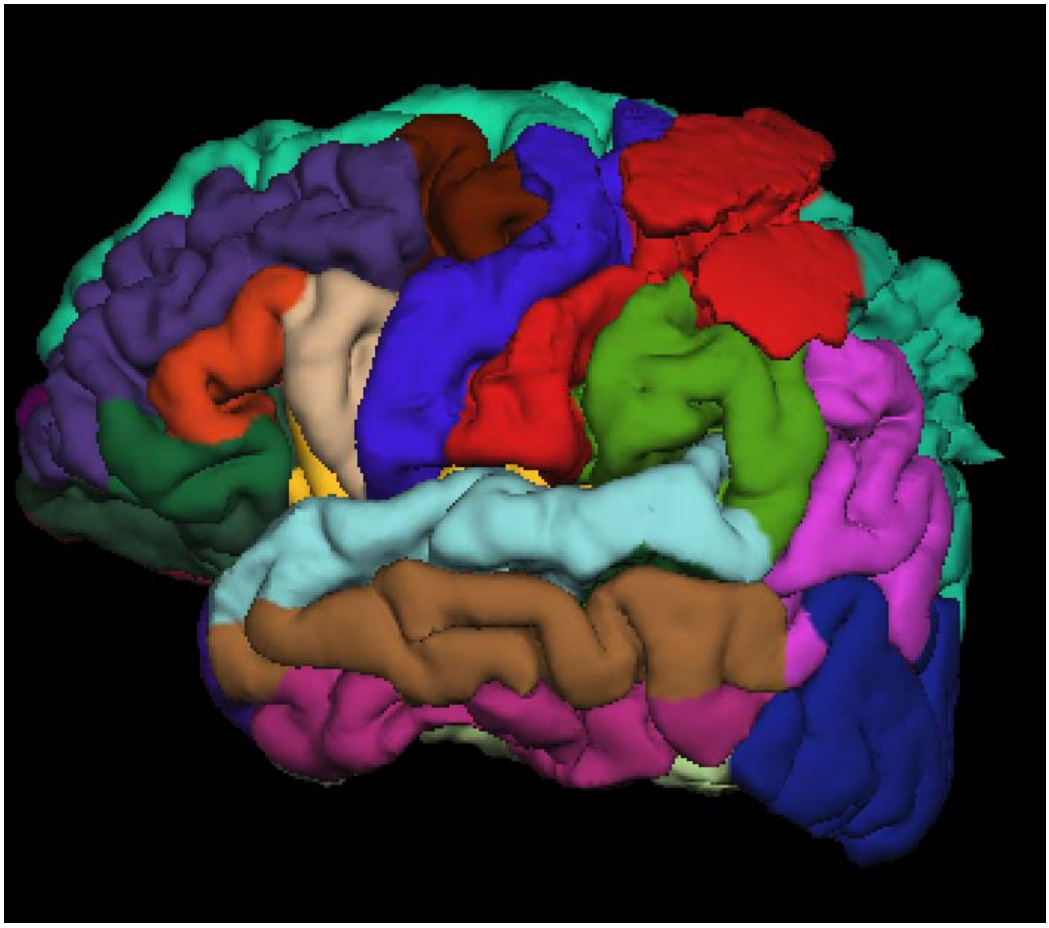

Figure 11. Skull strip error

The accuracy of FreeSurfer volumetric segmentation is obviously paramount for science exportation of the brain. The reliability of measurement is important, but also the validity of measurements in comparison to manual tracing by anatomical experts. In general, the larger the region with the more pronounced boundaries, the easier to both manually and automatically segment (Desikan, et al., 2006; Morey, et al., 2009). Smaller regions have proven to be more difficult to accurately measure and have therefore been the subject of evaluation. Two of the

most difficult areas have been the amygdala and the hippocampus. Data evaluating the accuracy of measuring these areas will therefore be discussed.

FreeSurfer compared to manual tracing

The amygdala, given its small size, is challenging to measure either through manual boundary tracing technique or automated segmentation. It is also one of the most studied regions given its importance in emotion, as discussed on page 60 . On an anatomical level, the amygdalae are bilateral, ovoid, grey matter structure the temporal lobe, anterior to and overlapping with the hippocampus (Brierley, Shaw, & David, 2002). The two amygdalae are composed of several cortical and subcortial nunclei but current resolution of MRI is unable to distinguish between these nuclei (unless a high-field, 4.7T and above, magnet is used). The fact that the amygdala shares borders with other grey structures, such as the hippocampus, makes measurement even more difficult, and most methodologies rely on external landmarks to improve reliability. For example, the anterior border is often arbitrarily defined as the slice which shows the lateral sulcus closing to form the entorhinal sulcus (Watson et al., 1992). There are several methods of delineation which are widely used causing differences in reported normal amygdalae sizes (Brierley, et al., 2002).

A meta-analysis (Brierley, et al., 2002) of studied that reported amygdalae volumes in healthy controls showed that reported volume between 1050 and 3880 mm^3, with the left ($M=1726.74mm^3$) amygdala being significantly larger than the right ($M=1691.71mm^3$), a disparity that was more pronounced in men. Additionally, women have smaller amygdalae then men, even when correcting for total brain volume. This study also highlighted biases of reported

volumes depended on measurement method and suggested that standardised measurement practices were paramount.

Anatomically the hippocampus and amygdala are joined, which means that definition of the border between the hippocampus and amygdala is crucial for accurate volume measurements (Watson, et al., 1992), although hippocampal tracing techniques are far more accurate and straight forward compared to amygdalae tracings. From the coronal orientation, however, the two structures are divided by a sheet of white matter referred to as the alveus.

While post-mortem examination of hippocampal and amygdalae volumes is considered the gold standard in measurement, and manual tracing was once considered the next best, automated measurement tools are increasing being used. Evaluating of the accuracy of automated segmentation has thus been subject to comparative evaluation.

Morey et al. (2009) sought to evaluate the accuracy of automated tracing against manual tracing using a large database of high-resolution structural MR images. In particular, their study quantitatively examined the relationships between different methods of amygdala and hippocampus measurements. Indeed, this research found that there was a high degree of correlation between manual tracing and automated FreeSurfer analysis. *Figure 12* shows the correlation between manual and automated amygdalae volumes and *Figure 13* shows the same for hippocampal volumes.

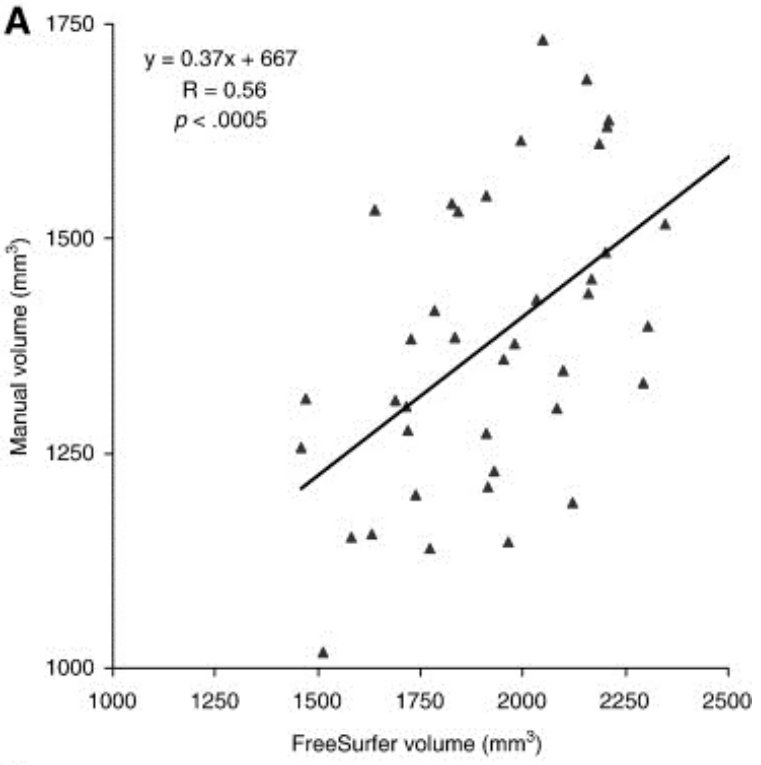

Figure 12. Amygdalae volume derived from FreeSurfer correlated with manual tracing (R = 0.56; p < 0.0005), From (Morey, et al., 2009)

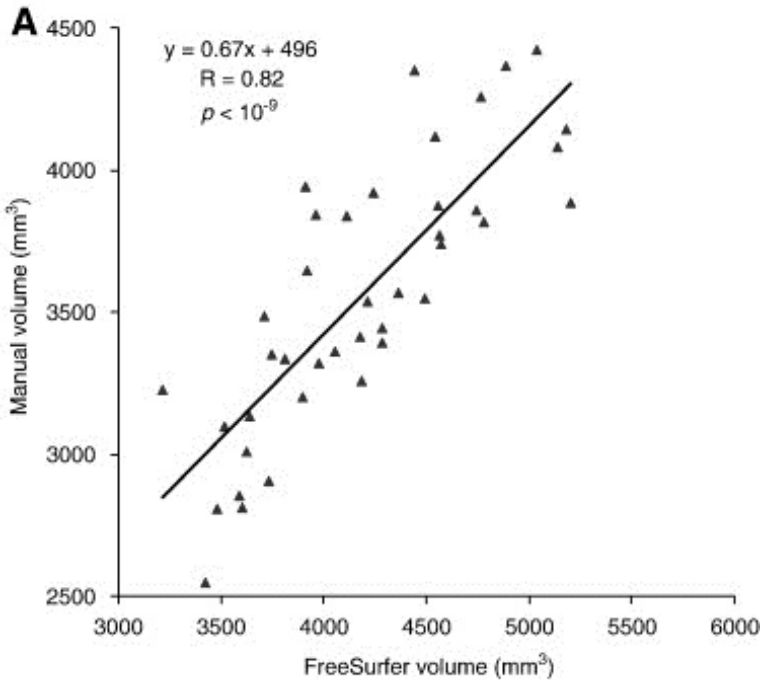

Figure 13. Hippocampal volume derived from FreeSurfer segmentation correlated with manual tracing (R = 0.82;p < 10− 9), From (Morey, et al., 2009).

The data presented in *Figure 12* and *Figure 13* indicates there is an adequate level of agreement among the manual method and FreeSurfer; with there being stronger agreement for hippocampal volumes. The lower level of agreement for amygdalae volumes does not necessarily mean that FreeSurfer is less accurate for that region. Indeed, there is measurement error for both manual and automated methods, so the reduced correlation could be due to measurement error for either method, or a combination of the two.

Nevertheless, Morey et al. (2009) concluded that FreeSurfer is a sound method for measuring hippocampal and amygdalae volumes. This is important given that these areas are among the most difficult to automatically segment. In contrast, Freesurfer automated segmentation of areas of the cerebral cortex is straight-forward and provides volumetric data of high quality (Morey et al., 2009).

In addition to the data provided above, various other studies have investigated the accuracy of FreeSurfer. For example, thalamic volume measurement reliability has also been assessed (Keller et al., 2012). This data demonstrated that the extent of agreeability between manual tracing and FreeSurfer is equal to the agreeability between two human anatomists estimating thalamic volume using traditional manual methods. This data compellingly suggests that automated segmentation is not only more efficient but also has similar levels of reliability compared to manual tracing. Perhaps the most accurate method of evaluating the accuracy of FreeSurfer would be to compare it against post-mortem examination of regional volumes. However, to our knowledge no such a study has not been completed.

In summary, FreeSurfer has been found to be a reliable way of measuring anatomically valid brain volumes. Additionally, given its "hands off" method it has reduced susceptibility to

human error and also allows examination of many areas within the brain. FreeSurfer yields 139 brain regions for each participant allowing for a more comprehensive analysis of brain pathology (not withstanding statistical difficulty with a large number multiple comparisons). By contrast, manual tracing traditionally required very small numbers of specified regions of interest. The next chapter is the complete empirical study comparing BDD and control regional brain volumes. The paper is submitted for publication and is currently under review.

Chapter 6

Regional brain volumes in body dysmorphic disorder compared to controls

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Sarah Brennan, & David Castle

Paper currently under review for publication

Monash University

Declaration of Authorship for Thesis Chapter 6

Regional brain volumes in body dysmorphic disorder compared to controls.

Ben Buchanan, Susan Rossell, Jerome Maller, Wei Lin Toh, Sarah Brennan, & David Castle

Declaration by candidate

In the case of this chapter, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
I collected the MRI and participant data, developed hypotheses, completed data analysis and wrote the entire chapter intended for publication with feedback from co-authors.	75%

The following co-authors contributed to the work.

Name	Nature of contribution	Extent of contribution (%)
Susan Rossell	Helped in formulating hypotheses, data analysis and gave feedback on final report.	10%
Jerome Maller	Guided data analysis and gave feedback on final report.	9%
Wei Lin Toh	In the initial recruitment stage of the project we shared participants and therefore some demographic data.	2%
Sarah Brennan	In the initial recruitment stage of the project we shared participants and therefore some demographic data.	2%
David Castle	Instrumental in recruitment of BDD participants	2%

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date 13/8/2013**
Main Supervisor's Signature	[redacted]	**Date 13/8/2013**

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

Abstract

Background: Body dysmorphic disorder (BDD) is characterized by a preoccupation with a misperceived flaw in appearance, causing significant distress and disability. Neuropsychological research has revealed a range of cognitive deficits in BDD, including executive function and inhibitory control of emotional responses. However, the few previous structural neuroimaging studies have shown inconsistent findings in part due to their small sample sizes.

Methods: Twenty BDD participants and 20 matched controls underwent high-resolution structural T1-weighted magnetic resonance imaging (MRI) (512 slices per slab; slice thickness = 1mm). The MRI data was subjected to cortical reconstruction and volumetric segmentation using Freesurfer software, and regional brain volumes were compared between BDD and control groups.

Results: The right orbitofrontal cortex, bilateral thalamus, left anterior cingulate cortex, hippocampus and amygdala were significantly smaller in the BDD sample. The most pronounced differences were in the right orbitofrontal cortex and left anterior cingulate cortex, as these areas were smaller in BDD participants independent of reduced global brain volumes. Duration of illness significantly negatively correlated with right orbitofrontal cortex volumes.

Conclusions: This is the largest volumetric neuroimaging study in BDD to date, which provides robust findings of smaller regional volumes compared to controls. The orbitofrontal and anterior cingulate cortex are both important to circuits that mediate inhibitory control, emotional learning and guide thoughts and behaviour. This evidence provides a neurocognitive foundation for BDD symptomatology, including ruminative symptoms, dysfunction in self-reflection, emotion regulation and executive function.

Introduction

Body dysmorphic disorder (BDD) is a mental disorder characterised by a preoccupation with an imagined defect in physical appearance, or if a slight abnormality is present, that the concern for it is excessive. Individuals with BDD have comparable levels of disability to other mental disorders, including social phobia (Coles, et al., 2006) and major depression (Phillips, Didie, & Menard, 2007). In particular, BDD and OCD have been linked in terms of symtomatology, familial prevalence and the high degree of comorbidity (Bienvenu, et al., 2000; Marazziti et al., 2006).

Neuropsychological studies have provided evidence of cognitive impairments in BDD, including executive function (Dunai, et al., 2009; Hanes, 1998), selective attention (Buhlmann, McNally, et al., 2002), information processing (Deckersbach, et al., 2000), recognition of facial affect (Buhlmann, et al., 2004), and a bias towards detailed visual processing (Buhlmann, et al., 2004; Feusner, Moller, Altstein, Suger, et al., 2010; Feusner, Moody, Hembacher, Hoffman, et al., 2010). Such research has started to elucidate the cognitive basis of BDD symptoms, and also provided data to compare BDD against related disorders such as OCD. For example, Hanes' (1998) executive function results using the Stroop and the Tower of London tasks suggest deficits in prefrontal brain regions. OCD patients show similar difficulties on these tasks, and have had convergent neuroimaging evidence that compellingly confirms prefrontal deficits (Remijnse, et al., 2006; Venkatasubramanian, et al., 2012). In fact, a pathogenic explanation of pathways involving the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) has received consistent support in OCD, while there is a paucity of neurobiological and neuroimaging data in BDD.

Research has begun to provide some characterization of the neurobiology of BDD, with results so far suggesting widespread but varying functional and structural abnormalities (reviewed in Buchanan, Rossell, & Castle, 2011). Most recently, two diffusion tensor imaging (DTI) studies have investigated white matter integrity in BDD participants. The smaller of these studies (N=14) found a significant negative correlation between white matter integrity and BDD symptoms (Feusner, et al., 2013). The larger DTI study, with the same participants as the current study, found widespread white matter degradation in the BDD participants (Buchanan et al., 2013). Given that performance on cognitive tasks is related to wide distributions throughout the brain, the findings of inefficient white matter communication between distinct grey matter regions may go some way to explain the neuropsychological deficits in BDD.

Functional neuroimaging in BDD patients has tended to focus on activation levels while the participants engage in visual processing tasks, as their symptomatology is closely related to these systems. For example, Feusner et al. (2010; 2007) found that, during facial processing, there was a higher level of right amygdala and right prefrontal cortex activation in BDD participants compared to controls, underlining the potential importance of frontostriatal systems.

In addition, there have been a small number of structural imaging studies in BDD similar to the current study. Atmaca et al. (2010) investigated brain volumetric parameters in 12 male BDD participants via manually tracing regions of interest (ROIs). They found that OFC and ACC volumes were significantly smaller in BDD than in healthy controls. Length of illness was inversely correlated with OFC volumes in the patient group on both the left and right sides.

Using voxel-based morphometry (VBM), an automated method of group comparisons, Feusner et al. (2009) investigated regional volumes in 12 BDD participants and 12 controls.

Analysis revealed no statistically significant volumetric differences; subsequent hand-traced ROI analysis also revealed no regional volumetric differences. However, a trend toward a positive correlation between symptom severity and right amygdala and left inferior frontal gyrus volumes was noted. Given the small sample size, it is likely that the study had inadequate power to detect significance differences.

Perhaps the only consistent property of previous volumetric studies with BDD is that they have all had relatively small sample sizes, from six to 12 participants. In addition, the variety of imaging techniques used, together with the absence of replications, limits the conclusions from neuroimaging studies thus far.

The current study's aim was to provide robust evidence of volumetric differences in grey matter regions in BDD using automated brain segmentation software: (Freesurfer). We sought to investigate global brain characteristic including gross volumetric differences in the four cortical lobes, and subsequently, across our ROIs. We developed specific hypotheses based on past neuroimaging findings; specifically, that there would be reduced volumes in the OFC, ACC, hippocampus, amygdalae and changes in thalamic volumes between BDD patients and healthy controls. We also conducted exploratory comparisons on 121 other brain regions. In addition, it was hypothesized that symptom severity would correlate to amygdale and OFC volumes, and that OFC volumes would have a negative correlation with duration of illness.

Methods

Participants

Forty individuals were recruited comprising 20 individuals with BDD and 20 healthy controls, aged between 19 and 64 years (Table 1). BDD patients were excluded if they had a past or current psychotic disorder, OCD, bulimia nervosa, anorexia nervosa, alcohol or substance abuse history, intellectual/cognitive impairment, metal implants or neurological disturbance. Furthermore, BDD participants were excluded if they had a co-morbid mental disorder that was considered to be their primary diagnosis, ensuring that all individuals in the patient sample had BDD as their primary diagnosis.

The control group had no personal or family history of a mental disorder. All participants had English as their preferred language and an Wechsler Test of Adult Reading (WTAR) pre-morbid intelligence quotient (IQ) score of >80. Participants were assessed with the Mini-International Neuropsychiatric Interview (MINI; Sheehan. et al. 1998), as well as the Body Dysmorphic Disorder Diagnostic Module (BDD-DM; Phillips *et al.*, 1997). Handedness was assessed with the Edinburgh Inventory (Oldfield, 1971). A detailed account of selection criteria and demographic characteristics is described elsewhere (Buchanan, et al., 2013).

Magnet resonance imaging acquisition

Participants were scanned using a 3T scanner (Siemens Magnetom TrioTim, Germany) at the Murdoch Children's Research Institute (Royal Children's Hospital, Melbourne, Australia). An AC-PC aligned high-resolution structural T1-weighted MPRAGE sequence (512 slices per

slab; slice thickness = 1 mm; TE = 2.15 ms; TR = 1900 ms; field of view = 256 mm; in plane resolution 0.5 x 0.5 mm^2) was acquired allowing for high quality data for Freesurfer brain processing. The image acquisition was completed as a component of an hour long sequence comprising a number of different scanning sequences, with other data presented elsewhere (Buchanan, et al., 2013).

Data Analysis

The MRI data was subjected to cortical reconstruction and volumetric segmentation analysis using the FreeSurfer software package (Version 4.5) [http://www.martinos.org/freesurfer] based on established and largely automated processing steps. These steps included motion correction, removal of non-brain tissue using a hybrid watershed/surface deformation procedure, segmentation of the sub-cortical white matter and deep grey matter volumetric structures, intensity normalization, tessellation of the grey matter - white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the grey/white and grey/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Ségonne, et al., 2007). Registration to a spherical atlas was employed which utilized individual cortical folding patterns to match cortical geometry across subjects. The procedures for the measurement of volumes has been validated against manual tracing methods (e.g. Keller, et al., 2012).

Raw volumetric data composed 139 brain regions for each participant. Each participant's brain segmentation was visually inspected and particular attention was paid to regional volumes that fell outside two standard deviations from the group mean. There were ten regions in total

among four participants where it was apparent that there was measurement error due to problems with the automated skull strip, white matter identification or segmentation. These ten values were replaced with group mean values. One participant's scans were reanalyzed after adjusting skull strip tolerances.

Statistical analyses

Statistical analyses was performed using the Statistical Package for Social Sciences (SPSS). We restricted the initial analysis to *a priori* hypothesised brain regions so to reduce potential type 1 errors. The *p value* for our specific hypotheses was set at .05, two tails, and a series of one-way analysis of variance (ANOVA) were conducted to compare the control and BDD group volumes. In addition, an analysis of covariance was conducted to adjust for global brain volume differences, and determine whether volumes for ROIs changed independently from whole brain changes. We used the Freesurfer output measure of supratentorial volume as a proxy of total brain excluding cerebellum (grey and white matter) and brain stem. It is computed based on everything inside the pial surface, plus any structures that might fall partially or totally outside of the pial, e.g., hippocampus, amygdala and corpus callosum.

Given that Freesurfer automatically computes many regional brain volumes, an exploratory analysis with a more conservative *p value* of .01, two tails, was conducted for remaining 121 regions, some of which were components of the larger ROI already measured. For example, caudal and rostral areas of the ACC combine to create the ACC. For brevity, only areas that were significantly different or showed a trend towards being different across the groups are reported.

Pearson's correlations were conducted between symptom severity as measured by BDD-YBOCS scores, and the bilateral amygdalae and OFC volumes. Duration of illness was also correlated to our ROIs, for these analyses partial correlations were conducted controlling for the confounding effect of age.

Results

The two participant groups were well matched on age, gender, education, estimated IQ and handedness, as shown in Table 5. The clinical data indicated that mean BDD severity was in the "moderate" range which is defined as scores between 16 and 30 on the BDD-YBOCS (Phillips, et al., 1997). Areas of aesthetic concern for our sample were generally the face, skin and hair. Duration of illness was included for 17 participants because onset was not determined for three participants.

Table 5. Demographic and Clinical Variables

	BDD N=20 (mean ± SD)	**Controls N=20 (mean ± SD)**	**Group Comparison**
Demographic Characteristics			
- Age (Years)	34.6 ± 11.5	31.9 ± 11.4	$p = 0.45$
- Years of Education	14.9 ± 2.4	16.3 ± 3.0	$p = 0.11$
- WTAR IQ estimate	106 ± 10.7	110 ± 6.5	$p = 0.13$
- Handedness (L/R)	3/17	3/17	
- Gender (M/F)	6/14	6/14	
Clinical variables			
- BDD severity (BDD-YBOCS)	24.9 ± 9.6	-	
- Duration of illness (Years)*	10.8 ± 6.9	-	

*Data for duration of illness was available for 17 BDD participants

Whole brain

The mean volumes (cm^3) for global brain characteristics are presented in Table 6, as well as the *p* value derived from the one-way ANOVA to compare groups. The results indicated that differences between groups in intracranial volume, cerebrospinal fluid and white matter volumes were not statistically significantly. Total grey matter volume, however, was significantly smaller among BDD participants.

Table 6. Gross Brain Volume (cm3) Between BDD and Control Groups.

	BDD	**Control**	***p***
Intracranial volume	1504 ± 128	1544 ± 112	.31
Cerebrospinal fluid	1307 ± 195	1365 ± 252	.42
Total grey matter volume	652 ± 63.2	700 ± 57.9	.02
White matter volume	491 ± 58.0	509 ± 50.0	.29
Supratentorial volume	1047 ± 104.9	1101 ± 91.2	0.9

Our measure for total brain volume supratentorial volume was found to not be significantly different between groups, $F = 3.01$, $p = .09$, though the trend was sufficient to make it a suitable covariate.

Regions of interest

Table 7 shows the mean volumes for our ROIs across groups, as well as the two *p* values; the group comparison during an ANOVA, and the ANCOVA to co-vary for global brain differences.

Table 7. Cortical Lobes and Regions of Interest Volumes (cm3) Across the Groups.

Brain Region		BBD Mean	SD	Control Mean	SD	Raw *p* value	Co-varied *p* value
Frontal Lobe	Left	85.5	8.4	90.3	9.4	.098	.668
	Right	54.1	8.0	90.1	9.8	**.038***	.232
Parietal Lobe	Left	57.0	6.9	61.0	6.5	.068	.453
	Right	58.3	7.4	63.7	6.3	**.043***	.093
Temporal Lobe	Left	54.0	5.6	57.7	5.5	**.042***	.249
	Right	54.3	6.4	57.9	5.7	.073	.534
Occipital Lobe	Left	22.8	2.9	25.0	3.3	**.035***	.196
	Right	23.5	2.4	25.0	3.0	.075	.377
Orbitofrontal Cortex (OFC)	Left	12.5	1.5	13.2	1.4	.152	.722
	Right	11.8	1.1	13.3	1.5	**.002***	**.007***
Anterior Cingulate Cortex (AAC)	Left	4.43	0.67	5.10	081	**.007***	**.040***
	Right	4.20	0.79	4.39	0.74	.438	.797
Thalamus	Left	6.99	0.82	7.50	0.70	**.041***	.225
	Right	7.15	0.77	7.64	0.58	**.028***	.165
Hippocampus	Left	4.19	0.32	4.44	0.36	**.025***	.143
	Right	4.33	0.35	4.52	0.39	.109	.577
Amygdalae	Left	1.59	0.19	1.70	0.14	**.049***	.238
	Right	1.61	0.20	1.69	0.14	.134	.702

* indicates significance at .05. Raw: Group comparisons based on raw data. Co-varied: Group comparison based on data co-varied with total brain volume supratentorial volume

In terms of lobar differences, the BDD group had significantly smaller right frontal, right parietal, left temporal and left occipital lobes. When co-varied for total brain volume the results ceased to have statistical significance, indicating that lobe reductions occurred in the context of total brain reduction rather than a lobe-specific reduction.

In terms of our ROIs, the right OFC, left ACC, bilateral thalamus, left hippocampus and amygdala were significantly reduced in volume in the BDD sample. When co-varying for the

total brain difference the significant differences remained for the right OFC and left ACC, indicating that these areas were smaller in BDD participants independent of smaller global brain volumes. *Figure 14* shows the orbitofrontal cortex segmented into medial and lateral regions, and *Figure 15* shows rostral and caudal areas of the ACC.

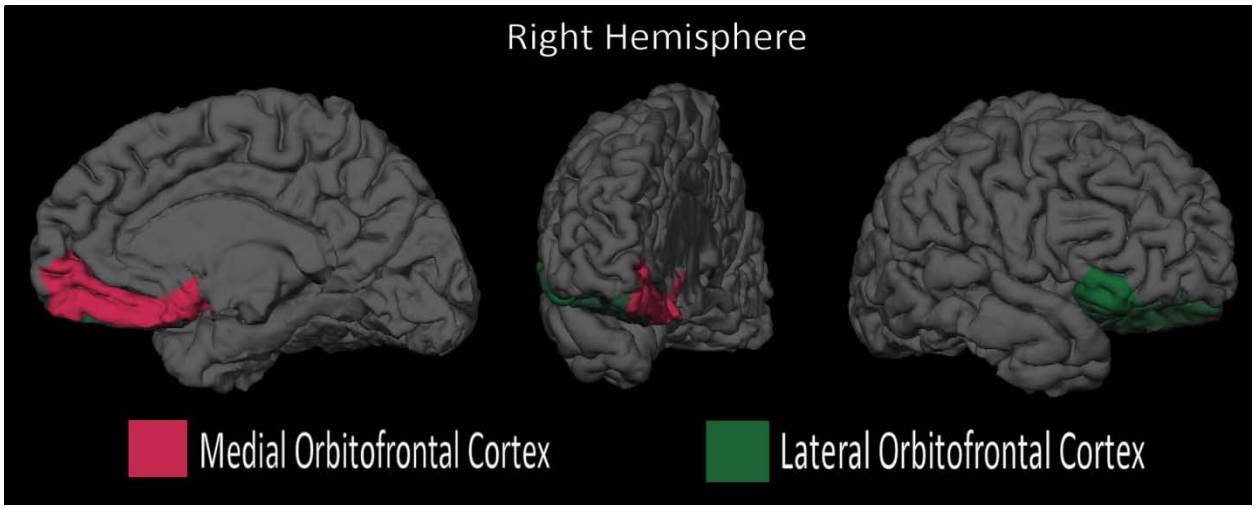

Figure 14. Reduced right orbitofrontal cortex (OFC) in BDD, lateral and medial regions.

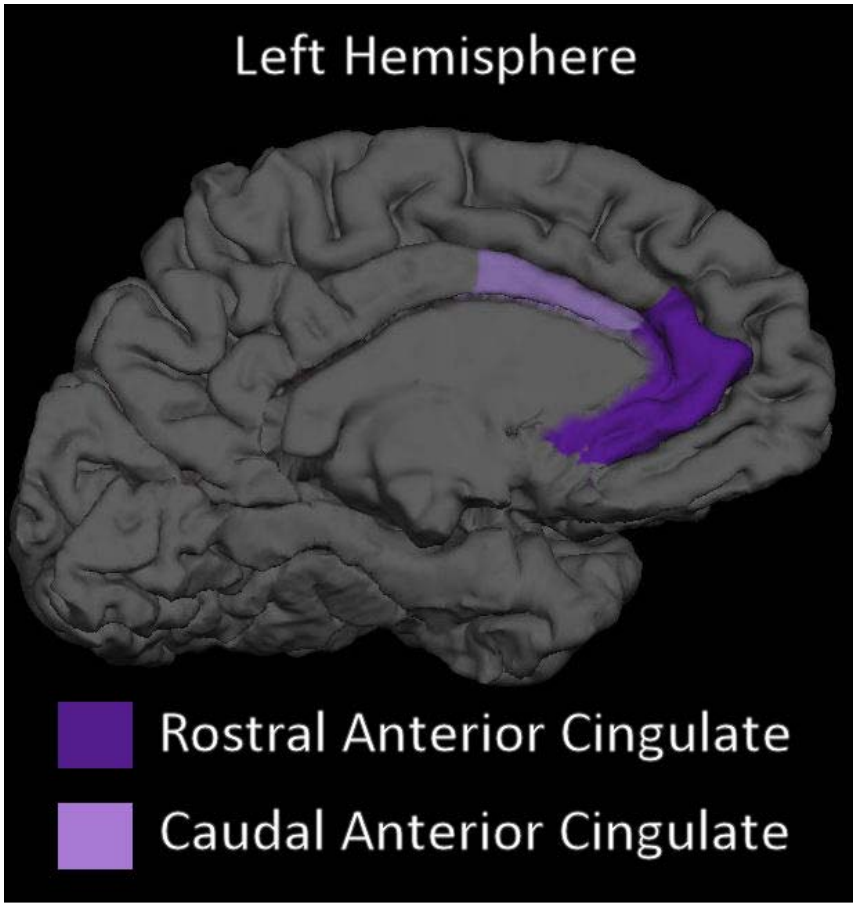

Figure 15. Reduced anterior cingulate cortex (ACC) in BDD, rostral and caudal regions.

The exploratory analysis revealed that four areas were significantly different between groups as defined by a $p < .01$, both for raw volumes and volumes co-varied for total brain volume. The right superior parietal, right precuneus, right lateral OFC and left caudal ACC were significantly smaller in the BDD group compared to controls. The latter two areas were simply smaller components of our *a priori* ROIs (OFC and ACC) and thus were the predominant contributors to the reduction in the larger areas. The left cerebellum was also significantly smaller in the BDD group for raw volumes but lost its significance when volumes were co-varied for whole brain volume. Other areas that did not reach the required significance value but

nevertheless showed substantive difference (p <.05) for raw volumes are also presented in Table 8. For example, the bilateral fusiform gyri were close to, but did not meet, our strict significant test.

Table 8. Exploratory Analysis of Regional Brain Volumes.

	BDD group		Control Group		Raw	Covaried
	Mean	SD	Mean	SD	*P*	*P*
Right Cerebellum Cortex	56.8	6.40	61.1	5.28	.026	.155
Left Cerebellum Cortex	55.1	6.01	59.7	4.31	**.008***	.045
Left Superior Parietal	13.1	1.28	14.3	1.58	.013	.071
Right Superior Parietal	13.0	1.09	14.8	1.44	**<.001***	**<.001***
Right Lateral Occipital	11.5	1.23	12.7	2.13	.037	.213
Left Supramarginal Gyrus	10.8	1.54	11.9	1.38	.027	.154
Left Fusiform Gyrus	9.80	1.35	10.8	1.33	.018	.074
Right Fusiform Gyrus	9.27	1.58	10.5	1.39	.011	.064
Right Precuneus	9.73	1.31	11.0	1.23	**.002***	**.008***
Left Lateral Orbitofrontal	7.46	0.84	8.12	0.82	.017	.094
Right Lateral Orbitofrontal	7.06	0.73	8.05	0.89	**<.001***	**.002***
Right Caudal Middle Frontal	6.65	1.26	6.77	1.02	.016	.089
Right Medial Orbitofrontal	4.75	0.55	5.20	0.80	.041	.194
Left Pars Opercularis	4.69	0.87	5.32	0.71	.016	.064
Left Ventral Diencephalon	3.97	0.46	4.24	0.35	.039	.239
Left Posterior Cingulate	3.34	0.36	3.70	0.56	0.02	.101
Right Cuneus	3.09	0.50	3.46	0.52	.024	.107
Left Posterior Banks	2.55	0.37	2.91	0.53	.019	.075
Left Caudal Anterior Cingulate	1.79	0.31	2.14	0.41	**0.004***	**.009***

Volumes represented as cm^3. * indicates significance at .01. Raw: Group comparisons based on raw data. Co-varied: Group comparison based on data co-varied with total brain volume supratentorial volume

Correlation analysis revealed a significant negative relationship between symptom severity scores and the left amygdala volumes (r = -0.492 p = .027). For the right amygdala there

was a non-significant trend toward a negative correlation (r = -0.421, *p* = .065). There was no correlation between symptom severity and OFC volumes on either the left (r=0.10, *p* =.675) or the right (r= -0.056, *p* = .814).

There was a significant negative correlation between duration of illness and the right OFC (r= -.520, *p* = .032; *Figure 16*). The results of the partial correlation between right OFC and illness duration controlling for age revealed a slightly stronger correlation (r=-.537, *p* = .032), indicating that duration of illness was related of OFC volumes independently of age. Left OFC volumes were not correlated with illness duration (r=-216, *p* = .405).

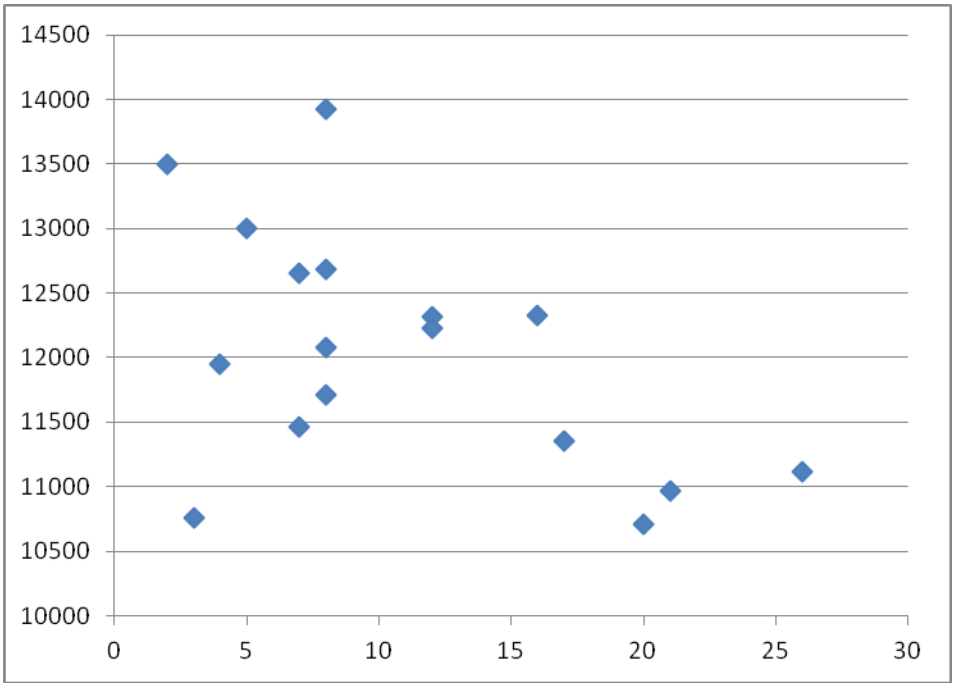

Figure 16. Right orbitofrontal cortex (OFC) volume (mm³) vs illness duration (years).

Discussion

This is the largest volumetric neuroimaging study in BDD patients to date, providing robust data for hypothesised regions of interest, as well as offering rich exploratory findings. The main finding was that there were reduced volumes in BDD in the right orbitofrontal cortex (OFC) and left anterior cingulate cortex (ACC). The bilateral thalamus, left hippocampus and amygdala were also smaller in the BDD group, although these differences were no longer significant when co-varying for total brain volume.

Our result of reduced left ACC volumes is in part consistent with the findings of Atmaca et al. (2010) who found bilateral volume reductions in this region in BDD patients compared to controls. This finding is important given that the ACC has an important inhibitory effect over emotional responses and is involved with other executive tasks (Albert, López-Martín, Tapia, Montoya, & Carretié, 2012). Within BDD, dysregulation of emotion is a central affective symptom that has been demonstrated in neuropsychological research using emotion Stroop tasks (Buhlmann, McNally, et al., 2002). Thus, pathology in the ACC may mediate these symptoms. Reduced inhibitory control mediated by the ACC has also been conceptualized as being of central importance in the pathogenesis of OCD, and is among the most consistent findings in this disorder (Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005a; Kühn, et al., 2012; Radua, van den Heuvel, Surguladze, & Mataix-Cols, 2010; Venkatasubramanian, et al., 2012).

Reduced OFC volumes is also noteworthy given it is a common finding in OCD (Rotge, 2010) and its involvement in decision-making, emotion regulation, and self-focussed thinking. It facilitates behavioural flexibility after negative feedback, allowing the unlearning of (emotional) associations (Remijnse, et al., 2006). Not only were OFC volumes significantly reduced

compared to controls generally, but our data showed that individuals with longer duration of illness at the time of the scan were likely to have smaller right OFC volumes. The average duration of illness for our BDD participant was almost 11 years (between 2 and 26 years) and the relationship with OFC volumes was confirmed to exist independent of age.

The importance of the OFC in BDD has also been highlighted in functional MRI work by Feusner et al. (Feusner, Moody, Hembacher, Townsend, et al., 2010), whereby BDD participants showed relative hyperactivity in the left OFC when shown their own face or the faces of others. Furthermore, their study also showed that within the BDD group the level of symptom severity was related to activation in the right OFC. Our results did not indicate that symptom severity was related to right OFC volumes, but taken together with the past activation data and our own illness duration results, it seems likely that differences in the OFC is a key region in BDD pathophysiology. Indeed, OFC volume reductions due to pathogenic development may lead to poorer outcomes and chronic BDD.

The OFC and ACC are thought to be important to both frontostriatal circuits that mediate inhibitory control, emotional learning, flexibility in responses, and guide behaviour based on action-outcome associations. In addition, these areas are consistent with fronto-limbic dysfunction. Recent DTI results in BDD show that a major white matter connection between frontal areas and amygdalae, the uncinate fasciculus, was degraded (Buchanan, et al., 2013). In this context, individuals with BDD may have difficulty with top-down regulation of amygdalae reactivity to control negative affect and mediate threat perception, explaining BDD symtompatology. Such fronto-limbic involvement may be related to the frontostriatal explanation that has become well established in OCD (Harrison, et al., 2009; Saxena, Bota, et al., 2001; Venkatasubramanian, et al., 2012).

The left amygdala volumes were significantly negatively correlated with symptom severity, indicating that an increase in symptom state at the time of the scan was related to decreased left amygdala volumes. Feusner et al.'s (2009) investigation found that right amygdala volume was positively correlated to BDD symptom severity, while the left amygdala was negatively correlated to depressive symptoms within their BDD group. Further demonstrating the amygdala's importance in BDD, past fMRI data has shown abnormal right amygdala activation (Feusner, et al., 2007). In fact, the amygdalae are of central importance to many psychiatric and in particular anxiety disorders. Similar findings have been reported in related disorders such as general anxiety disorder (M. Stein, et al., 2002) and are thought to be a key pathology in emotional dysregulation, eliciting speculation that reduced connection between the amygdala and OFC region could reflect a phenotype that is common among disorders involving emotional dysregulation or impaired social-emotional functioning (Phan, et al., 2009).

Our exploratory analysis revealed significantly smaller volumes in the right superior parietal and right precuneus regions. While these results should not be considered to be as reliable as our *a priori* hypothesis, due to the multiple comparisons and the chances of type 1 errors, they may still be of importance to BDD. Indeed, the right superior parietal lobule is involved in maintaining internal representations and kinaesthetic attention (Stoeckel, et al., 2004). The precuneus is a component of the superior parietal lobule and has specifically been implicated in the recall of imagery, self-reflection and in self-related mental representations (Cavanna & Trimble, 2006). Thus, dysfunction in this area may help explain two important symptoms in BDD: distortions in body awareness, and lack of insight.

In terms of whole brain volumes, the BDD group had significantly lower total grey matter. Past BDD studies have shown a similar, yet non-significant, reduction in total grey

matter (Atmaca, et al., 2010; Feusner, et al., 2009). Our data showing relatively stable intracranial volume across groups combined with reduced grey matter volume indicate that it is a true effect and not sampling error. The findings may be due to either different developmental trajectories or degradation associated with BDD onset. These results are broadly consistent other anxiety disorders (Koolschijn, et al., 2009; Syal et al., 2012), and there is a growing consensus that grey matter changes associated with anxiety-related psychiatric disorders are structural preconditions rather than consequences or side effects of these pathological states (Kühn, Schubert, & Gallinat, 2011). Future research could focus on the neurobiological dynamics by investigating developmental pathways for BDD patients at onset and during remission.

The knowledge of smaller ACC and OFC volumes gives light to possible treatments for BDD, with evidence showing that short-term meditation has specific benefits for the ACC and medial frontal cortex in healthy controls (Hölzel et al., 2007; Tang et al., 2010), and CBT and fluoxetine have also shown to influence these two specific areas in OCD while reducing symptoms (Hoexter, et al., 2011).

In summary, this is the largest volumetric sample of BDD to date, showing a general reduction in grey matter volumes consistent with other psychiatric disorders and highlights the importance of the OFC and ACC in BDD. The contribution of high quality evidence is key to creating a coherent neurobiological model of BDD onset and maintenance involving the fronto-limbic and frontostriatal circuits.

Chapter 7

Diffusion Tensor Imaging Method

Magnetic Resonance Imaging (MRI) has become a useful tool in neuroimaging and is the premier modality for visualizing anatomy in the brain**.** However, the standard MRI procedure that measures grey matter (GM) based on proton density-, T1- and T2-weighting, is limited because of the inability to display the inherent structure of the brain's white matter (WM). Conventional MR has not been successful in providing good contrast within the WM, which usually looks homogeneous (Assaf & Pasternak, 2008). Having detailed data on WM structures is important because while GM is the tissue where information is processed, WM serves as a channel of communication between GM regions. Complex cognitive processes that involve different functional areas GM of the brain are mediated by WM neural networks (Mori et al., 2002). Many of the neurobiological models described in Chapter 3 are explicitly dependent on evidence related to how separate brain regions integrate and communicate neural signals.

The introduction of Diffusion Tensor Imaging (DTI) in the mid-nineties by Basser et al. (1994) has offered a modality of anatomical imaging to examine micro structural properties inherent in WM, and therefore study the physical connections between brain regions. DTI has revolutionized the neuroimaging field and is able to output the strength of WM tracts that were hitherto unmeasured.

Measurements in Diffusion Tensor Imaging (DTI)

Diffusion Tensor Imaging (DTI), also known as diffusion MRI is a MRI technique that allows for in vivo images of brain overlayed with local measures of water diffusion. The core

data that DTI collects is values within each voxel, which is a three dimensional pixel. The value is associated with it is a measurement of the rate and direction of water diffusion at that location. "Diffusion" is the random motion of molecules and within DTI each voxel is either anisotropic or isotropic. Anisotropy is the quality of having direction which implies that the water molecules, when excited through the DTI process, will tend to diffuse in a particular direction. The direction is based on many factors, but in the context of the brain's white matter, diffusion is highly depended on neuronal microstructures (Assaf & Pasternak, 2008). On the other hand, isotropic voxels indicate diffusion of water uniformly in all orientation, or no overall directionality of water diffusion. Diffusion in grey matter is typically isotropic (directionless) while diffusion in white matter generally anisotropic (directional). In the white matter, myelinated fibres resist water diffusion orthogonal to the local dominant fibre orientation, and diffusion occurs preferentially along local fibre tracts.

By measuring the diffusion along different directions, an estimate of its directional dependence can be calculated. Most DTI protocols in clinical research have the ability to assign a vector's directionality to 1 of 30 gradient directions (Mukherjee, Chung, Berman, Hess, & Henry, 2008). In the current research, however, we used 60 directions to better delineate connectivity in regions of complex white matter architecture such as crossing fibre tracts. Using 60 directions gives a robust estimation of anisotropy and allows better accuracy of eigenvectors one, two and three.

As DTI is a three dimensional imaging technique, measurements are expressed in three directions, eigenvalues one, two and three. The eigenvector corresponding to the largest eigenvalue, termed the principal eigenvector, defines the main direction of diffusion of water molecules in that voxel.

Eigenvectors two and three are perpendicular to eigenvector one. The figure below is a representation of the eigenvalues within one voxel.

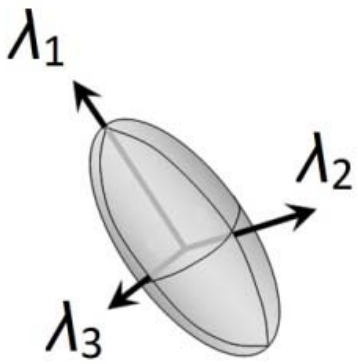

Figure 17. The diffusion ellipsoid within a voxel

Fractional anisotropy (FA)

During DTI acquisition the water molecules level of diffusion in these three directions are measured. For the data to be meaningful these values are converted in to fractional anisotropy (FA) for each voxel. FA is the main measurement within DTI and quantifies the magnitude of the directional preference of water molecules in each voxel. In clinical research, white matter fibre integrity is commonly assessed using FA, which determines how strongly diffusion is directionally constrained.

The calculation of FA from the eigenvalues of the diffusion tensor is:

$$\mathrm{FA} = \frac{\sqrt{3}}{\sqrt{2}} \frac{\sqrt{(\lambda_1 - \lambda)^2 + (\lambda_2 - \lambda)^2 + (\lambda_3 - \lambda)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

Consequently, FA can be reduced if eigenvalue one is reduced or if eigenvalue two or three are increased. High FA is considered to be indicative of a strongly directional white matter pathway in the brain, where neural signals travel efficiently. While FA is the single most used measure of diffusion it is essential to look at the individual eigenvalues to determine if changes in FA can be accounted for by increased eigenvalues one or reductions in eigenvalues two or three.

Mean diffusivity (MD)

A complementary method for looking at the individual eignevalues to determine the cause of FA changes is focussing on mean diffusivity (MD), which is another measure that is a composite of the three eigenvalues. The calculation for mean diffusivity is:

$(\lambda_1 + \lambda_2 + \lambda_3)/3$.

Instead of measuring the strength of the dominant direction of the water diffusion, MD measures that the degree to which there is diffusion that is orthogonal to dominant direction. In doing so, MD can be used to imply white matter degradation where water is able to diffuse (or leak) through the myelinated fibres. High MD implies that neural signals travel less efficiently along the dominant white matter directions.

White matter

While most MRI modalities investigate grey matter volumes or functions, DTI is squarely focussed on white matter connectivity. Its main measure, FA, is sensitive to the presence and integrity of white matter fibres**.** This white matter consists of thousands of neuronal

fibres (axons) in each image pixel, as well as a dense array of various kinds of glial cells with oligodendrocytes that are unique to white matter (Assaf & Pasternak, 2008). White matter consists of mostly myelinated axons that connect various grey matter areas. White matter takes up a large proportion of the human brain and is composed of millions of communications fibres, each one containing a long individual axon, coated with a white fatty substance, myelin. The myelin acts as an insulator that increases the speed of transmission of the nerve signals and also helps prevent impulses being dissipated to unintended parts of the brain. If there is degradation of the myelin then transmission can be slowed or simply lost, impacting upon the speed and integration of different cognitive processes (Westlye, Bjrnebekk, Grydeland, Fjell, & Walhovd, 2011).

Myelin is unique to white matter and is therefore believed to hold one of the main influences over the DTI signal**.** The exact contribution of myelin to the DTI signal and anisotropy measures is difficult to estimate because there are multiple factors that influence FA signals, including other demyelinating diseases and premyelination conditions. FA will typically show a similar reduction in all these pathologies and is therefore nonspecific. Another limitation of DTI is that the observed signal is averaged over the entire voxel which masks the ability to distinguish between the different pathologies affecting different cellular components (Assaf & Pasternak, 2008).

Neurological disorders that are primarily a result of white matter can be divided into two groups: dysmyelinating disorders, in which normal myelin fails to form, and the demyelinating diseases, in which normal myelin has formed and is later destroyed by a myelinoclastic process. While BDD and mental illnesses are not considered to be a classic "white matter diseases", the distinction between problems with white matter development and white matter degradation is an

important one, as it may help decipher the causes and development of the disorder. Indeed, there is a known familial predisposition to BDD (Phillips, Menard, et al., 2005). This, combined with environmental triggers during critical brain development stages, may impact on BDD onset.

In healthy individuals, total grey matter starts to decrease during childhood but white matter continues to develop throughout adolescence and early adulthood (Courchesne et al., 2000). This final developmental stage roughly coincides with average age of onset for BDD, reported to be at approximately 17 years of age (Altamura, et al., 2001). Therefore, white matter under genetic and neurodevelopment control could play a crucial role in BDD development. The normal ageing process has reliably been shown to influence white matter, with radial diffusivity generally following a U-curve and FA following a inverted U-curve (Hasan et al., 2010). This indicates that, in healthy individuals, the most efficient brain communication occurs during middle life (approximately age 35). In general, reduced FA is linked with a general lower level of functioning and higher rate of psychiatric illness (Westlye, et al., 2011), though the results are inconsistent.

White matter has been considered as less plastic than grey matter. However, recently the environment has been shown to influence white matter, with a DTI study finding that there were changes in white matter volumes as a result of learning a new motor task (Scholz, Klein, Behrens, & Johansen-Berg, 2009). Subsequently, other studies have also demonstrated the plastic qualities of white matter, showing increased FA after participants learned meditation (Luders, Clark, Narr, & Toga, 2011; Tang, et al., 2010) and strategy based games (Jang, Kang, & Kwon, 2010). Such findings are interesting because white matter development has previously been considered to be under genetic control and largely non-plastic, whilst learning was thought only to influence grey matter areas. The mechanism by which white matter changes is thought to

be related to a modulation of its degree of myelination (Scholz, et al., 2009), but such interpretations at this stage remain speculative. Nevertheless, such experience-dependent white-matter changes shows that white matter substance is a dynamic process that may result from mental illness and not just be related to an underlying phenotype. Therefore, if white matter differences were to be established in BDD the likely cause would be a combination of genetic and environmental conditions.

Specific white matter tracts

Within the brain there are three different kinds of tracts within the white matter:

1. Projection tracts, which carry information from the cortex to other brain regions, out of the brain to muscles, or into the brain from sense receptors.

2. Commissural tracts, which send action potentials between the left and right hemispheres through the corpus callosum**.** The highest density of white matter with the highest FA values can generally be found in the corpus callosum given the large amount of information that is communicated between the hemispheres.

3. Association tracts, which carry information between lobes within the same hemisphere. Long association fibres connect different lobes of a hemisphere with one another and short association fibres connect different gyri within a single lobe.

Analysis and segmentation of white matter tracts has been less intensive than investigations of grey matter, but recently white matter atlases have attempted to delineate white matter regions in the brain into specific and standardised regions. Mori et al. (2008) has

developed a computer based white matter atlas with 50 tract labels by hand segmentation of standard-space averages of DTI maps from 81 subjects, named the *ICBM-DTI-81 white-matter labels atlas.* This atlas was used in the current research. As white matter tracts do not always have clear anatomical landmarks to discretely identify them, defining the tracts has been optimized in references to large external anatomical landmarks, such as the frontal, temporal, and occipital lobes (Mori, et al., 2002). Tracts are partially defined, therefore, by what grey matter structures they intersect with. While it is beyond the scope of this thesis to discuss each of the 50 white matter pathways within the atlas, some major white matter tracts that have been shown to be particularly relevant to mental disorders, and therefore could be related to BDD, will be discussed. After major white matter tracts are described, existing DTI research in OCD will be introduced. How such findings relate to hypothesised neurobiological models of BDD will be examined.

Corpus callosum

The corpus callosum (CC), the brain's largest fibre tract, is the main conduit for interhemispheric transfer. The CC is not a unitary body, but rather a collection of pathways with the ability to act independently, transmitting different types of information to difference places. The middle portions of the corpus callosum connect motor and somatosensory regions. (De Lactostre, Kirkpatric, & Ross, 1985)**.** Fibres that pass through the posterior splenium connect regions in the temperoparietal-occipital junction (Bloom & Hynd, 2005; Pannek et al., 2010). Consistent with other white matter structures the CC continues development into adolescence and even early adulthood (Pujol, Vendrell, Junqué, Martí Vilalta, & Capdevila, 1993). Neuropsychological studies with healthy controls have shown a relationship between FA levels

in the CC and various cognitive functions, including response inhibition tasks, language and visuospatial skills (e.g. Fryer et al., 2008).

To fully understand the role of the CC it is important to discuss brain lateralisation. Given that in most individuals language processing and detailed thinking is dominated by the left cerebral hemisphere and spatial and holistic cognitive processes reside mostly in the right hemisphere (Van Kleeck, 1989), communication between the hemispheres is essential for integration of different types of information processing. Additionally, the CC may play an important excitatory and inhibitory role, whereby specific regions of one hemisphere activate or suppress processing in areas on the other hemisphere (Bloom & Hynd, 2005; Pannek, et al., 2010).

In BDD, interhemispheric communication may relate to the deficits in the integration of detailed and holistic processing. Individuals with the disorder tend to process images in a detailed fashion rather than in a more holistic way (Deckersbach, et al., 2000; Feusner, Moller, Altstein, Suger, et al., 2010), suggesting difficulties with communication between the hemispheres. Indeed, neuroimaging data in BDD has demonstrated abnormal widespread left hemisphere hyperactivity in extended face-processing networks including temporal, parietal and frontal regions (Feusner, et al., 2007). This occurred even for images with low detail, which are normally processed by the right hemisphere. Predominant left hemisphere activity suggests greater detail encoding and analysis relative to configural processing. As such, the only BDD sample (n=14) to be investigated using DTI found that there is also evidence of abnormal connectivity between regions involved in lower-order visual processing and higher-order visual and emotional processing, as well as interhemispheric visual information transfer (Arienzo, et al., 2013). On a clinical level, the perceptual distortions and fixation on small aspects of appearance

may come from a failure to integrate details into a visual gestalt. This difficulty may be mediated by reduced connectivity in the CC, though this prediction has not yet been directly tested.

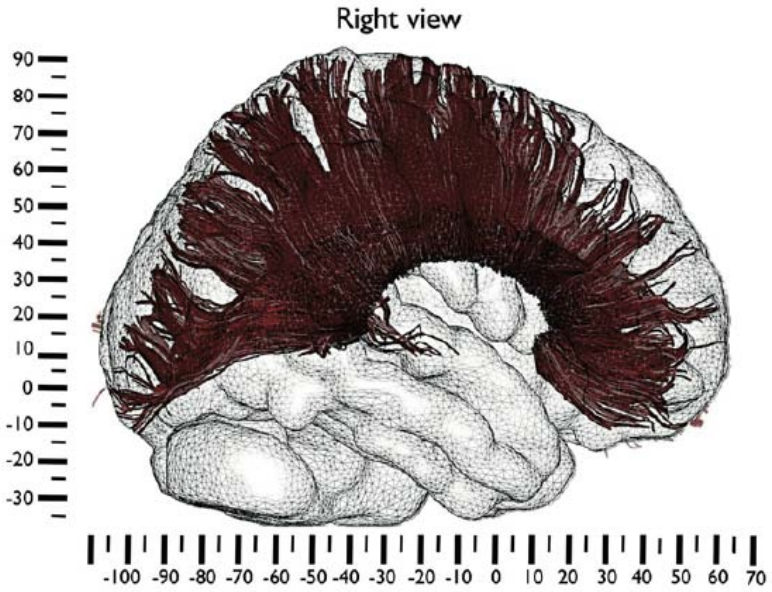

Figure 18. The corpus callosum as shown by Catani (2008)

Superior longitudinal fasciculus (SLF)

The superior longitudinal fasciculus (SLF) is a pair of long bi-directional bundles of neurons connecting the front and the back of each cerebrum, connecting the frontal, occipital, parietal, and temporal lobes (Mori, et al., 2002). The pathways travel from the frontal lobe through the operculum to the posterior end of the lateral sulcus where numerous neurons radiate into the occipital lobe and other neurons are directed towards the putamen and radiate to portions of the temporal lobe This inferior portion of the left SLF, also termed the arcuate fasciculus, is involved in language organization and is thought to connect cortical areas needed for language comprehension (Wernicke's area) with areas of language production (Broca's area) (Bernal & Altman, 2010). Importantly for BDD, the left SLF integrity as measured by FA is associated with

spatial working memory tasks with healthy individuals (Vestergaard et al., 2011). Individuals with BDD have a range of cognitive declines including in both spatial working memory (Dunai, et al., 2009) and verbal functioning (Deckersbach, et al., 2000), indicating that there may be reduced FA in the SLF in BDD. The only DTI study in BDD to date did not find any differences in the SLF (Arienzo, et al., 2013; Feusner, et al., 2013). However, given that the SLF is a major white matter tract, if reduced functioning was established in this area may be indicative of general white matter degradation rather than representing a core BDD neuropathology. Nevertheless, a general degradation of white matter would be supportive of the disconnection hypothesis proposed in Chapter 3, page 55.

Inferior longitudinal fasciculus (ILF)

The inferior longitudinal fasciculus is a ventral associative bundle with long and short fibres which connects regions of the occipital and temporal cortices (Catani & Thiebaut de Schotten, 2008). More specifically, the long fibres connect visual areas to the amygdala and hippocampus to the occipital lobe. The ILF is involved in face recognition, visual perception and visual memory (Fox, Iaria, & Barton, 2008), all of which are of importance to BDD. For example, a major finding of the only DTI study in BDD was that poor insight negatively correlated with FA and positively correlated with MD in the ILF (Feusner, et al., 2013). This correlation was present despite the fact that there were no significant between-group differences detected. The authors of this study reasoned that distorted visual perceptions which are difficult to refute, mediated by the ILF, may therefore explain the correlation between this tract and poor insight/delusionality.

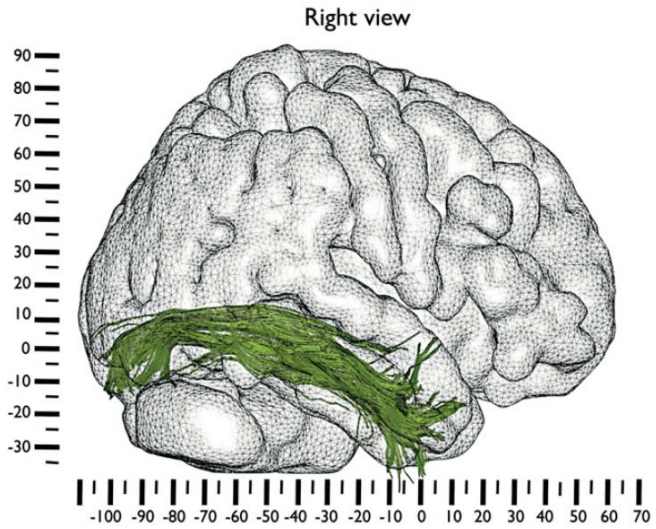

Figure 19. The inferior longitudinal fasciculus, as shown by Catani (2008)

Cingulum

The cingulum is a medial associative bundle that runs within the cingulate gyrus around the corpus callosum. Some fibres within the cingulum run from the anterior temporal gyrus to the orbitofrontal cortex. The short U-shaped fibres connect the medial frontal, parietal, occipital, and temporal lobes and different portions of the cingulate cortex (Catani & Thiebaut de Schotten, 2008). The cingulum is part of the limbic system and is involved in attention, memory and emotions, which are all of importance to BDD phenomenology. However, no significant DTI differences in the area have been reported in BDD (Arienzo, et al., 2013; Feusner, et al., 2013). *Figure 20* shows a visualization of the cingulum using DTI produced by Catani et al., (2008).

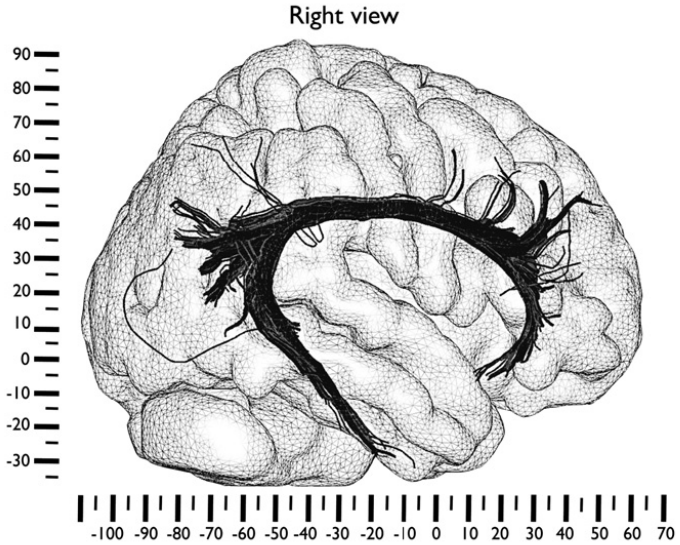

Figure 20. Cingulum visualization using DTI by Catani et al., (2008).

Uncinate fasciculus (UF)

The uncinate fasciculus is a white matter pathway that connects the inferior frontal and anterior temporal cortices (Mori, et al., 2002). It is a hook shaped bundle that originates rostrally in the temporal lobe and terminates in the ventral, medial and orbital parts of the frontal cortex, connecting the amygdalae, hippocampus and frontal regions. Thus, the UF is often considered to be part of the limbic system. Additionally, the UF connects cortical regions involved in sound and object recognition (superior and inferior temporal gyri) and recognition memory (entorhinal, perirhinal and parahippocampal cortices) (Price et al., 2008). Importantly to BDD, the UFs have a central role in top-down regulation of amygdala reactivity to control negative affect and mediate threat perception (Barrett, et al., 2007; Kim & Whalen, 2009; Ochsner, Bunge, Gross, & Gabrieli, 2002; Phan, et al., 2009). Therefore, the UF may be of particular importance to the fear circuitry hypothesis discussed on page 55.

More specifically, given that a major finding of past neuroimaging research in BDD was that right amygdala volumes are positively correlated with symptom severity (Feusner, et al., 2009), the UF which connects to the amygdala is of particular interest. Additionally, reduced FA in this area has been reported in related disorders such as general anxiety disorder (Phan, et al., 2009). Indeed, in healthy individuals that UF integrity has been shown to be related to trait anxiety (Kim & Whalen, 2009). Thus, the strength of this white matter pathway is thought to be critical in the development of emotional regulation, eliciting speculation that reduced connection between the amygdala and orbitofrontal region could reflect a phenotype that is common among disorders involving emotional dysregulation or impaired social functioning (Phan, et al., 2009).

Over and above the specific role of the UF in emotional inhibition, there is evidence showing that it is a white matter tract that is susceptible to general neurodegeneration in psychosis. For example, in a study of first-episode schizophrenia (Price, et al., 2008) the left UF had significantly reduced FA compared to controls. The emerging model of disconnectivity within schizophrenia states that psychotic symptoms as well as cognitive declines are mediated by white matter degradation. If white matter degradation in BDD could be shown it could possibly explain the neuropsychological deficits that have been found in BDD samples, which have been similar but less severe than those found is schizophrenia (Hanes, 1998). Thus far, however, there have been no differences in the UF reported in BDD.

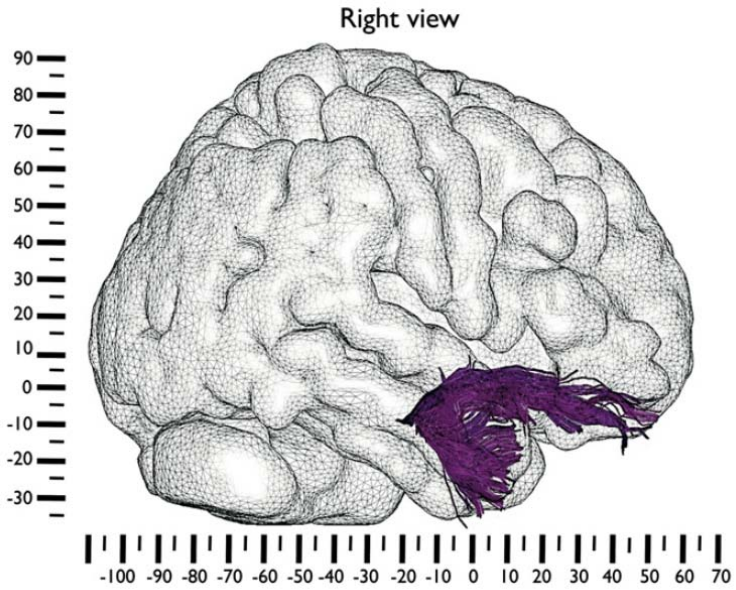

Figure 21. The uncinate fasciculus as shown by Catani (2008)

Inferior fronto-occipital fasciculus

The inferior fronto-occipital fasciculus is a large white matter tract connecting the frontal, temporal and occipital lobes (Mori, et al., 2002). The inferior fronto-occipital fasciculus also anatomically connects the prefrontal cortex and auditory and visual association cortex in the temporal lobe, although its specific role in these connections is still largely not understood. FA measurements in the area have been shown to be related to healthy individual's ability for attentional set-shifting (Perry et al., 2009), and high levels of anxiety are related to reduced FA in this area (Westlye, et al., 2011), though the reduced FA was widespread and not limited to this area.

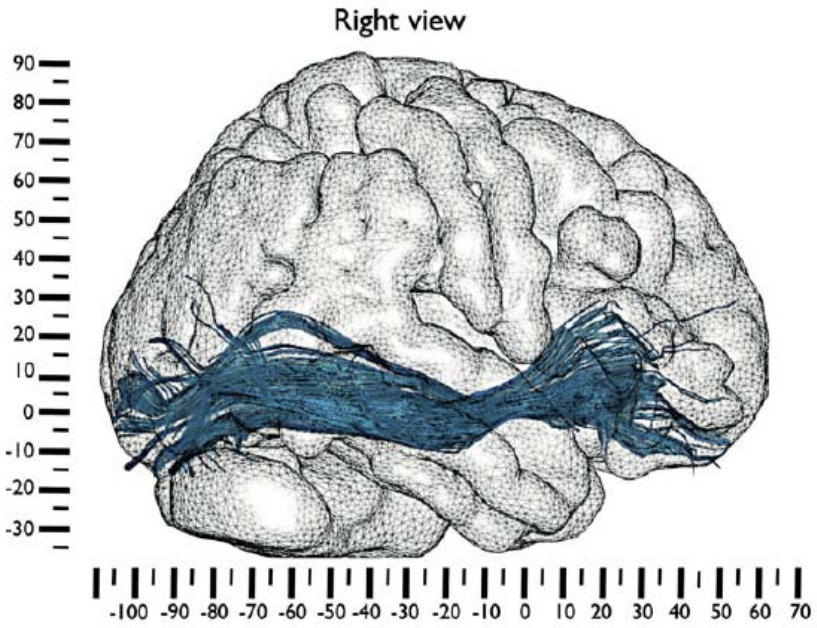

Figure 22. The inferior fronto-occipital fasciculus as shown by Catani (2008)

Anterior thalamic radiation

The anterior thalamic radiation connects the frontal lobe and the thalamus (Mori, et al., 2002). More specifically, it consists of fibres between mediodorsal thalamic nuclei and the frontal cortex, and fibres between anterior thalamic nuclei and the anterior cingulate cortices (Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004). This area has been shown to be compromised in patients with schizophrenia, leading to speculation that because it connects the prefrontal cortex with the thalamus, it may be partially responsible for the executive function and planning difficulties within the disorder (Mamah et al., 2010). Another study in healthy individuals showed the anxious personality characteristics were significantly correlated to reduced FA in anterior thalamic radiation (Westlye, et al., 2011).

White matter in patients with OCD has also shown deficits in the anterior thalamic radiation microstructural level (Chiu et al., 2011; Jayarajan et al., 2012), and FA has been shown

to increase after 12 week citalopram treatment (Yoo, et al., 2007). In OCD this data has been used to support the cortico-striato-thalamo-cortical circuit hypothesis, discussed in detail in Chapter 3, page 67. These DTI findings combine to create multimodal neuroimaging evidence for cortico-striato-thalamo-cortical (CSTC) deficits in OCD. The evidence converges with volumetric and functional differences in frontal and striatal regions. Thus far there is been no evidence of anterior thalamic radiation degradation in BDD, but if this area was found to be compromised in the current study it would lend support to the CSTC hypothesis. Much of the OCD neuroimaging literature has begun to focus on the CSTC hypothesis, which will now be discussed.

Diffusion tensor imaging studies in OCD

This section will discuss the DTI data in OCD in the hope that it will guide our analysis of BDD. While there has only been one DTI study (reported in two papers), to date, in BDD there have been at least 18 DTI studies in OCD over recent years, however, the findings have not been consistent. Table 9 summarises the OCD findings, and shows that there have been reported both increases and decreases in FA. For example, studies of the anterior cingulate have provided particularly inconsistent results showing higher values (Cannistraro et al., 2007), lower values (Szeszko et al., 2005), or no changes (Menzies, Williams, et al., 2008; Nakamae et al., 2011; Yoo, et al., 2007) in the FA of OCD patients compared with control groups.

Despite the inconsistencies, the reported white matter changes in OCD have been widespread. Notably, there have been changes reported in the corpus callosum (Yoo, et al., 2007), anterior cingulate (Cannistraro, et al., 2007; Szeszko, et al., 2005), internal capsule (Cannistraro, et al., 2007; Yoo, et al., 2007), white matter in the area super lateral to the right

caudate (Yoo, et al., 2007), subinsular white matter (Nakamae, et al., 2011), and the right inferior parietal and medial frontal regions (Menzies, Williams, et al., 2008).

More recent studies have begun to focus on white matter connecting the cortical and subcortical regions relevant to the fronto-striato-thalamic circuitry, as this represents a major hypothesis in the OCD literature, and as discussed on page 67 may be a promising neurobiological model for BDD. For example, Chiu et al. (2011) used DTI to measure the microstrucutral integrity of the cingulum bundle and the anterior thalamic radiation, proposing that these are the two main white matter tracts implicated in the pathophysiology of OCD.

These tracts are considered important because of their connections: The cingulum bundle connects the anterior cingulate cortex to other frontal sites as well as to the amygdalae, nucleus accumbens, and medial dorsal thalamus. On the other hand, the anterior thalamic radiation forms a reciprocal connection between the dorsomedial thalamic nucleus and the prefrontal cortex. Deficits in either of the two tracts will thus result in the disintegration of the CSTC circuitry and the disruption of functional connectivity between regions linked by these tracts (Chiu, et al., 2011).

Indeed, the cingulum bundle has been an area of relatively common finding (Cannistraro, et al., 2007; Chiu, et al., 2011; Fontenelle et al., 2011; Garibotto, et al., 2010), though not always consistent, with one study showing FA increases in paediatric OCD (Gruner et al., 2012). Chiu and colleagues finding of reduced integrity of the anterior thalamic radiation has also been supported by a treatment study showing increased FA in the same area after treatment (Yoo, et al., 2007). Furthermore, reduced FA in the anterior thalamic radiation has also been a significant finding in subclinical levels of anxiety (Westlye, et al., 2011).

In summary, the findings in OCD to date have been widespread and inconsistent, yet promising evidence has emerged that is supportive of the CSTC circuit hypothesis. Reduced structural integrity in areas connecting amygdalae, thalami and prefrontal cortices could be the basis for OCD symptoms, mediated by the cingulum bundle and the anterior thalamic radiation. Given the similarities between OCD and BDD, therefore, parallel DTI findings could support the CSTC hypothesis in BDD.

To date, however, the only DTI study in BDD has not provided data that is supportive of this model (Arienzo, et al., 2013; Feusner, et al., 2013). However, given the multiple comparisons and limited statistically significant between group differences in this study, further research is needed. The empirical paper presented in the current thesis (Chapter 7) provides a larger sample size (20 compared to 14) and higher directional resolution (60 compared to 34) which is therefore more sensitive to group differences.

Table 9. DTI findings in OCD (adapted from Bora et al., 2011).

Authors	Sample Characteristics	Main Findings
(Szeszko, et al., 2005)	15 OCD - Medicated 15 HC	• FA decrease in bilateral anterior cingulate, parietal, right posterior cingulate, left occipital white matter. • Lower parietal FA correlated with symptom severity
(Cannistraro, et al., 2007)	8 OCD - Not medicated 10 HC	• Increased FA in left anterior limb of the internal capsule. • OCD group exhibited abnormal asymmetry (left > right) of FA in the cingulum bundle. Left had greater FA, right had reduced FA compared to controls.
(Yoo, et al., 2007)	13 OCD - Treatment study 13 HC	• After 12 week treatment increased FA compared to baseline in the anterior thalamic radiations • No group difference at 12 weeks
(Menzies, Williams, et al., 2008)	30 OCD - Medicated 30 HC	• Decreased FA in right inferior parietal cortex and increased FA on right medial frontal cortex
(Saito et al., 2008)	16 OCD Medicated 15 HC	• FA was decreased in rostrum of CC • FA decrease was correlated with obsessive symptoms
(Ha et al., 2009)	25OCD - Medicated 25HC	• Left anterior cingulate FA reduction • Obsessive symptoms correlated with cingulate FA
(Garibotto, et al., 2010)	15 OCD - Medicated 15 HC	• FA reduced in CC (splenium) cingulum bundle, SLF, optic radiation, inferior fronto-occipital fascicule • Symptom severity correlated with FA decreases in these regions.
(Nakamae, et al., 2011)	30OCD - Unmedicated 30HC	• Reduced FA in the anterior body of corpus callosum • Trend to a lower FA in the large portion of CC, the right cingulum, and the left anterior limb of internal capsule
(Bora, et al., 2011)	21OCD - 10 taking medication 29HC	• Decreased FA in the body of the CC, underpinned by increased radial diffusivity.
(Fontenelle, et al., 2011)	9OCD 9HC	• Reduced FA values bilaterally in regions of the posterior limb of the internal capsule and in the SLF and increased MD values bilaterally in the posterior limb of the internal capsule, in the left cingulate bundle, and in the splenium of CC.
(Li et al., 2011)	23 OCD 23 HC	• Increased FA in the genu and body of CC and white matter of right superior frontal gyrus and CC; no areas of significantly decreased FA were found.

(den Braber et al., 2011)	20 twin pairs, one with OCD one without 28 twin pairs with OCD	• Environmental risk was associated with an increase in dorsolateral-prefrontal FA • Concordant pairs showed that the genetic risk was associated with a decrease in inferior frontal white matter connectivity through FA
(Zarei, et al., 2011)	26 OCD Adolescence 26 HC	• Higher FA values in left inferior longitudinal fasciculus, bilateral SLF, right inferior fronto-occipital fasciculus, bilateral corticospinal tract, CC, left cingulum, and right uncinate fasciculus. • Symptom severity positively correlated with increased FA in various WM tracts
(Chiu, et al., 2011)	12 OCD - Medicated 12 HC	• There was a significantly lower mean FA in both the right anterior thalamic radiations and left anterior segment of cingulum bundles in OCD
(Jayarajan, et al., 2012)	15 OCD - Paediatric 15 HC	• OCD had widespread increased axial diffusivity as well as radial diffusivities, but not FA • Supports orbitofrontal-striato-thalamo-cortical circuitry deficits in the development of OCD
(Oh et al., 2012)	20 OCD (15 drug-naive and 5 currently unmedicated) 20 HC	• Significant FA decreases were observed in orbitofrontal and dorsolateral prefrontal projections of the CC • OCD patients exhibited higher ventral-greater-than-dorsal asymmetry of FA values
(Gruner, et al., 2012)	23 OCD - paediatric (9 and 17 years) 23 HC	• OCD exhibited greater FA in the left dorsal cingulum bundle, splenium of the CC, right corticospinal tract, and left inferior fronto-occipital fasciculus. There were no regions of significantly lower fractional anisotropy
(Silk, Chen, Seal, & Vance, 2013)	16 OCD paediatric 22 HC	• Decreased axial diffusivity in both the genu and the splenium of the CC • Axial diffusion correlated with greater severity of symptoms within the OCD group

Chapter 8

Brain Connectivity in Body Dysmorphic Disorder Compared with Controls: A Diffusion Tensor Imaging Study

Published paper

Reference:

Buchanan, B., Rossell, S., Maller, J., Toh, W., Brennan, S., & Castle, D. (2013). Brain connectivity in body dysmorphic disorder compared with controls: a diffusion tensor imaging study. *Psychological Medicine*, 1-9.

The published manuscript is include in Appendix E.

Introductory note:

At the time of publication there were no other DTI studies in BDD, however a study reported in two papers (Arienzo, et al., 2013; Feusner, et al., 2013) was published in parallel to our study. This data was not discussed in this published manuscript but was incorporated into the previous chapter and the thesis discussion.

Monash University

Declaration of Authorship for Thesis Chapter 8

Brain connectivity in body dysmorphic disorder compared with controls: a diffusion tensor imaging study

Ben Buchanan, Susan Rossell, Jerome Maller, Wei Lin Toh, Sarah Brennan, & David Castle

Declaration by candidate

In the case of this Chapter, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
I collected the MRI and participant data, developed hypotheses, completed data analysis and wrote the entire chapter intended for publication with feedback from co-authors.	75%

The following co-authors contributed to the work.

Name	**Nature of contribution**	**Extent of contribution (%)**
Susan Rossell	Helped in formulation of hypotheses, data analysis and gave feedback on final report.	10%
Jerome Maller	Guided data analysis and gave feedback on final report.	9%
Wei Lin Toh	In the initial recruitment stage of the project we shared participants and therefore some demographic data.	2%
Sarah Brennan	In the initial recruitment stage of the project we shared participants and therefore some demographic data.	2%
David Castle	Instrumental in recruitment of BDD participants	2%

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date 13/8/2013**
Main Supervisor's Signature	[redacted]	**Date 13/8/2013**

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

Abstract

Background: Several neuroimaging studies have investigated brain grey matter in people with body dysmorphic disorder (BDD), showing possible abnormalities in the limbic system, orbitofrontal cortex, caudate nuclei and temporal lobes. This study takes these findings forward by investigating white matter properties in BDD compared to controls using diffusion tensor imaging. It was hypothesised that the BDD sample would have widespread significantly reduced white matter connectivity as characterized by fractional anisotropy.

Methods: Twenty participants with BDD and 20 healthy controls matched on age, sex and handedness underwent diffusion tensor imaging. Fractional anisotropy (FA), a measure of water-diffusion within a voxel, was compared between groups on a voxel-by-voxel basis across the brain using Tract Based Spatial Statistics within FSL.

Results: Results showed that, compared with healthy controls, BDD patients demonstrated significantly lower FA (p <.05) in most major white matter tracts throughout the brain, including in the superior longitudinal fasciculus, inferior fronto-occipital fasciculus and corpus callosum. Lower FA levels could be accounted for by increased radial diffusivity as characterised by eigenvalue 2 and 3. No area of higher FA was found in BDD.

Conclusions : This study provided the first evidence of compromised white matter integrity within BDD patients. This suggests that there are inefficient connections between different brain areas, which may explain the cognitive and emotion regulation deficits within BDD patients.

Body dysmorphic disorder (BDD) is a mental disorder characterised by a preoccupation with an imagined defect in physical appearance, or if a slight abnormality is present, the concern about it is excessive. Individuals with BDD often engage in repetitive and ritualistic behaviours, including skin picking, camouflaging their supposed defect, and checking their appearance in the mirror. The prevalence of BDD is approximately 1.8% in community self report samples (Buhlmann, et al., 2010), with slightly higher prevalence among females. Individuals with BDD have impaired psychosocial functioning and quality of life (Phillips, Menard, et al., 2005), they may experience prolonged unemployment, severe social isolation and suicidal ideation, with approximately 25% of individuals with BDD attempting suicide (Buhlmann, et al., 2010; Phillips, Coles, et al., 2005). Many individuals with primary BDD also fulfil the criteria for other mental disorders, including social phobia (Coles, et al., 2006), major depression (Phillips, Didie, et al., 2007) and obsessive compulsive disorder (Stewart, et al., 2008). The high level of comorbidity may represent conceptual similarities between BDD and other disorders or etiological links.

The severe body image distortions that individuals with BDD experience suggest that fundamental cognitive and perceptual abnormalities are involved. Indeed, neuropsychological research has revealed a range of deficits in BDD, including in executive function (Dunai, et al., 2009; Hanes, 1998; Labuschagne, Castle, & Rossell, 2011), selective attention (Buhlmann, McNally, et al., 2002), information processing, verbal and non-verbal memory (Deckersbach, et al., 2000; Dunai, et al., 2009), recognition of emotion in others (Buhlmann, et al., 2004) and visual processing (Feusner, Moller, Altstein, Suger, et al., 2010; Feusner, et al., 2007). The combination of deficits in response inhibition, combined with hightened attention to threatening

stimuli compared with controls, has suggested that frontostriatal circuits may be important in BDD (Buchanan, et al., 2011).

Several neuroimaging studies have directly investigated structural and functional brain abnormalities in BDD. To date, these investigations have focussed primarily on grey matter structures. The right amygdala has been shown to have increased activation in response to visual stimuli in a functional magnetic resonance imaging (fMRI) study (Feusner, et al., 2007), while structural MRI techniques have shown that right amygdala volume correlates to symptom severity (Feusner, et al., 2009; Rauch, et al., 2003). Other abnormalities in areas related to emotion processing, such as the cingulate cortex (Atmaca, et al., 2010), suggest that there are deficits in the limbic system. The orbitofrontal cortex has been shown to be reduced in volume compared to controls using structural MRI (Atmaca, et al., 2010), and an fMRI study found hyperactive activation in the same area (Feusner, Moody, Hembacher, Townsend, et al., 2010). Furthermore, neuropsychological (Dunai, et al., 2009) research has shown deficits in cognitive functioning that may be related to the orbitofrontal cortex. Consistent with BDD symptomatology centred around visual stimuli, occipital lobe activation has been found to be different to that of controls (Feusner, Moody, Hembacher, Townsend, et al., 2010). Less consistent abnormalities have been shown in the caudate nucleus (Atmaca, et al., 2010), and temporal lobes (Carey, et al., 2004), which could possibly be associated with memory dysfunction found in BDD samples (Deckersbach, et al., 2000).

BDD and obsessive compulsive disorder (OCD) are often compared as they share symptomatology (McKay, Neziroglu, & Yaryura-Tobias, 1997; Stewart, et al., 2008). There is a high comorbidity rate (Stewart, et al., 2008) between these disorders, they have comparable demographic characteristics (Frare, et al., 2004), and have a genetic overlap (Monzani et al.,

2012). In terms of neurobiology, abnormalities of the caudate nucleus (Rauch, 2000; Whiteside, et al., 2004) and orbitofrontal cortices (Atmaca, et al., 2010; Rotge, 2010) are common to both disorders. However, neuroimaging data is well replicated in OCD but scarce in BDD, and no study has directly compared the two disorders using neuroimaging techniques.

Diffusion tensor imaging (DTI) is a neuroimaging technique developed to examine the integrity of white matter tracts. Recent methodological advances in DTI have motivated a growing interest in disconnection models proposing that white matter structural connectivity modulates symptoms in various mental disorders. In OCD samples there are at least nine separate studies that have reported DTI data, whereas this technique has not yet been reported on in a BDD sample. Within OCD samples DTI has found abnormalities in the frontostriatal neural pathway, the corpus callosum, superior longitudinal fasciculus as well as a generalised disorganisation among neural tracts (Bora, et al., 2011; Garibotto, et al., 2010).

Within DTI analysis, fractional anisotropy (FA) is the most widely used measurement, and represents the normalized standard deviation of three tensor eigenvalues. In white matter the movements of water molecules are restricted by various tissue components (e.g. myelin sheath or membranes), so that diffusion is reported to be anisotropic (Basser, et al., 1994; Basser & Pierpaoli, 1996). FA reflects the degree of directionality (anisotropy) within a voxel. High FA suggests that there is highly directional diffusion such as that seen in white matter fibre tracts, and low FA values are associated disorganised white matter (Mori, Wakana, Van Zijl, Nagae-Poetscher, & Corporation, 2005). This technique, therefore, can allow investigators to examine the neural organisation of white matter, which reflects the efficiency of how different parts of the brain communicate with each other.

This study has two main aims: (1) to investigate whether white matter abnormalities exist within a BDD cohort by comparing them to healthy controls, (2) characterise the biological abnormalities underlying the disorder, using FA. Given that OCD shares nosological links with BDD, our hypotheses were partly based on the reported OCD white matter abnormalities (although it is acknowledged that there is some inconsistency in the OCD literature). In addition the neuropsychological deficits and grey matter differences reported within BDD samples were used to inform our hypothesis that white matter integrity may be compromised in BDD. Specifically, it was hypothesised that the BDD sample would have widespread significantly reduced FA, including in the corpus collosum, superior longitudinal fasciculus, and inferior fronto-occipital fasciculus. Past neuroimaging studies (Feusner, Moody, Hembacher, Townsend, et al., 2010; Feusner, et al., 2009) have suggested a relationship between structural and functional abnormalities and BDD symptom severity. Thus, the relationship between symptoms severity and FA was also investigated in this study. In addition, FA was also correlated with current anxiety and depression scores to help investigate the influence of these co-occurring symptoms on white matter integrity.

Method

Participants

Two cohorts were recruited comprising of 20 individuals with BDD and 20 (after one exclusion) healthy controls, aged between 19 and 64. The BDD participants were recruited from the St Vincent's Hospital Body Image clinic in Melbourne, Australia. Recruitment was conducted via referrals from this clinic, where clients were identified as having BDD and

introduced to the research project. Participants gave their informed consent and diagnosis was then confirmed using the Body Dysmorphic Disorder Diagnostic Module (BDD-DM) and symptom severity was recorded using the Yale Brown Obsessive Compulsive Scale Modified for Body Dysmorphic Disorder (BDD-YBOCS) (Phillips, et al., 1997). BDD patients were excluded if they had a past or current psychotic disorder, obsessive compulsive disorder, bulimia nervosa, anorexia nervosa, alcohol or substance abuse history, intellectual/cognitive impairment, metal implants or neurological disturbance. Furthermore, BDD participants were excluded if they had a comorbid mental disorder that was considered to be their primary diagnosis, ensuring that all individuals in the patient sample had BDD as their primary concern. Because primary diagnosis can be difficult to delineate when there is comorbid OCD, individuals with OCD were excluded, whereas individuals who also fulfilled the criteria of social phobia or major depression were allowed if BDD was clearly assessed as their primary diagnosis. As BDD shows very high rates of psychiatric comorbidity (Phillips, Pinto, et al., 2007) our exclusion criteria was calibrated to obtain a highly representative sample.

Healthy control participants were sourced from a voluntary healthy research database, comprising members of the public. The control group had no personal or family history of a mental disorder and met the same exclusion criteria outlines for the BDD group. All participants had a Wechsler Test of Adult Reading (WTAR) premorbid IQ score of >80, and all participants had English as their preferred language. One control participant was excluded after MRI acquisition due to incidental brain pathology and is not presented in any of the data tables.

Participants were assessed with the Mini-International Neuropsychiatric Interview (Sheehan, et al., 1998) (MINI) to evaluate the presence or absence of other mental disorders. Handedness was assessed with the Edinburgh Inventory, and social anxiety and depression were

measured by the Social Interaction Anxiety Scale (SIAS) (Brown, et al., 1997) and the Zung Self-Rating of Depression Scale (Zung, 1965), which has been shown to be sensitive to the clinical severity of depression in psychiatric samples (Biggs, et al., 1978) . Group comparisons were computed using an independent sample t-tests at $p = .05$. Demographic and clinical data are displayed in Table 10.

Table 10. Demographic and Clinical Variables.

	BDD (mean ± SD)	Controls (mean ± SD)	Group Comparison (df = 38)
Demographic Characteristics			
- Age (Years)	34.6 ± 11.5	31.9 ± 11.4	$p = 0.45$
- Years of Education	14.9 ± 2.4	16.3 ± 3.0	$p = 0.11$
- WTAR IQ estimate	106 ± 10.7	110 ± 6.5	$p = 0.13$
- Handedness (L/R)	3/17	3/17	
- Gender (M/F)	6/14	6/14	
Clinical variables			
- BDD severity (BDD-YBOCS)	24.9 ± 9.6	-	
- Duration of illness (Years)	10.8 ± 6.9	-	
- Depression (Zung)	46.0 ± 11.3	23.3 ± 8.7	**$p < 0.05$**
- Social Anxiety (SIAS)	41.7 ± 18.0	17.1 ± 4.2	**$p < 0.05$**

The two participant groups were well matched on age, gender, education, estimated IQ and handedness. The clinical data indicates that mean BDD severity was in the "moderate"

range which is defined as scores between 16 and 30 on the BDD-YBOCS (Phillips, et al., 1997). Scores below 15 indicate “mild” BDD symptoms and scores from 31 to 48 are defined as “severe” symptoms. At the time of MRI acquisition our sample comprised two participants in the mild range, thirteen with moderate symptoms and five in the severe range.

The depression scores as measured by Zung depression ratings scale indicated that the BDD sample had a higher level of depressive symptoms compared to controls. On average the BDD group fell in the subclinical range of depressive symptoms, defined as a score below 50 (Zung, 1965). A score between 50 and 59 on the scale represents mild depression, scores between 60 and 69 indicate moderate symptoms and above 70 indicates severe symptoms (Zung, 1965). The SIAS scores showed that the BDD sample had a moderate level of social anxiety symptoms; less than people diagnosed with social phobia but higher than other anxiety disorders (Peters, 2000), which is typical of BDD samples (Coles, et al., 2006). Assessment with the MINI showed that four BDD participants fulfilled the diagnostic criteria for current major depressive disorder or dysthymia, and five had current agoraphobia or social phobia, showing that our sample was representative of a typical BDD profile (Coles, et al., 2006). Areas of aesthetic concern for our sample were generally the face, skin and hair. All but two members of the BDD sample were taking psychoactive medication: five where taking seroquel, four escitalopram, two duloxetine, two desvenlafaxine, two diazepam, and one each paroxetine, mirtazapine, lorazepam, methylphenidate, sodium valproate or clomipramine.

MRI acquisition

Participants were scanned using a 3T scanner (Siemens Magnetom TrioTim, Erlangen, Germany) at the Murdoch Children's Research Institute (Royal Children's Hospital, Melbourne). The DTI scanning sequence was conducted as component of an hour long scan. The scanner acquired an isotropic diffusion tensor imaging sequence for FA estimations (Number of directions = 60, b-value = 2000s/m^2, slice thickness = 2.5mm). Data were transferred to a Linux workstation for image processing and analyses.

Fractional anisotropy analysis

Tract Based Spatial Statistics (TBSS) developed by Smith et al. (2006) was used to create a mean FA skeleton that was representative of our 40 participants. TBSS uses nonlinear registration to create a template for FA comparisons that allows voxelwise analysis of multi-subject diffusion data. The TBSS module in the FSL package (Oxford, UK [http://www.fmrib.ox.ac.uk/fsl/]) was used to compute statistics. A two sample t-test was conducted using the randomize tool, which tests the t-value at each voxel against a null distribution generated from 5,000 random permutations of group membership. The output contained statistical maps corrected for multiple comparisons ($p < 0.05$) using threshold-free cluster enhancement (TFCE). This method has a high level of sensitivity to true differences while minimising false positives by avoiding the specification of a subjective cluster-forming threshold (Smith & Nichols, 2009). Specific white matter areas were defined using integrated white matter atlases within FSL: the ICBM-DTI-81 White-Matter Labels Atlas and the JHU White-Matter Tractography Atlas, both developed in the Laboratory of Brain Anatomical MRI, Johns Hopkins University, USA.

In addition, a Pearson product-moment correlation analysis at $p<0.05$ was performed between voxelwise FA and symptom severity as measured by the BDD-YBOCS, Zung Self-Rating of Depression Scale and Social Interaction Anxiety Scale.

Results

Fractional Anisotropy

The BDD patients exhibited widespread significant reductions in corrected FA values compared with controls. Table 11 shows decreased FA values in BDD divided into anatomical regions, and shows areas of significant increase in eigenvalue two and three. There were no significant differences between BDD and controls on eigenvalue one.

Table 11. Areas of Decreased Fractional Anisotropy and Increased Eigenvalue Two and Three Values in BDD

x	*y*	*z*	*P value FA*	*P value* Eigenvalue *2*	*P value* Eigenvalue *3*	*Anatomical Region*
-39	-47	22	<0.05	<0.05	<0.05	†Superior longitudinal fasciculus (left)
40	-44	19	<0.05	NS	<0.05	†* Superior longitudinal fasciculus (right)
-37	-53	0	<0.05	<0.05	<0.05	*Posterior thalamic radiation (left)
13	44	-16	<0.05	<0.05	<0.05	*Uncinate fasciculus (right)
31	42	3	<0.05	<0.05	<0.05	† Inferior fronto-occipital fasciculus (right)
-28	31	12	<0.05	<0.05	NS	† Inferior fronto-occipital fasciculus (left)
-42	-29	-7	<0.05	<0.05	NS	† inferior longitudinal fasciculus (left)
-1	-11	25	<0.05	<0.05	<0.01	* Body of corpus callosum
18	-37	30	<0.05	<0.05	<0.05	* Splenium of Corpus Callosum (right)
-9	29	11	<0.05	<0.05	<0.05	* Genu of the Corpus callosum, or † forceps minor left
9	29	10	<0.05	NS	NS	* Genu of the Corpus callosum, or † forceps minor (right)
-8	-5	11	<0.05	NS	NS	† Anterior thalamic radiation (left)
9	-31	-23	<0.05	NS	NS	† Corticospinal tract (right)
-28	-20	-7	<0.05	NS	NS	* Fornix or stria terminalis (cannot be resolved with resolution)

* Area identified using the ICBM-DTI-81 White-Matter Labels Atlas
† Area identified using the JHU White-Matter Tractography Atlas
NS = Not significant

Table 11 shows that there are widespread white matter differences in BDD. Since FA is a composite of eigenvalues one, two and three and there was no differences on eigenvalue one, the majority of FA reductions can be accounted for by an increase of radial diffusivity as represented by eigenvalues two and three.

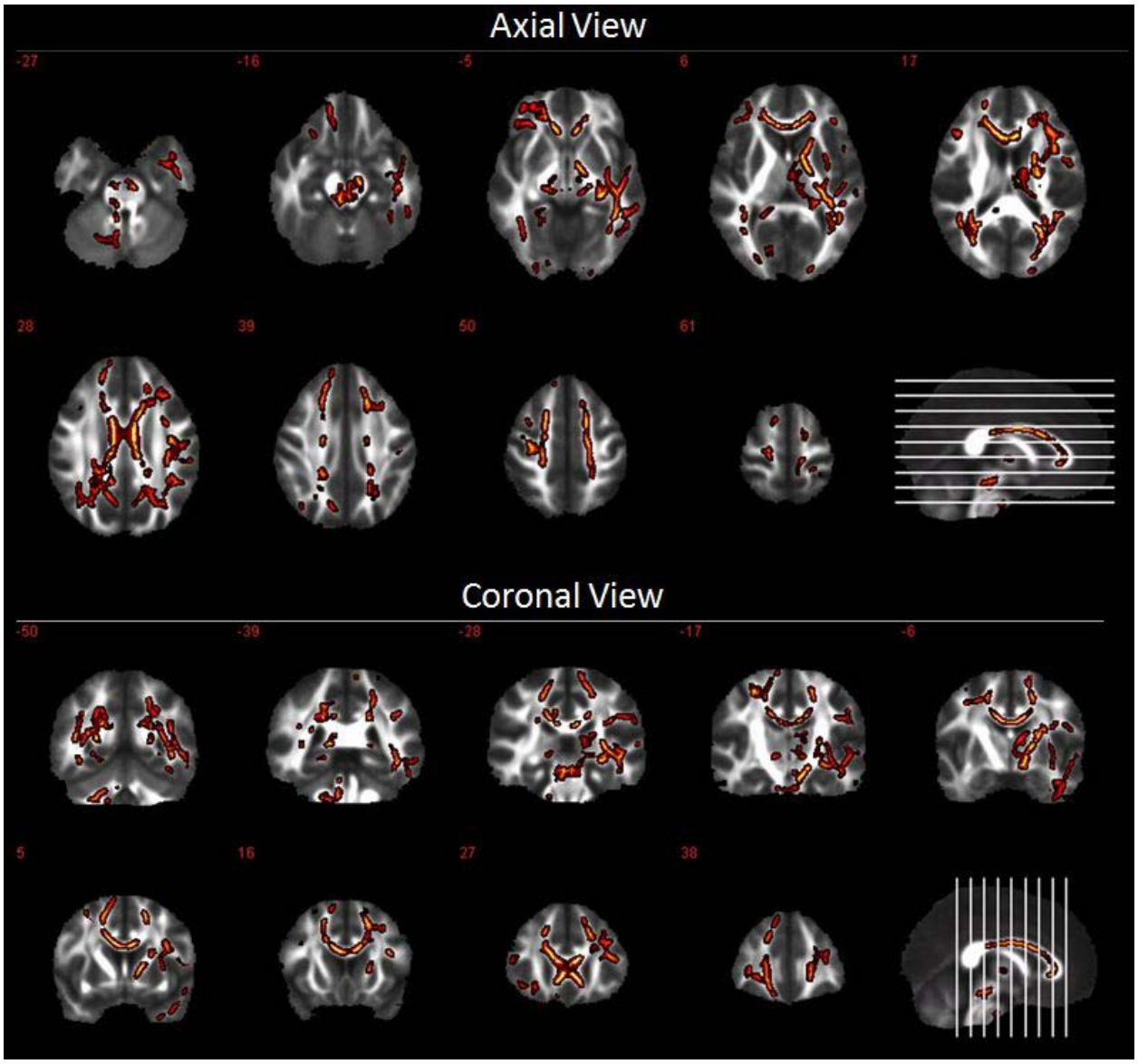

Figure 23. Statistically significant fractional anisotropy reductions in BDD sample compared with controls. Numbers in red represent mm from the anterior commissure.

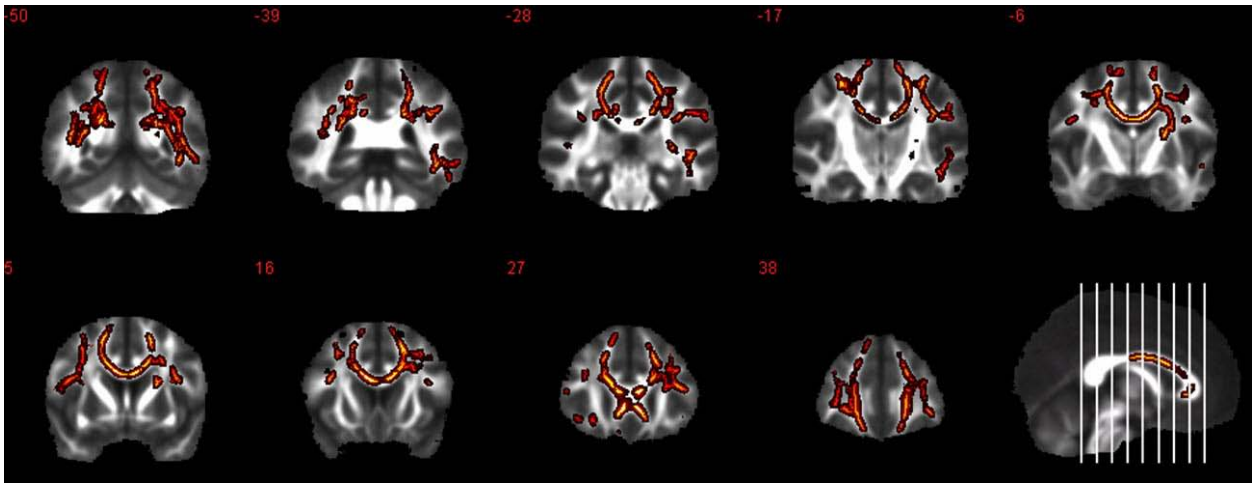

Figure 24. Statistically significant mean diffusivity increases in BDD sample compared with controls, coronal view.

Correlation Analysis

The correlation analysis found that there was no significant correlation between BDD symptom severity scores and corrected FA in any voxel within the BDD sample. Likewise, there was no significant correlation between depression scores and FA in the BDD group. In the BDD group, social anxiety scores were found to correlate negatively with corrected FA values on the left superior longitudinal fasciculus (X=-38, Y=2, Z=22) at $p<0.05$. There was no correlation between depression and anxiety in any voxel in the control group.

Discussion

As far as we are aware, this is the first study to examine white matter differences within a BDD sample using DTI. Additionally, this study had the largest BDD sample in a neuroimaging study to date, and our sample was thoroughly screened to ensure that BDD was the primary

condition and that it was representative of the patient population (Phillips, Didie, et al., 2007). Importantly, this study provides preliminary evidence of neural abnormalities in BDD; specifically, evidence for a widespread loss of integrity in white matter connectivity.

Consistent with the hypothesis that we would find similar reductions in FA in BDD as has been shown in OCD (Garibotto, et al., 2010; Szeszko, et al., 2005), we found reduced FA in the corpus callosum, superior longitudinal fasciculus, and inferior fronto-occipital fasciculus, bilaterally. The widespread FA reductions in our BDD sample can be accounted for through increases in radial diffusivity rather than reduced eigenvalue one. Of the 12 areas identified in Table 2 as having significantly reduced FA, nine can be accounted for by eigenvalues two and three. A comparison between *Figure 23* and *Figure 24* shows that mean diffusivity was more widespread than FA differences. This suggests loss of integrity in the white matter whereby attenuated white matter pathways allow water diffusion in directions that are not consistent with overall white matter directionality. Reduced FA has been shown in other work to be driven by myelin abnormalities which is largely under genetic control (Menzies, Williams, et al., 2008). Therefore, neurodevelopment irregularities leading to abnormal myelination may be important to the predisposition to BDD. Reduced FA due to increased radial diffusivity has also been found in OCD (Bora, et al., 2011).

While the loss of white matter integrity was widespread, it is worth considering the impact of specific neural pathways on BDD cognition. For example, reduced FA in the corpus callosum indicates attenuated interhemispheric communication. This may explain the neuropsychological research in BDD that has shown difficulties with integration of detailed and global information processing (Deckersbach, et al., 2000; Feusner, Moller, Altstein, Suger, et al., 2010). Moreover, white matter operating inefficiently may explain the Stroop task difficulties

associated with BDD (Hanes, 1998), as reduced FA and other neurobiological correlates in frontostriatal-limbic regions have been shown to relate to performance on the Stroop and planning tasks in depression and OCD (Murphy et al., 2007; van den Heuvel, Veltman, Groenewegen, Witter, et al., 2005). Furthermore, reduced FA in bilateral superior longitudinal fasciculi suggests that connectivity between the prefrontal, parietal, occipital and temporal regions (Makris et al., 2005) may be compromised.

The reduced FA in the uncinate fasciculus is of particular interest because it is a major white matter fibre tract that connects the inferiorfrontal and anterotemporal cortices, and it travels over the lateral nuclei of the amygdala. Thus, lower FA within this tract suggests compromised fronto-amygdala structural connectivity in BDD. In the context of BDD, this is interesting when considering that frontal regions such as the orbitofrontal cortex serve important roles in top-down regulation of amygdala reactivity to control negative affect and mediate threat perception (Barrett, et al., 2007; Ochsner, et al., 2002).

It is clear from past research that there are grey matter differences in BDD patients compared to non-psychiatric controls, but how these interact with the white matter abnormalities reported here remains speculative. Volumes of the right amygdala and the inferior frontal gyrus have been shown to correlate with current BDD symptom severity (Feusner, et al., 2009) suggesting that differences in these grey matter structures are the most proximal contributor to symptoms, while white matter differences can be considered as a more distal, or perhaps predisposing factor in BDD.

Our examination of whether BDD symptom severity correlated with FA was not significant, despite such a correlation being found in OCD samples (Garibotto, et al., 2010).

Given that we had a large range of symptom severity and a sample size that was able to provide robust correlation results, our non significant results suggest that BDD has a distinct neurobiological makeup that is state-independent. Such a finding suggests important trait related white matter abnormalities in BDD. This result would need to be replicated; further research could establish if these brain differences are present in an individual whether or not illness is active, and provide preliminary evidence for a BDD phenotype that is perhaps related to the emerging phenotype considered important in OCD (Menzies, Williams, et al., 2008).

The results showing a significant negative correlation between social anxiety scores and FA in the left superior longitudinal fasciculus is interesting considering that the main measure of BDD symptom severity (the BDD-YBOCS) was not significantly correlated. It is possible that our social anxiety measure was sensitive to an important feature of BDD that our main symptom severity rating scale was not. Indeed, social anxiety can be seen as a important factor within BDD symptomatology and is best conceptualised as an expression of higher BDD symptoms rather than a separate problem of social phobia (Coles, et al., 2006). The findings that there was no correlation between depression scores and FA in any voxel indicated that the FA differences among the two groups can be accounted for by the diagnosis of BDD independent from depression ratings. Indeed, this finding taken together with the non-significant contribution of BDD symptoms to FA suggests that state based symptoms scores bear less importance to white mater than state independent diagnosis.

The parallels that have been drawn between OCD and BDD in terms of clinical features (Stewart, et al., 2008) are yet to be robustly supported using DTI imaging techniques. In fact, to date, the nine DTI studies in OCD have yielded inconsistent results with both local FA increases and decreases reported (e.g. Bora, et al., 2011; Lochner et al., 2012; Menzies, Williams, et al.,

2008). The inconsistent data in OCD and the preliminary evidence of widespread FA decreases provided by the current study in BDD should be supplemented by future studies to help determine biological similarities and differences between the two disorders.

A limitation of this study is that nearly all of our BDD participants were taking medication at the time of MRI acquisition. This may be problematic as treatment is likely to have reduced the severity of BDD symptoms, thereby possibly influencing FA. However, as white matter integrity is generally considered state independent, current BDD symptomatology is unlikely to have significantly influenced results. At the time of MRI acquisition two of the BDD participants rated as having mild BDD symptoms on the BDD-YBOCS, although an active diagnosis of BDD was still confirmed using the BDD-DM.

In conclusion, we believe this to be the first study to examine white matter integrity in a BDD sample. The main contribution of our data is that it provides evidence that individuals with BDD have compromised white matter fibres, reflected by changes in fibre directionality as indicated by eigenvalues two and three. This reduced connectivity among different regions of the brain is widespread in nature and is not related to symptom severity.

Chapter 9

Altered fronto-limbic functional connectivity in Body Dysmorphic Disorder: A resting-state fMRI study.

Susan L Rossell, Ben Buchanan, Richard Nibbs, Alex Volziker, Wei Lin Toh, Jerome Maller and David J Castle

Manuscript submitted for publication and currently under review

Introductory note:

This study used 17 BDD participants and 18 healthy controls from the other two studies. One BDD participant withdrew due to anxiety and did not complete the scanning sequence, and there were problems with the acquisition of two other BDD and control scans due to motion artefact.

Monash University

Declaration of Authorship for Thesis Chapter 9

Altered fronto-limbic functional connectivity in Body Dysmorphic Disorder: A resting-state fMRI study.

Susan L Rossell, Ben Buchanan, Alex Volziker, Richard Nibbs, Wei Lin Toh, Jerome Maller and David J Castle

Declaration by candidate

In the case of this chapter, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
I collected the MRI data on which this study was based, formulated hypotheses and was involved in preparing the final article to be submitted for publication.	50%

The following co-authors contributed to the work.

Name	**Nature of contribution**	**Extent of contribution**
Susan Rossell	Formulated hypotheses, data analysis and prepared write up of final report.	35%
Alex Volziker	Data analysis and write up	6%
Richard Nibbs	Data analysis	3%
Wei Lin Toh	In the initial recruitment stage of the project we shared participants and therefore some demographic data.	2%
Jerome Maller	Data analysis and gave feedback on final report.	2%
David Castle	Instrumental in recruitment of BDD participants	2%

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date 13/8/2013**
Main Supervisor's Signature	[redacted]	**Date 13/8/2013**

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

Abstract

Background: Neuroimaging research in Body Dysmorphic Disorder (BDD) has revealed abnormalities in the visual, cortico-striatal and limbic systems, in both task based and volumetric MRI studies. The current study aimed to further our understanding of BDD using resting-state fMRI, specifically investigating task-independent functional connectivity (FC) patterns between brain regions. It was hypothesized that the BDD group would demonstrate abnormal FC in frontostriatal regions as has been shown in OCD (a nosologically similar condition).

Methods: Seventeen BDD participants and 18 healthy controls matched on age, sex and handedness underwent a resting-state functional MRI scan. Functional Connectivity (FC), a measure of activation correlation between brain regions, was compared between groups via a seed-based and voxel-based approach across the brain, using CONN Connectivity Toolbox.

Results: Results did not lend support to the frontostriatal hypothesis in BDD; however, abnormalities in fronto-amygdala and hippocampal connectivity with several key brain regions were demonstrated. In addition, preliminary evidence of improper communication within the visual systems in BDD was found.

Conclusions: This data lends support for the argument that BDD lies on a spectrum of anxiety spectrum disorders, characterized by emotional dysregulation and socio-cognitive deficits, which includes abnormalities in processing visual information.

Introduction

Body Dysmorphic Disorder (BDD) is characterized as a preoccupation with an imagined deficit or slight anomaly in physical appearance, which results in significant distress or impairment in social, occupational and other areas of functioning (DSM-IV; American Psychiatric Association, 1994). The most common areas of concern for BDD patients involve facial features; however other bodily features such as buttocks, abdomen, hands, and breasts can also be the focus (Phillips, 1998; Phillips, McElroy, Kec, Pope, & Hudson, 1993). Individuals with BDD tend to carry out time-consuming, obsessive behaviours such as prolonged mirror checking, camouflaging or concealing the perceived defect (Buhlmann & Wilhelm, 2004; Castle, Rossell & Kyrios, 2006; Phillips et al; Veale, 2004).

A core feature of BDD is the abnormalities in visual information processing. Clinically, patients with BDD tend to focus their attention primarily on the fine details of their appearance at the expense of more global and configural features. A neuropsychological study utilizing the Rey Complex Figure Test (RCFT) supported this idea by showing that the BDD patients performed poorly in comparison to the control group as a result of their organizational strategy (Deckersbach et al., 2000). Recent neuroimaging studies have elucidated abnormalities of primary and secondary visual processing systems in BDD (Fuesner et al., 2007; Feusner et al., 2011), as well as visual association areas such as the parahippocampal gyrus (PHG), lingual gyrus, and the precuneus (reviewed in Buchanan, Rossell & Castle, 2011).

In addition, behavioural data has suggested that BDD patients tend to misinterpret the facial expressions of others as contemptuous (Buhlmann et al., 2004; Buhlmann et al., 2006). Fuesner and colleagues elaborated on this latter finding during a functional neuroimaging

experiment (Feusner et al., 2010). Their BDD group significantly under activated the left-hemisphere occipital regions when viewing their own face, indicating a potential deficit of the dorsal-stream magnocellular pathway activity (Berson, 1988; Peuskens et al., 2007).

There are noteworthy similarities between BDD and OCD in terms of their phenomenology, epidemiology, comorbidity, familial aggregation, and response to treatment (Hollander, 1993). Indeed, the DSM–5 (APA, 2013) groups BDD with OCD. Behaviourally, both BDD and OCD have similar preoccupations; which are described as obsessional, persistent and recurrent thoughts that are distressing, anxiety provoking and difficult to inhibit and control (Perugi et al., 1997). It is therefore reasonable to hypothesise that analogous pathophysiological processes may exist in BDD as in OCD. In terms of neurobiological dysfunction of the frontostriatal circuits of the brain, in particular the orbitofrontal and caudate regions have been implicated with both BDD and OCD. Such dysfunction has been suggested to account for the pattern of obsessive thoughts and compulsive behaviours in OCD (Menzies et al., 2008). The extant literature on brain morphometry of BDD patients has also revealed volumetric changes and hemispheric asymmetries in these frontostriatal regions (Rauche et al., 2003; Atmaca et al., 2010). However, discrepant findings amongst these studies make it difficult to draw clear inferences about the nature of the specific dysfunctions. In addition, Feusner et al. (2010) showed a relative hyperactivity in the left OFC and bilateral head of caudate for the own face vs. familiar face task in a BDD cohort. There was also a positive correlation with symptom severity and aversiveness ratings of the ‘own face’ stimuli. These finding supports the idea that BDD patients may be exhibiting obsessive thoughts and compulsive tendencies when viewing a reflection of their own face or in response to internally generated thoughts about their appearance.

Due to the scarcity and inconsistency of the current literature in BDD, it is important to consider the methodological constraints of the existing research paradigms. This refers to the predominant use of statistical tools to resolve imaging differences (e.g. patient vs. control) at a voxel-by-voxel or intraregional level, thereby ignoring interrelationships or interactions between brain regions. A recent study using the same cohort as the current study employed Diffusion Tensor Imaging (DTI) to investigate fractional anisotropy in BDD compared to control participants. This study revealed significant, relative reductions in most white matter tracts, suggesting aberrant connectivity between cortical regions (Buchanan et al., 2013).

Recent advances in brain mapping have made it possible to use fMRI technology to map the brain's connectivity features. Resting-state, functional connectivity MRI (fcMRI) is a technique that involves the assessment of coherent spontaneous low frequency (<0.08Hz) fluctuations of the blood oxygenation level–dependent (BOLD) signal (Rogers et al., 2007) and is assumed to relate to neural activity (Leopold et al., 2003). In essence, this technique allows for mapping of the intrinsic connectivity within the brain without any overt task or stimulus presentation.

Use of resting-state fMRI has the potential to provide further insight into the nature of the abnormalities in visual processing systems, especially in primary, secondary and association visual cortices. We report such as study here.

No published literature to date has utilized resting-state fMRI to investigate BDD, hence the current study made predictions on the basis of the existing clinical, neuropsychological and neuroimaging studies in BDD. In addition, the current study made predictions based on the existing resting-state fMRI research in OCD. In particular, symptom provocation studies in

OCD have found abnormalities in OFC and caudate regions, as well as anterior cingulate cortices (Breiter et al., 1996), and symptom severity scores have also been found to correlate with the functional connectivity between OFC and caudate regions (Harrison et al., 2009), as well as ACC volumes (Breiter et al., 1996).

The current study investigated the frontostriatal hypothesis of BDD, predicting an increased functional connectivity between the OFC and caudate regions. Secondly, based on the underlying phenomenology and previous neuroimaging studies, we expected to find altered connectivity between both primary, secondary and association visual processing systems.

Methods

Participants

The participants comprised of 17 BDD patients after removal of one patient due to an incomplete resting state scan (11 females, 6 males) and 18 healthy aged, sex and handedness matched controls (12 females, 6 males). The BDD participants were recruited from the St Vincent's Hospital Body Image clinic in Melbourne, Australia. Participants gave their informed consent and diagnosis was then confirmed using the Body Dysmorphic Disorder Diagnostic Module (BDD-DM) and symptom severity was recorded using the Yale Brown Obsessive Compulsive Scale Modified for Body Dysmorphic Disorder (BDD-YBOCS) (Phillips et al., 1997).

BDD patients were excluded if they had a past or current psychotic disorder, obsessive compulsive disorder, bulimia nervosa, anorexia nervosa, alcohol or substance abuse history,

intellectual/cognitive impairment, metal implants or neurological disturbance. Furthermore, BDD participants were excluded if they had an alternative comorbid mental disorder that was considered to be their primary diagnosis, ensuring that all individuals in the patient sample had BDD as their primary concern. As BDD shows very high rates of psychiatric comorbidity (Phillips et al., 2007), our exclusion criteria was calibrated to obtain a highly representative sample while ensuring that BDD was the primary diagnosis. Because primary diagnosis can be difficult to delineate when there is comorbid OCD, individuals with OCD were excluded whereas individuals who also fulfilled the criteria of social phobia or major depression were allowed, given that BDD was clearly their primary diagnosis.

Healthy controls were sourced from a voluntary healthy research database, comprising members of the public. The control group had no personal or family history of a mental disorder and met the same exclusion criteria as for the BDD group. All participants had a Wechsler Test of Adult Reading (WTAR) premorbid IQ score of >80, and all had English as their preferred language.

Participants were assessed with the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) to evaluate the presence or absence of other mental disorders. Handedness was assessed with the Edinburgh Inventory (Oldfield, 1971), and the Zung Self-Rating of Depression Scale (Zung, 1965) and the Social Interaction Anxiety Scale (SIAS) (Brown et al., 1997) measured depression and social anxiety, respectively. Group comparisons were computed using an independent sample t-tests at $p = .05$.

MRI data acquisition

A 3T Tim Trio Siemens MRI scanner was utilized at the Murdoch Research Institute (Royal Children's Hospital, Melbourne). The resting state scan consisted of 160 T2*-weighted, gradient echo, echo-planar images, acquired over 6.5 minutes (TR = 2400ms, TE= 40ms). Thirty-six 3mm interleaved slices were acquired with a 210mm FOV and 64x64 acquisition matrix giving a 3.3x3.3 mm in-plane resolution. A 3D T1-weighted MPRAGE sagittal volume sequence (176 slices; slice thickness = 1mm; TE = 2.15ms; TR = 1900ms; field of view = 256 mm; in plane resolution 1 x 1 mm^2) was used for co-registration of the functional resting-state scans. A gradient echo sequence (TR=501ms TE1= 5.19ms TE2=7.65ms) was acquired to produce phase and magnitude images for distortion correction.

Resting state functional connectivity analysis

Resting state fMRI data were processed using SPM8 (Wellcome Department of Imaging Neuroscience). Images were distortion corrected using field map, realigned, slice time corrected, normalised to the MNI, space spatially smoothed with a 6mm kernel and band-pass filtered (0.009-.09 Hz). Additionally, potential temporal confounds were regressed from the bold time series using the aCompCor strategy (Behzadi et al., 2007) as implemented in the Conn Toolbox (Whitfield-Gabrieli & Ford, 2012). Significant movement related covariates as well as white matter and CSF covariates were removed.

All functional connectivity analyses was performed within the CONN toolbox. ROI to ROI analysis was performed using all Brodmann areas. Additional ROIs were also included based on our hypotheses. These included striatal seeds, as defined in Di Martino et al. (2008) and

orbito-frontal ROI's as defined in the AAL atlas, as well as additional subcortical ROI's used for the amygdala, caudate and hippocampus. Default mode network seeds, as supplied with the CONN toolbox were also used. The average BOLD time series was computed across all voxels for each ROI. A complete voxel to voxel correlation matrix was then computed for each participant using bivariate correlation. Correlation coefficients were converted to normally distributed z-scores using the Fisher transform to allow them to be used in a second level general linear model analysis. BDD patients and controls were compared using a 2 sided t-test between each ROI and every other ROI. Correction for multiple comparisons was via false discovery rate (FDR) corrected p-values (p <0.05). In addition, we examined whether depression or anxiety scores influenced FC using ANCOVA, as described below.

Results

Clinical and demographics

Demographic and clinical data are displayed in Table 12. The mean age of the BDD participants was 34, ranging from ages 20 and 64. The mean age of the control participants was 30, ranging from ages 19 and 51. The clinical data indicate that mean BDD severity was in the "moderate" range which is defined as scores between 16 and 30 on the BDD-YBOCS (Phillips et al., 1997). Scores below 15 indicate “mild” BDD symptoms and scores from 31 to 48 are defined as “severe” symptoms. At the time of MRI acquisition our sample comprised two participants in the mild range, twelve with moderate symptoms, and three in the severe range. The depression scores as measured by Zung depression ratings scale indicate that the BDD sample had a higher level of depressive symptoms compared to controls. On average the BDD

group fell in the subclinical range of depressive symptoms, defined as a score below 50 (Zung, 1965). A score between 50 and 59 on the scale represents mild depression, scores between 60 and 69 indicate moderate symptoms and above 70 indicates severe symptoms (Zung, 1965). The SIAS scores showed that the BDD sample had a moderate level of social anxiety symptoms, lower than usually reported for people diagnosed with social phobia but higher than other anxiety disorders (Peters, 2000); this pattern is typical of BDD samples (Coles et al., 2006).

Table 12. Demographic and Clinical Variables

	BDD (mean ± SD)	**Controls (mean ± SD)**	**Group Comparison^ (df = 33)**
Demographic Characteristics			
- Age (Years)	34.0 ± 12.0	30.56 ± 10.0	>.05
- WTAR IQ estimate	106.65 ± 9.99	110.78 ± 6.69	>.05
- Handedness (L/R)	3/14	3/15	>.05
- Gender (M/F)	6/11	6/12	>.05
Clinical variables			
- BDD severity (BDD-YBOCS)	23.59 ± 7.14	-	
- Duration of illness (Years)	10.36 ± 6.9	-	
- Depression (Zung)	48.12 ± 10.27	23.78 ± 8.5	***p* < 0.001**
- Social Anxiety (SIAS)	41.12 ± 18.09	16.39 ± 3.84	***p* < 0.001**

^ Group comparisons were either independent t tests or Chi-squared depending on type of data

Assessment with the MINI showed that three BDD participants also fulfilled the diagnostic criteria for current major depressive disorder or dysthymia, and five had current

agoraphobia or social phobia, showing that our sample reflected a typical BDD profile (Coles et al., 2006). Areas of aesthetic concern for our sample were generally the face, skin and hair. All but two members of the BDD sample were taking psychoactive medication: four where taking quetiapine, three escitalopram, two duloxetine, two desvenlafaxine, one diazepam, and one each paroxetine, mirtazapine, lorazepam, methylphenidate, sodium valproate or clomipramine.

ROI-ROI

Second level analyses were conducted to perform between-groups comparison of Functional Connectivity (FC) for ROI-ROI. Two-tailed t-tests (FDR corrected; $p < 0.05$) were performed for each ROI-ROI comparison, contrasting functional connectivity between BDD patients and healthy controls. There were no significant FC differences between BDD and control participants between the inferior, medial, middle, and superior OFC's, with the inferior and superior ventral and dorsal striatal regions. The most prominent finding in the current study was the altered FC between various cortico-limbic structures, particularly the medial temporal lobe structures of the left amygdala and right hippocampus. The results of the two-tailed t-tests between BDD and control participants showing interregional correlations of functional connectivity are depicted in Table 13 below. In addition, the amygdala and hippocampal connectivity differences are depicted graphically in *Figure 25* and *Figure 26*.

Table 13. Analysis of Significant ROI-ROI correlations

ROI	ROI target	Beta	T(33)	P (corrected)
L Amygdala	BA23 L PCC	0.21	4.30	0.01
	BA31 L PCC	0.17	3.98	0.01
	BA23 R PCC	0.21	3.86	0.01
	Precuneus	0.17	4.25	0.01
	L medial orbitofrontal cortex	0.21	3.99	0.01
	BA29 ACC	0.19	3.66	0.01
	L medial prefrontal cortex	0.19	3.62	0.03
BA17 L Primary Visual Area	BA17 R primary visual area	0.16	4.69	0.006
	L Putamen	0.18	3.80	0.04
R Hippocampus	BA9 L dorsolateral prefrontal	-0.22	-4.3	0.02
	BA24 L ACC	-0.25	-3.86	0.03
	BA32 L ACC	-0.21	-3.78	0.03
BA 43 L subcentral region / primary somatosensory cortex	BA4 R primary motor area	-0.30	-4.63	0.007
	BA4 L primary motor area	-0.25	-3.79	0.02
	BA3 R primary somatosensory area	-0.24	-3.78	0.02
	BA 43 R subcentral	-0.34	-3.72	0.02

Note: corrected for False Discovery Rate Correction; Beta = Fisher-transformed correlation coefficient (r); L=left, R=right; BA= Brodmann's Area. PCC – Posterior Cingulate Cortex, ACC – Anterior Cingulate Cortex

The data in Table 13 shows that, when comparing BDD and healthy control participants, the left amygdala had greater FC with the left and right posterior cingulate cortex (PCC), precuneus, left medial orbitofrontal cortex, anterior cingulate cortex (ACC) and left prefrontal cortex in the BDD participants. In addition the left primary visual area (i.e. BA 17) also had increased FC with right primary visual area (BA 17) and left putamen in the BDD participants. In contrast, the right hippocampus had reduced FC with the left DLPFC and left ACC in the BDD participants; whilst the left primary somatosensory cortex had reduced FC with right primary somatosensory cortex and left and right primary motor area in BDD.

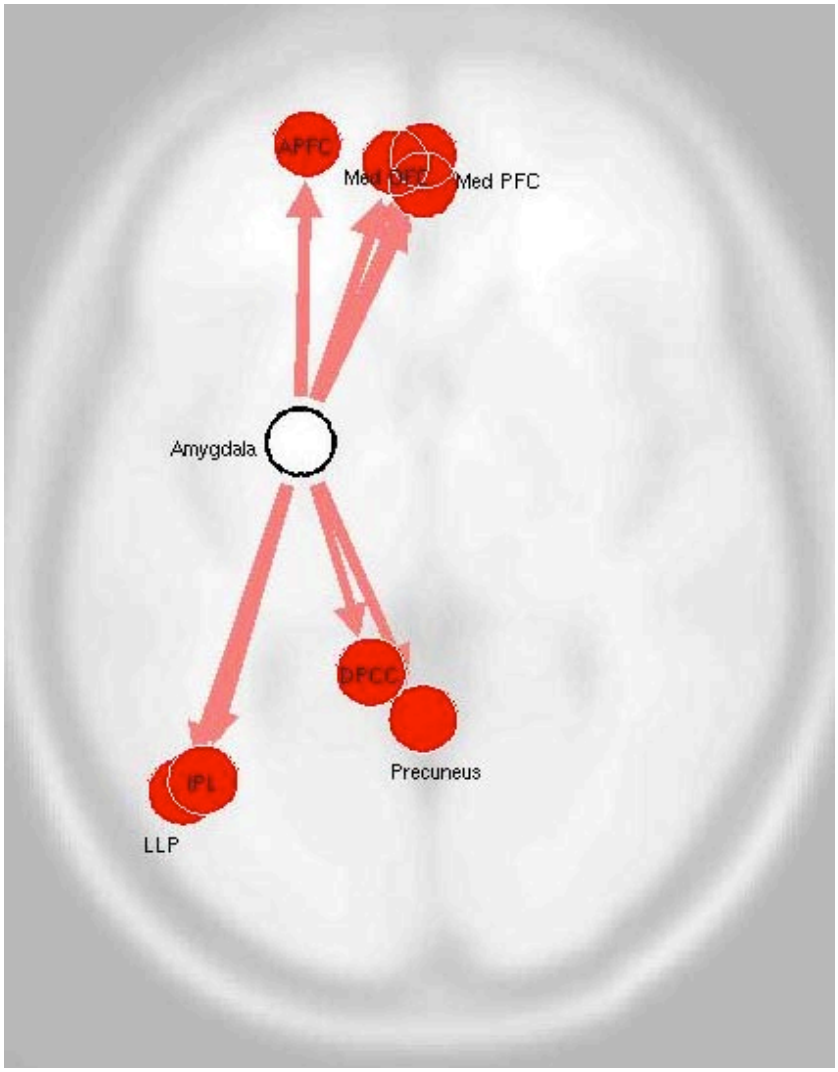

Figure 25. Left amygdala functional connectivity, contrasting patients and controls.

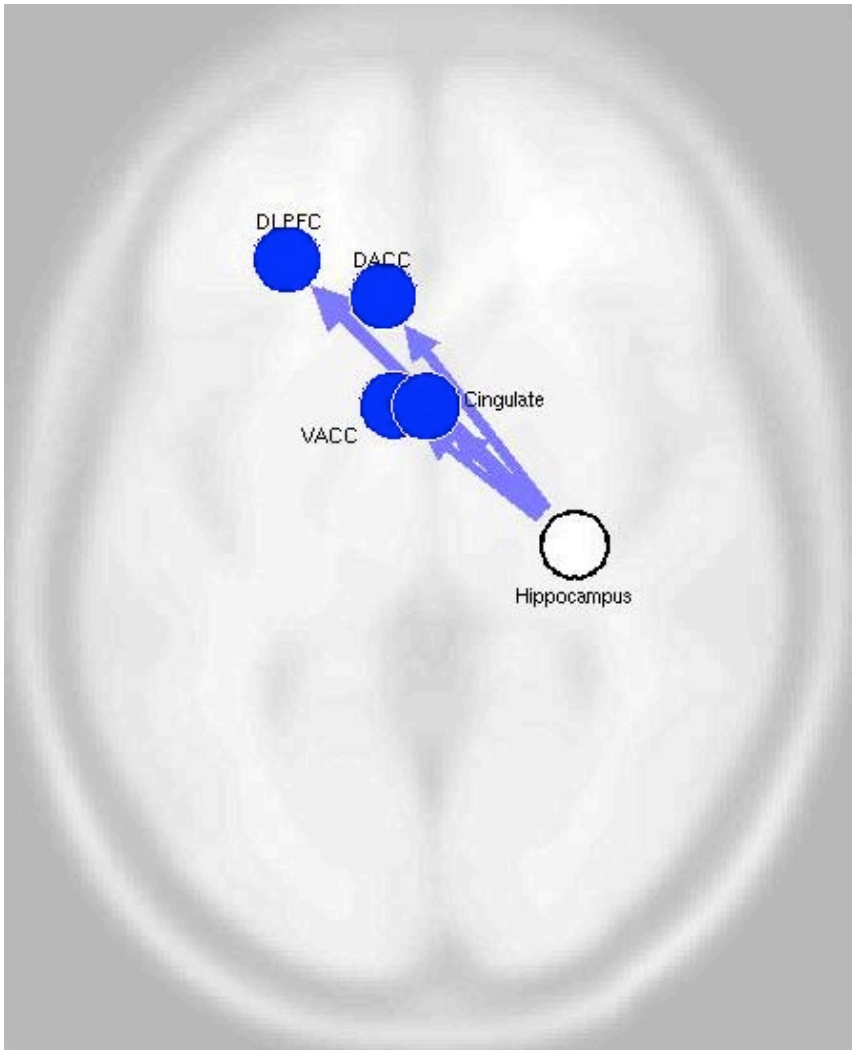

Figure 26. Right hippocampal functional connectivity, contrasting patients and controls.

The equivalent of two one-way analyses of covariance (ANCOVA) were also performed in CONN connectivity toolbox to regress out the effects of individual performance on the Zung Self-Rating of Depression Scale (Zung, 1965) and Social Interaction Anxiety Scale (SIAS) (Brown *et al.*, 1997). There was no change to the reported data using the Zung depression scores. However, when SIAS was investigated the reduction in right hippocampus and left DLPFC FC in BDD became more significant (Beta = 0.29, t = 4.84, $p_{\text{corrected}} = 0.004$).

Discussion

As far as we are aware, this is the first study to employ resting-state functional connectivity magnetic resonance imaging (fcMRI) to study Body Dysmorphic Disorder (BDD). The findings provide preliminary evidence of altered intrinsic connectivity within some of the major grey matter structures of the brain. However, contrary to expectations, our study did not support the frontostriatal hypothesis of BDD; a hypothesis based on studies in OCD that found patients to display altered orbitofrontal (OFC) and striatal activity as well as a previous resting-state investigation using fcMRI that found altered OFC-caudate FC to predict OCD symptom severity scores (Harrison et al., 2009).

The main finding in the current study is the increased FC between fronto-limbic regions. This finding supports a previous BDD investigation using diffusion tensor imaging, which found a reduction in the fractional anisotropy (FA) of the uncinate fasciculus; a major white matter tract involved in fronto-amygdala connectivity (Buchanan et al., 2013). That is, given that fronto-amygdala interaction is largely inhibitory (especially medial PFC - amygdala connections), the reduced microstructural integrity of this pathway identified using DTI (Buchanan, et al., 2013) would reduce the capacity for frontal regions to down regulate limbic activity. Such findings have also been reported in Generalized Anxiety Disorder (Phan et al., 2009; Do et al., 2012).

Amygdala functional connectivity (FC)

We found greater positive FC of the left amygdala and the left medial OFC. This finding is important, considering the OFC has an important neuromodulatory role in mediating threat

perception, negative affect, cognitive dysregulation and biases in emotion processing, via the amygdala (Barrett, et al., 2007; Ochsner, et al., 2002). A previous resting-state functional connectivity fMRI study of Social Anxiety Disorder (SAD) found a similar pattern of hyperactive functional connectivity between the left OFC and amygdala (Hahn et al., 2011). Furthermore, the connectivity between these two regions predicted social anxiety scores (although there was no such relationship with anxiety symptoms in the current study). A brain volumetric study of OCD patients found a significant reduction in bilateral OFC and amygdala volumes between patients with OCD and controls (Szeszko et al., 1999). Although speculative, it may be that smaller brain volumes in these regions results in a compensatory action that increases the functional coupling as represented by resting-state hyper-connectivity in the current study (e.g. Kim, Gee, Loucks, Davis, & Whalen, 2011).

There is a link between OCD and BDD in terms of symptomology and demographic factors (Labuschange et al., 2013; Phillips et al., 2007; Neziroglu et al., 1999), and SAD is a common comorbidity (Coles et al., 2006), which is evidenced by the moderate levels of social anxiety scores in the current BDD cohort. Therefore, it is conceivable that similar pathophysiological abnormalities may be occurring between these disorders, representing a potential phenotype that is common amongst disorders involving emotional dysregulation and/or impaired social functioning.

The finding of an increased FC between the left amygdala and medial PFC (mPFC) in the current study is also an important finding in anxiety disorders. For example, a recent study of social anxiety showed that individual anxiety levels correlated with the strength of FC between the mPFC and amygdala (Kim et al., 2011). In previous task-based fMRI studies, the mPFC was thought to play a regulatory action on the amygdala (e.g. Hariri, Mattay, Tessitore, Fera, &

Weinberger, 2003), and this is supported by FC data showing that greater connectivity in these regions predicts lower anxiety scores (e.g. Pezawas et al., 2005) Furthermore, studies provide direct physiological support for the role of the mPFC on reducing fear responses by reducing amygdala output (Milad, Vidal-Gonzalez, & Quirk, 2004). Therefore, mPFC-amygdala connectivity may play a crucial role in emotion regulation, dysregulation of which may contribute to sustaining threat-related emotional processing biases in patients with anxiety disorders, whereby the normal extinction of a fear response is not attenuated (Akirav & Maroun, 2007). Furthermore, this mPFC regulates the output from the central amygdala through the excitation of GABAergic neurons in basolateral complex of the amygdala (Rosenkranz & Grace, 2002), suggesting the involvement of this neurotransmitter pathway in BDD.

The involvement of the parietal lobes in BDD has been documented in an early single photon emission computed tomography (SPECT) study, which showed relative perfusion deficits in the parietal lobules (Carey et al., 2004). The current study found an increased FC between the left Inferior Parietal Lobe (IPL) and the left amygdala. The IPL has also been associated with the perception of body image, particularly in studies of anorexia nervosa (AN). For example, an fMRI study of body image distortion in AN showed that patients showed significantly increased bilateral IPL activity during presentation of digitally altered pictures of their own bodies (Wagner, Ruf, Braus, & Schmidt, 2003). The IPL has a role in the perception, and the amygdala plays an affective component in body image distortions, abnormalities in which have been shown to contribute to excessive unpleasant responses towards body image in AN (reviewed by Gaudio & Quattrocchi, 2012). Both BDD and AN have distorted body image as a core symptom, thus this finding may add support for the pathophysiological link between these two disorders in terms of the underlying disturbances in body image processing.

Hippocampus functional connectivity (FC)

Damage to the right hippocampus has been associated with a decrement in performance on non-verbal memory indices (Gleiβner, Helmstaedter, & Elger, 1998) as well as short-term memory deficits for spatial associations (Piekema, Kessels, Mars, Petersson, & Fernández, 2006). The results of the current study show a decrease in FC between the right hippocampus and left DLPFC. Previously, communication of these regions has been associated with spatial working memory (Wang & Cai, 2006). Neuropsychological research in BDD has suggested a potential deficit in spatial working memory compared to healthy controls (Dunai et al., 2010), and another study found that BDD patients performed poorly on a free recall version of the Rey-Osterrieth Complex Figure Test (RCFT) even after partialling out for the effects of their aberrant organizational strategies at encoding. Therefore, the results of the current study may support the presence of higher order memory deficits, particularly for spatial associations, which may be associated with hypoactive communication between the DLPFC and hippocampus that are evident in the resting-state.

After partialling out the effects of SAIS score, the analysis revealed that the decrease in FC between the left DLPFC and right hippocampus remained significant. Therefore, it seems that the aberrant connectivity between these two regions remains a significant effect when controlling for variation in social anxiety scores across the participants in the current study, and may potentially represent a more enduring FC pattern that separates BDD and healthy controls.

The current study also showed a decrease in FC of the right hippocampus with the left-hemisphere ventral and dorsal ACC regions. In a recent volumetric MRI study, bilareral ACC volumes were found to be decreased in BDD patients compared to controls (Atmaca et al., 2010).

Also, in studies of OCD, hyperactivity of the ACC has been associated with symptom provocation (Breiter, et al., 1996), which seems to normalize after successful treatment of OCD (Perani et al., 1995). The ventral ACC plays a role in the identification of emotional significance of stimuli, as well as the production of a corresponding affective state in response to the stimuli. In contrast, the dorsal ACC has been suggested to exert a modulatory role of affective states on the ventral ACC, while the hippocampus is also engaged in this regulatory process (Sotres-Bayon, et al., 2004). The results of the current study may indicate a potential defect in this system of normal emotion perception and regulation, which is related to improper communication between these regions.

Visual system

The results showing differences in synchrony between the left and right primary visual areas and the left putamen may be indicative of the visual concerns central to BDD. The primary visual cortex transmits information via two primary pathways, the ventral and dorsal streams. In the dorsal stream, information travels through to the posterior parietal cortex, and is associated with motion and spatial relations. The visual association cortex, however, is involved in more complex higher order processing of visual information, and in particular, processing of complex visual information such as faces, hands, or abstract forms (Tanaka et al., 1991), areas of visual processing that have been implicated in the pathology of BDD (e.g. Feusner et al., 2007; 2010; 2011).

The current study was not able to infer how the visual cortical abnormalities are associated with any specific pathophysiological process in BDD. That is, we cannot infer whether the abnormalities represent pure visual cortical abnormalities, or whether there is a top-

down influence from higher order affective, cognitive control, or perceptual systems. Nonetheless, abnormal functional connectivity in the visual areas supports previous neuroimaging studies in BDD that have found variable discrepant abnormalities in task based activation of the visual systems (Feusner et al. 2010). Our findings provide evidence of an underlying defect in the visual system which prevails without subjecting participant to any overt task, indicative of the utility of resting-state fcMRI in detecting more enduring aspects of these deficits.

Limitations

Although hypothesized based on previous task-based fMRI research in BDD (Feusner et al., 2010) and fcMRI data in OCD (Harrison et al., 2009), as well as the link that OCD has with BDD, the current study did not find FC differences in OFC-striatal regions between healthy controls and BDD patients. The research conducted by Harrison and colleagues displays critical differences to the current investigation in terms of factors including research design, such as parcellating the striatal regions for each individual participant. This technique has been suggested effective in detecting striatal connectivity differences (Di Martino et al., 2008), and may therefore have rendered their investigation more sensitive to changes in frontostriatal FC. In addition, our study controlled for diagnosable aspects of OCD, that is, there was no detectable OCD comorbidity in our BDD sample, a critical factor that may have contributed to our inability to detect frontostriatal FC differences.

Suggestions for future research

The phenomenology of BDD is such that patients suffer from a fundamental visuo-perceptual abnormality, with facial features being the common focus of their disconcertion. Previous neuroimaging studies using task-based fMRI have indeed revealed aberrant processing of facial information in BDD patients (Feusner et al., 2007; 2010). An important question to address is, whether these individuals possess an underlying deficit in the brain networks specializing in the processing of faces whilst not engaging in any specific task. To address this question, the use of functional connectivity fMRI in delineating specific resting-state networks (RSN's) is an attractive tool. Zhang et al. (2009) for example, utilized fcMRI to compare activations of facial responsive regions of interest with object responsive regions of interest, and in effect were able to reveal a distributed cortical network specific to perception of faces at rest. Future investigations into BDD may employ this method to determine whether any differences exist in the FC in this particular RSN, and whether it is correlated with facial perception tasks. In addition, to further investigate aberrant facial processing in BDD, one may utilize eye-tracking devices in order to follow the specific ocular movements that may be suggestive of detailed searching behaviour, which has not been thoroughly explored in BDD neuroimaging and neuropsychological research.

Conclusion

We believe this is to be the first study to examine resting-state functional connectivity using fMRI in a BDD sample. The main contribution of our data is that it provides evidence that several frontal and limbic regions of interest show altered functional connectivity when comparing BDD and healthy control participants. The nature of the findings supplements the

converging evidence that BDD may lie on a spectrum of anxiety disorders other than OCD, and this is evidenced by the findings of aberrant connectivity in fronto-limbic regions involved in regulation and processing of emotion and social cognition. In addition, the current study lends support to the view that BDD patients indeed have defective visual systems that are present without any formal task activation.

Chapter 10

General Discussion and Conclusions

This chapter aims to summarise the key findings established in the three empirical papers in this thesis; Chapter 6, Chapter 8 and Chapter 9. To this end, a general summary of significant results is provided, as well as additional discussion topics that were not presented in the published manuscripts. The results from each study will be separately discussed in terms of the neurobiological models presented in Chapter 3. The strengths and weaknesses of each imaging modality to test specific hypotheses will also be examined.

This is followed by a discussion of how these findings can collectively inform the neurobiological understanding of BDD, and in essence, support or refute neurobiological models. Furthermore, the potential nosological implications in terms of BDD's relationship to OCD will be considered. Finally, limitations of this research are highlighted, possible therapeutic applications are reflected upon, future research directions are proposed, and overarching conclusions are made.

Summary of Structural Study Results

The volumetric study presented in Chapter 6 aimed to provide robust regions of interest data in BDD, both hypothesised and exploratory regions were presented, offering a rich dataset. Volumetric changes are proposed to be indicative of altered cognitive functioning and may underpin the phenomenology and symptomatology of the disorder. The main finding was that there were reduced volumes in BDD in the right orbitofrontal cortex (OFC) and left anterior cingulate cortex (ACC). The bilateral thalamus, left hippocampus and amygdala were also

smaller in the BDD group, although these differences were no longer significant when covarying for total brain volume. Likewise, BDD had smaller lobar volumes, in the right frontal, right parietal, left temporal and left occipital lobes, however, these reductions occurred in the context of globally reduced volumes rather than being strongly lobe-specific.

As well as examining *a priori* hypotheses based on past literature, the FreeSurfer method allowed for a rich exploratory investigation into brain volumes, with 139 regions (and subregions) for each participant measured. These findings revealed that right superior parietal, right precuneus, right lateral OFC and left caudal ACC were significantly smaller in the BDD group compared to controls. However, given the high number of multiple comparisons and the likelihood of type 1 errors, confirmation in future research is needed.

Overall, these results are broadly consistent with other anxiety disorders (Koolschijn, et al., 2009; Syal, et al., 2012), and there is a growing consensus that grey matter changes associated with anxiety-related psychiatric disorders are structural preconditions rather than consequences or side effects of these pathological states (Kühn, et al., 2011). In contrast to past findings, the current research found a trend towards smaller thalamus volumes whereas other BDD (e.g. Atmaca, et al., 2010) and OCD research (e.g. Atmaca, et al., 2007) has found a trend toward increased volumes. This difference is counter to the idea that both OCD and BDD might share the same phenotype characterized by increased thalamus volumes among general grey matter volume reductions, as proposed in Chapter 3.

Broadly, the structural findings of reduced OFC, ACC and amygdalae volumes support the fear circuitry hypothesis (page 60) most strongly, followed by the frontostriatal hypothesis (page 65). There was a degree of consistency between OCD and BDD volumetric findings,

however these findings only provide tentative support for the cortico-striatal-thalamo-cortical (CSTC) circuitry model (page 67), as reduced OFC and ACC volumes are consistent with this model, whereas, as noted, the thalamus findings are inconsistent.

Anterior cingulate cortex (ACC)

Two lines of discussion regarding the ACC were not pursued within the paper but nevertheless are important to consider in this thesis. First, the analysis of left versus right ACC asymmetry. Second, the distinction between different regions within the ACC. These two points will be considered in further detail over the next few paragraphs.

As reported in the paper, BDD participants had statistically significant smaller volumes in left ACC, compared to controls. Further analysis not included in the paper reveals that on average the left ACC was reduced by 13% while the right was reduced by only 4.3%, compared to controls. ACC asymmetry was statistically examined by subtracting the left from right ACC volume across both groups to create asymmetry metrics, which were then statistically tested with an analysis of variance. This showed a trend towards disproportionately asymmetrically reduced volumes on the left side ($F=3.3$, $p = 0.077$). Although not meeting the 0.05 statistical threshold, this finding is consistent with past research, with a trend towards the left ACC having disproportionately reduced volumes compared to the right, documented in both BDD (Atmaca, et al., 2010) and OCD (Atmaca, et al., 2007). In the present research, this occurred despite the left ACC being slightly larger than the right in raw terms in the BDD group (given that the left ACC was significantly larger in controls).

The second finer point about the ACC is a dissection of one of the *a priori* hypotheses; that there would be significantly smaller ACC volumes in the BDD group. To produce the total ACC volumes two smaller volumes, the rostral and caudal ACC were summed. While the main analysis revealed significantly smaller left ACC volumes, the exploratory analysis statistically examined these two areas separately, and showed that the left caudal ACC was significantly smaller whereas the rostral section was not. In fact, the difference in the total ACC could be accounted for entirely by the difference in the caudal section.

The distinction between the caudal and rostral areas is important given that the two sections are thought to have different functions: the caudal (a.k.a. dorsal) part of the ACC is connected to the prefrontal cortex, parietal cortex as well as the motor system, making it a central station for processing top-down and bottom-up stimuli, and an important component in attention, cognitive control and "error signals" (Sotres-Bayon, et al., 2004). Indeed, the caudal section of the ACC has also been specifically implicated in OCD (Rotge, 2010; Venkatasubramanian, et al., 2012).

Our finding that the caudal ACC was significantly smaller in the BDD group is important when considering the neurocognitive hypothesis of heightened "error signals" introduced in Chapter 3. The overall evidence and discussion of the error detection hypothesis will be further elaborated in light of the current data on page 206.

By contrast to the caudal section, the rostral (a.k.a. ventral) part of the ACC is functionally connected to the amygdala, nucleus accumbens, hypothalamus, and anterior insula, and is involved in assessing the salience of emotion, regulating emotion and motivational processing. This section has been shown to be important in depression and there has even been

speculation that it represents a biomarker for the illness (Boes, McCormick, Coryell, & Nopoulos, 2008). Our findings that this area was similar in volume to controls suggests that it is not important to BDD symptoms, and indeed, given its connections to the limbic system, suggests that it is not the root of the fear circuitry problems in BDD, as proposed in Chapter 3.

Bilateral fusiform gyrus

Another exploratory finding that was relevant to the symptomatology of BDD was the finding of smaller bilateral fusiform gyrus volumes compared to controls. This was not discussed in the paper itself so will be briefly examined here. While this area did not meet the strict statistical threshold ($p < .01$) employed in the exploratory analysis, given that the differences were bilateral and relevant for a major neurobiological model in BDD, they are perhaps worth examining further.

The fusiform gyri are central to our face processing network, allowing recognition of faces in general and also perception of emotions conveyed via faces, a task in which BDD participants are known to have deficits (Buhlmann, et al., 2006). Our findings of reduced bilateral volumes in this area lend support to the visual and face processing hypothesis proposed in Chapter 3, although given the exploratory nature of this finding further evidence is needed.

In summary, the volumetric study showed a general reduction in grey matter volumes consistent with other psychiatric disorders, and highlights the importance of the OFC and ACC in BDD. The contribution of high quality evidence provides tentative support of varying levels for the error detection hypothesis, visual and face processing hypothesis, frontostriatal hypothesis and CSTC hypothesis. The findings relevant to the fear circuitry hypothesis were

inconsistent, with reduced amygdala volumes supporting it but the rostral ACC showing no change. The volumetric method was not able to provided support for the disconnection hypothesis (introduced in Chapter 3) given that this method is not conducive to testing this theory.

Summary of Diffusion Tensor Imaging (DTI) Results

In contrast to the region of interest study which investigated grey matter structures, the diffusion tensor imaging (DTI) research presented in Chapter 8 addressed the question of white matter connectivity within BDD. The study used the high quality DTI data with the largest BDD neuroimaging sample to date. The results of the study showed that BDD patients exhibited widespread significant reduced white matter integrity compared to controls, as represented by fractional anisotropy (FA). The results included reduced FA in the corpus callosum, superior longitudinal fasciculus, and inferior fronto-occipital fasciculus, bilaterally (these areas were reviewed in Chapter 7). The only other DTI study to examine BDD participants also found reduced FA in the superior longitudinal fasciculus, and inferior fronto-occipital fasciculus, although differences in this study did not reach statistical significance (Feusner, et al., 2013).

The widespread FA reductions in the BDD group, particularly in white matter tracts with diffuse connections such as the corpus callosum and superior longitudinal fasciculus indicate a general degradation of brain connectivity. Thus, these findings lend support to the disconnection hypothesis proposed on page 55. This model proposes that BDD symptomatology (such as emotional dysregulation and lack of insight) and phenomenology (cognitive deficits) is a result of a general disconnection between distinct areas.

Of particular note in the context of specific BDD symptomatology was the reduced integrity of the right uncinate fasciculus (detailed on page 139). Its connections to the amygdalae, hippocampus and frontal regions and role in trait anxiety (Kim & Whalen, 2009) has led to it often being considered to be part of the limbic system. Important to the fear circuitry hypothesis in BDD, the uncinate fasciculus has a central role in top-down regulation of amygdala reactivity to control negative affect and mediate threat perception (Barrett, et al., 2007; Kim & Whalen, 2009; Ochsner, et al., 2002; Phan, et al., 2009).

Another finding that is important in the context of CSTC hypotheses was the reduced FA in the anterior thalamic radiation, given that it connects the frontal lobe and the thalamus (as discussed on page 142). Indeed, white matter degradation in this area has been shown in patients with OCD (Chiu, et al., 2011; Jayarajan, et al., 2012), and FA has been shown to increase after 12 week citalopram treatment (Yoo, et al., 2007). Thus, our findings of reduced FA in the left anterior thalamic radiation represents support for the CSTC model of BDD proposed in Chapter 3.

Overall, the DTI study's contribution to the literature was substantial, with widespread reductions in brain connectivity shown. Indeed, the data compellingly supports the disconnection hypothesis. In addition, although perhaps overshadowed by the disconnection hypothesis, the fear circuitry hypothesis and the CSTC hypothesis were also supported. Furthermore, the correlation data between symptom severity and FA suggests that white matter differences constitute a structural precondition to the development of BDD which is largely state independent.

Summary of Resting State Results

This study was the first to have utilized resting-state functional connectivity magnetic resonance imaging (fcMRI) in a BDD sample. It used 17 BDD participants from the other two studies because one participant withdrew due to anxiety and did not complete the scanning sequence, and there were problems with the acquisition of two other BDD scans due to motion artefact. There were no significant functional connectivity (FC) differences between BDD and control participants between the inferior, medial, middle, and superior OFC's, with the inferior and superior ventral and dorsal striatal regions. The absence of FC differences therefore failed to support the frontostriatal or CSTC hypotheses.

The most prominent finding in the study was the altered FC between various cortico-limbic structures, particularly the left amygdala and right hippocampus of the medial temporal lobe. The left amygdala had greater FC with the left and right posterior cingulate cortex (PCC), precuneus, left medial orbitofrontal cortex, anterior cingulate cortex (ACC) and left prefrontal cortex in the BDD participants. The right hippocampus had reduced FC with the left DLPFC and left ACC.

The abnormalities in the fronto-amygdala and hippocampal connectivity are supportive of alterations in the fear circuitry model, as outlined in on page 60. The mPFC-amygdala connectivity plays a crucial role in emotion regulation whereby the normal extinction of a fear response is attenuated (Akirav & Maroun, 2007), dysregulation of which may contribute to sustaining threat-related emotional processing biases in patients with BDD. This is a model that has received support in other anxiety based disorders, including social phobia (M. Stein, et al., 2002) and OCD (van den Heuvel et al., 2004), suggesting that fronto-amygdala dysfunction is a

common abnormality among these disorders. However the dominant hypothesis in OCD is alterations in cortical-striatal systems rather than cortico-limbic, though functional connectivity alteration to the amygdala have been shown to be related to aggression symptoms in OCD samples (Harrison et al., 2012).

In addition, this study revealed preliminary evidence of improper communication within the visual systems in BDD, even without the presence of any overt task performance. This finding supports the visual and face processing hypothesis proposed in Chapter 3, page 57. The left and right primary visual areas had reduced synchronous FC, going some way to explain the difficulties individuals with BDD have with integration of holistic and detailed visual information (Deckersbach, et al., 2000).

Nevertheless, these visual system findings combined with the emotion regulation circuitry in this study could be the basis for two of the main symptoms of BDD, a fixation of visual appearance and emotional dysregulation. Disturbances in the visual system could be the key differentiating factor between BDD and other anxiety disorders. In terms of other hypotheses, the disconnection model received partial support, with FC increases possibly implicating problems with inhibitory pathways while FC decreases suggesting degradation in excitatory pathways. The evidence did not support the CSTC hypothesis and thus has little explanatory power in regards to the compulsive behaviours exhibited by BDD participants.

Table 14. Summary of Results Linked to Supported Hypotheses from the Three Imaging Studies.

Study	Results	Model
Volumetric	Global Reduced volumes	
	Right OFC	*Frontostriatal circuits*
	Left caudal ACC	
	Bilateral Thalamus	*CSTC circuitry*
	Left hippocampus	
	Left amygdala	
	Right parietal +precuneus	*Disconnection hypothesis*
	Bilateral fusiform gyrus	
DTI	Widespread FA reductions	*Visual and face processing hypothesis*
	Corpus callosum	
	Superior longitudinal fasciculus	
	Inferior fronto-occipital fasciculus	
	Right uncinate fasciculus	*Fear circuitry hypothesis*
	Anterior thalamic radiation	
fcMRI	Cortico-limbic connectivity differences	
	Reduced visual cortices synchronisation	*Error detection hypothesis*

Neurobiological Models of BDD

The previous section summarised the results from the three imaging modalities. This section furthers the discussion by approaching each hypothesis in term and synthesising the results to provide an overall perspective about the evidence for each hypothesis. Past data will also be combined with the evidence established in our three empirical papers. In addition, given that all three imaging modalities implicated the precuneus, this brain region's relevance to BDD will also be examined.

Disconnection hypothesis

The broadest hypothesis proposed in Chapter 3 was the disconnection hypothesis. This hypothesis was also the most strongly supported, with the DTI data strongly suggesting that there were compromised white matter fibres that reduces the efficiency of information travelling between grey matter areas. Indeed, this was reflected in the functional connectivity differences found in BDD. Both the DTI and fcMRI data, in general, reflect possible disconnections between excitatory and inhibitory pathways in the brain. Such disconnection may be the basis for affective dysregulation and cognitive segregation previously shown in BDD (e.g. Buhlmann, McNally, et al., 2002; Hanes, Andrewes, Smith, & Pantelis, 1996).

The white matter degradation was robust and widespread, such that the other hypotheses that rely on neural circuits could largely be accounted for by general white matter degradation. For example, reduced FA in the anterior thalamic radiation may be of fundamental importance to the CSTC hypothesis, while the uncinate fasciculus' role in top-down regulation of amygdala

may be fundamental for the fear circuitry hypothesis. Likewise, the functional connectivity differences between the amygdala and frontal regions can be thought of as a sign of problems with connection, supporting both the disconnection hypothesis in general and the fear circuitry hypothesis in particular.

The disconnection hypothesis could also explain the visual and face processing differences thought to play a significant role in BDD phenomenology, as proposed in the visual and face processing hypothesis which given that visual and especially facial processing occurs across many different brain regions, disconnection could explain these difficulties, as discussed in the next section.

A combination of the DTI and fcMRI data strongly indicated that the integration of different brain systems may be compromised. This is not to discount the influence of the alternative and more specific hypotheses; however, compromised integration may be the common thread which underpins the range of deficits in BDD. Therefore, disconnectivity may be fundamental to the aetiology of the disorder, as introduced in Chapter 3, page 55.

Visual and face processing hypothesis

The visual and face processing hypothesis was proposed given that BDD could very well be conceptualised as a disorder of visual perception, as individuals focus on a flaw in appearance. All three imaging modalities lent support to the idea that there is dysfunction in visual or face processing circuits, including;

- White matter degradation in the inferior longitudinal fasciculus which connects temporal and occipital regions.

- Bilateral reduction in fusiform gyrus volumes.
- Differences in occipital lobe functional connectivity.

The bilateral volume reduction in the fusiform gyrus is of particular interest given that this area is important for face perception. Indeed, individuals with BDD tend to (but not always) focus on a "defective" facial feature (Buhlmann, et al., 2006), and the face was the most common site of concern in our sample. Furthermore, individuals with BDD have been shown to have deficits in affective facial perception (Buhlmann, et al., 2006; Buhlmann, et al., 2004). Differences in the fusiform gyrus (structurally and functionally) could be the basis by which individuals with BDD become fixated on facial stimuli.

The functional connectivity differences found in the visual cortex are also supportive of the visual processing hypothesis. The reduced synchronization in this area suggests that lower order processing of visual information is compromised, which can then impact on processing of complex visual information down-stream, such as faces or abstract forms (Tanaka et al., 1991). Indeed, past data has implicated these systems in BDD (e.g. Feusner et al., 2007; 2010; 2011).

Moreover, DTI data showing reduced integrity of the inferior fronto-occipital fasciculus, which connections the occipital, temporal and frontal lobes. Face processing occurs via an integration of information from both regions. Thus, disintegration of temporal and occipital regions could cause the significant disruption in face perception which individuals with BDD experience.

This data adds to the growing body of literature that individuals with BDD process visual stimuli differently, through neuropsychological studies and (Deckersbach, et al., 2000) and imaging studies. The detailed bias has been shown in BDD to both pictures of objects (houses)

and faces (Feusner, Moody, Hembacher, Hoffman, et al., 2010). While our fMRI data measured functional connectivity in resting state without any deliberate visual stimuli, previous fMRI studies have shown greater left side activation in the lateral temporal lobe and dorsal anterior cingulate regions for face tasks (Feusner, et al., 2011; Feusner, et al., 2007).

This thesis' data supported the visual and face perception hypothesis by showing that there are differences in the brains of individuals with BDD that are independent from the presentation of visual stimuli and are likely to underlie differences in perception. All three imaging modalities supported the hypothesis, with the resting state fMRI and volumetric data providing the strongest support. Taken together with pervious data, visual system differences could now be considered a core feature of BDD pathophysiology.

Fear circuitry hypothesis

Differences in fear response systems, in particular the prefrontal cortex and the amygdalae, were confirmed with all three imaging modalities. The right OFC which plays an inhibitory role in the fear response had reduced volume. There were differences in the functional connectivity between the amygdalae and cortical areas, and the connection between this area and the amygdalae via the uncinate fasciculus was compromised.

The uncinate fasciculus has a central role in top-down regulation of amygdala reactivity to control negative affect and mediate threat perception (Barrett, et al., 2007; Kim & Whalen, 2009; Ochsner, et al., 2002; Phan, et al., 2009). Given the fact that past neuroimaging research has correlated symptom severity to right amygdala volumes (Feusner, et al., 2009) (though our

T1 study did not find this), the findings of compromised connectivity between the right amygdala and frontal regions are compelling.

The fear circuitry and threat perception model has received support in other anxiety based disorders (Stein & Nesse, 2011), including social phobia (M. Stein, et al., 2002) and OCD (van den Heuvel, et al., 2004), suggesting that fronto-amygdala dysfunction is a common thread among anxiety disorders. Indeed, degradation in white matter connecting frontal regions to the amygdala has also been shown to correlate with anxiety in healthy individuals (Westlye, et al., 2011).

The data from our three studies indicate that there are state independent differences in both brain structure, wiring and functional connectivity. Thus, our data provides neurobiological evidence that BDD has compromised fear circuitry, which may be the basis for fear of social judgement, high levels of anxiety and emotional dysregulation. The social anxiety that individuals with BDD experience could very well be mediated by an overactive amygdala, although the activation of this area during symptom provocation has not been directly tested in BDD.

This fear circuit, and in particular the OFC, is important to extinction learning and may be the basis for the long term concern of a visual feature that individuals with BDD often experience. One explanation of fear acquisition comes from conditioning theory (detailed in Chapter 3). This model suggests that once the concern about a body part is established through pairing of an aversive stimuli (perhaps an angry face), with a neutral stimuli (a body part), a negative association is created with the body part.

In healthy individuals a gradual reduction in fear will occur after repeated exposure to the conditioned stimulus (the body part) without the presence of the unconditioned stimulus (angry face). This process is generally considered to involve the establishment of inhibitory control of the mPFC over the amygdala-based fear process (Marek, et al., 2013; Sotres-Bayon, et al., 2004). Thus, the differences in the connection between the mPFC and the amygdala demonstrated with functional connectivity and DTI data may explain the longevity of aesthetic concern in BDD, where extinction learning does not take place. The disruption to this system might mean that an otherwise transient and normal body image concern develops into BDD. In BDD these disrupted neural circuits may mean that repeated exposure to the body part of concern could have reverse effect, and ultimately become self-perpetuating without appropriate intervention.

The fear and threat perception model is not only compelling on the basis of behavioural theory but also evolutionary theory (Stein & Nesse, 2011). In evolutionary terms heightened threat detection and precautionary responses may have been adaptive for survival. An effective treatment for BDD, CBT (with a focus on exposure and response prevention), partially works by undoing the maladaptive (but evolutionarily advantageous) persistence of a fear response. In neurobiological terms, exposure and response prevention works by activating the mPFC to down regulate hyperactive amygdalae responses, causing fear conditioning extinction. Indeed, this therapeutic technique is explicitly designed to unlearn maladaptive compensatory behaviours (Phillips & Rogers, 2011). Overall, perhaps fear circuitry dysfunction combined with visual system dysfunction might go some way to explain the excessive concern with appearance that individuals with BDD experience.

Error detection hypothesis

The error detection hypothesis posits that symptoms may be a result of the brain's tendency for inappropriate or hyperactive error detection signals, and thus giving rise to the urge for correction such as excessive grooming. This hypothesis is one component of the more comprehensive CSTC hypothesis. The error detection signals are thought to be generated by an internal monitoring system that resides in the anterior cingulate cortex (ACC). While much of the supporting neuroimaging evidence in OCD for this error detection hypothesis comes from fMRI studies during symptom provocation (Fitzgerald, et al., 2005; Nieuwenhuis, et al., 2005), no such evidence exists in BDD. Our data, of reduced ACC volumes in BDD, however, gives some support to this hypothesis and is broadly consistent with past volumetric results in BDD also showing smaller volumes (Atmaca, et al., 2010). As discussed on page 192, our data specifically implicated the caudal section of the ACC which specifically supports the error detection hypothesis.

In terms of BDD symptomatology, this model proposes that fixation on a part of the body (analogous to obsessions in OCD) arises due to increased error signals that leads to pathological doubt accompanied with increased anxiety. The checking behaviours in BDD (analogous to compulsions in OCD) occur as behavioural outputs aiming to relieve or to neutralise the anxiety induced by the error signals. Nonetheless, this relief is transient in the context of persistent error signals; hence, there occurs cyclical reproduction of these maladaptive behaviours. The caudal subdivision of the ACC has been specifically implicated in OCD, and there has been speculation that heightened error detection is a result of caudal ACC pathology (Venkatasubramanian, et al., 2012). Thus, our finding of specific reduction in the caudal section tentatively supports the error

detection model as the genesis of BDD symptoms, as proposed in Chapter 3. However, more data is needed using fMRI during behavioural tasks to more compellingly confirm the theory.

Frontostriatal circuits hypothesis

The caudal ACC findings are also important to the frontostriatal circuit hypothesis. The ACC is connected to the prefrontal cortex, parietal cortex as well as the motor system, making it a central station for processing top-down and bottom-up stimuli and an important component in attention and cognitive control (Sotres-Bayon, et al., 2004; Venkatasubramanian, et al., 2012). The frontostriatal model in BDD has been supported by past neuropsychological studies which have shown cognitive impairments in regards to executive functioning and motor speed (e.g. Labuschagne, et al., 2013).

The volumetric findings of reduced volumes in the caudal ACC and right OFC provide some evidence of compromised frontostriatal systems. In addition, the DTI data suggested that white matter pathways connecting frontal and striatal system were compromised; however the white matter degradation was so widespread that without compelling evidence from the other imaging modalities this hypothesis is not well supported.

In contrast to the hypothesis of the fcMRI study, FC was not different between BDD and controls in frontostriatal regions. Such findings are inconsistent with resting state data in OCD. For example, Harrison et al. (2009) found system-wide differences in functional connectivity of both ventral and dorsal cortico-stiatal systems. These findings, in particular, emphasised the heightened connectivity of ventral caudate/nucleus accumbens with the anterolateral and medical OFC, and found a relationship between symptom severity and cortico-stiatal connectivity. A

subsequent study further supported the frontostriatal hypothesis in OCD (Harrison, et al., 2012), and emphasised that frontostriatal dysfunction may be at the core of OCD neurobiology. Our data failed to replicate these findings, which suggests BDD and OCD have distinct neurobiology. While our evidence did not discount the frontostriatal circuit, it may occur in the context of widespread dysfunction and not be a core pathophysiology.

Cortico-striatal-thalamo-cortical (CSTC) circuitry hypothesis

An extension of the frontostriatal hypothesis, the CSTC hypothesis, also had mixed results. The functional connectivity study did not support the hypothesis. Data consistent with the hypothesis included the reduced volume in the left caudal ACC, reduced OFC volumes and reduced white matter integrity in the anterior thalamic radiation. Much of this data, however, is non-specific in nature. For example, reduced OFC volumes could relate to core pathology in the fear circuitry rather than CSTC circuitry.

An imbalance between the excitatory and inhibitory CSTC systems is thought to increase the activation of the thalamus. Indeed, it is thought that obsessive checking behaviours are "hard-wired" in the thalamus (Saxena, et al., 2008; Ting & Feng, 2011). The thalamus has also been comprehensively implicated in OCD (e.g. Atmaca, et al., 2007; Gilbert, et al., 2000; Hoexter, et al., 2011; Venkatasubramanian, et al., 2012). Past BDD data have shown that the thalamus is the only area with increased volume relative to controls (Atmaca, et al., 2010; Atmaca, et al., 2007). This parallels findings in OCD, where there is a general reduction in grey matter volume in the OFC, ACC, anterior cingulate gyrus and caudate nucleus, but a general increase in bilateral thalamus volumes. In contrast, the current volumetric data found that the thalamus was similarly reduced as other regions, making our data inconsistent with past BDD and OCD data.

One possible explanation is that all our participants were receiving some type of treatment, with 18 out of 20 on medication. Treatment research in OCD shows a normalisation of thalamic volumes after selective serotonin reuptake inhibitor (SSRI)(Gilbert, et al., 2000; Rosenberg, et al., 2000), and normalized activation after cognitive behavioural therapy (CBT) (Saxena, et al., 2008). In fact, reduction of thalamic activity may be fundamental to the improvement in OCD. Thus, the fact that all of our BDD participants were in treatment, though still were rated as having moderate BDD severity on average, may have influenced our results.

Data that was consistent with the CSTC hypothesis was the DTI results of reduced integrity of the anterior thalamic radiation. The anterior thalamic radiation connects the frontal lobe and the thalamus (Mori, et al., 2002). More specifically, it consists of fibres between mediodorsal thalamic nuclei and the frontal cortex, and fibres between anterior thalamic nuclei and the anterior cingulate cortices (Wakana, et al., 2004). White matter in patients with OCD has also shown deficits in the anterior thalamic radiation on a microstructural level (Chiu, et al., 2011; Jayarajan, et al., 2012). In OCD, white matter integrity has been shown to increase after 12 week SSRI treatment (Yoo, et al., 2007). The fact that our data still showed reduced FA despite treatment suggests the changes in the anterior thalamic radiation are not directly influenced by SSRI medication but rather due to general level of symptoms.

The functional connectivity data did not support the CSTC hypothesis, with no significant FC differences between BDD and control participants between the striatal regions and the OFC. Overall, given that the resting state fMRI modality was the most sensitive to CSTC differences the data from the three empirical studies does not compellingly support the CSTC model in BDD. The functional connectivity results were of key importance to the CSTC hypothesis, the lack of significant findings brings into question the applicability of the CSTC

hypothesis in BDD. Future research is warranted, and fMRI research during symptom provocation may produce the most compelling results.

Precuneus

A brain region that is independent of any of the preceding hypotheses, but was implicated in all three imaging modalities, was the precuneus. In fact, this region was not a hypothesised region of interest, but the findings are nevertheless relevant. The exploratory analysis revealed significantly smaller volumes in the right superior parietal and right precuneus regions. The left amygdala was also greater functionally connected with the precuneus during our resting state study and the DTI study found reduced FA in white matter fibres connecting the precuneus. Past neuroimaging studies during visual processing in BDD found incidental abnormalities in the area, as well as in the primary and secondary visual processing systems (Fuesner et al., 2007; Feusner et al., 2011). The fact the other BDD samples have found differences in this area goes some way to suggest that our findings were not particular to our sample.

There has been some speculation previously that the superior parietal lobe and precuneus may be involved in BDD, due to their role in self-perception (Kaplan, et al., 2013). Indeed, the right superior parietal lobule is involved in kinaesthetic attention (Stoeckel, et al., 2004), visual tasks that require spatial attention (Corbetta, et al., 1995) and integration of somatosensory and visual information. In addition, the precuneus is involved in recall of imagery, self-reflection and in self-related mental representations (Cavanna & Trimble, 2006). Individuals with BDD have deficits on many of these tasks (Deckersbach, et al., 2000; Hanes, 1998; Labuschagne, et al., 2013).

The precuneus' role in visual information could play an important part in BDD given the piecemeal way individuals with BDD process images. Additionally, its role in body perception and self-referential thinking seems important given that these are two of the main features of BDD symptoms. Thus, dysfunction in this area may help explain two important symptoms in BDD: distortions in body awareness, and lack of insight. The abnormalities in volume and connectivity in the precunous is an interesting and unexpected finding that requires replication and extension in subsequent studies.

Summary of hypotheses

Each of the preceding hypothesises have received some support, some via more than one imaging modularity. The hypotheses most compellingly supported were the disconnection hypothesis, visual processing hypothesis and the fear hypothesis. The three other hypotheses (error detection, frontostriatal and CSTC hypotheses) are all components of the same system and the current data did not strongly support them. Nevertheless, given their emerging importance in OCD, and the similarities between the disorders, further investigation is warranted.

Perhaps the most comprehensive understanding of BDD comes from an interaction of the above hypotheses. Indeed, each hypothesis is incomplete and even if comprehensively supported, would only explain a narrow component of BDD phenomenology. For example, the visual perception hypothesis might explain why BDD patients fixate on appearance, but it does not explain the cognitive deficits in BDD. While the fear circuitry hypothesis may explain the concern of social judgement in BDD, it does not explain all the executive functioning deficits in the disorder. Each hypothesis has its focus. Another factor that is important is whether these

neurobiological results are the cause of the illness or are caused by BDD. In light of the multimodal neuroimaging data, predisposing factors relevant to the disorder will be explored.

Aetiology

The aetiology and pathophysiology of BDD, as with most mental illnesses, is likely complex. The causative and contributory factors to the development of BDD are unclear. However, there is emerging evidence from this research, and other studies, of various factors that may contribute to the development and maintenance of BDD symptoms. Simply put, a comprehensive model would likely involve biological and genetic susceptibility upon which adverse life events interact with cognitive abnormalities and lead to maladaptive learned behaviours. The learning model of BDD was explored in on pages 60-64, while the psychological and sociocultural factors were examined in Chapter 1. This section will focus on the neurobiological factors.

A large portion of the aetiology of BDD is likely to be genetic, which is well demonstrated by a large twin study (n=2,148) (Monzani, et al., 2012) showing that BDD and OCD traits were largely accounted for by genetic influences common to both phenotypes (64%). This genetic overlap was even higher when specific OCD dimensions were considered, with up to 82% of the phenotypic correlation between the symmetry/ordering symptom dimensions and dysmorphic concerns being attributable to common genetic factors. Thus, the association between BDD and OCD is largely explained by shared genetic factors, and both are considered a subtype of an "obsessive compulsive spectrum".

While a genetic predisposition to neurobiological changes has not been studied in BDD, it has been demonstrated in an OCD family study (Menzies, Williams, et al., 2008). The study employed DTI to assess white matter integrity of OCD subjects, their (healthy) first degree relatives and control subjects to investigate if the genetic predisposition was manifest in white matter degradation. Results showed that white matter abnormalities were also evident in healthy first-degree relatives of patients, suggesting white matter degradation is a possible endophenotype. This is important when considering that a major finding of this thesis is compromised white matter connectivity in BDD. Taken together, this data suggests that this white matter degradation is a predisposing factor to BDD, and may therefore underpin its development. What remains unclear is why some people with compromised white matter (i.e. first degree relatives) do not develop BDD (or OCD).

The situational factors that likely interact with predisposing factors are not the focus of this thesis, so will only be briefly mentioned. One of these factors is likely to be childhood experience, with data showing that individuals with BDD have a higher level of childhood adversity. For example, one study found that 79% reported childhood maltreatment and 38% reported abuse (Neziroglu, Khemlani-Patel, & Yaryura-Tobias, 2006). Indeed, white matter degradation has been found in adults who have been exposed to childhood parental verbal abuse (Choi, Jeong, Rohan, Polcari, & Teicher, 2009), suggesting that predisposed neural vulnerability in BDD can be exacerbated by early experience. Interestingly, neuroanatomical differences in the precuneus have been shown to have a far lower level of genetic heritability compared to other brain regions (Winkler et al., 2010), suggesting that this brain region might be affected by environmental factors rather than genetics.

Putting situational factors aside, the brain changes observed in our three studies in BDD are likely to be preconditioned to the development of BDD, largely caused by genetic factors. Indeed, our data, in general, showed state independent differences in BDD, compared to controls. These brain differences may lead people to be predisposed to developing BDD through psychobiological processes discussed in the fear circuitry and error detection models.

Comparison to Obsessive Compulsive Disorder (OCD)

Many of the hypotheses and much of the discussion in this thesis has been based around a comparison to OCD. BDD shows several similarities to OCD, including, preoccupations that are often described as obsessive, engagement in repetitive and ritualistic behaviours, and a concern with aesthetics such as symmetry (Ipser, et al., 2009; Landeros-Weisenberger, et al., 2010). There is also a strong familial link between BDD and OCD (Bienvenu, et al., 2000; Phillips, Menard, et al., 2005).

BDD has been subsumed under the Obsessive-Compulsive and Related Disorders category in the DSM-5. This decision was made on the basis of symptomatology and prevailing theories about aetiological similarities (e.g. Phillips, Wilhelm, et al., 2010). Our three research studies provide another line of evidence that allows for an indirect comparison between the disorders.

Our data revealed many of the brain regions implicated in OCD are also abnormal in BDD, including the OFC (Remijnse, et al., 2006), ACC (Menzies, Chamberlain, et al., 2008; Togao, et al., 2010), amygdala and hippocampus (Kwon, Shin, et al., 2003). The similarities were particularly strong in our volumetric data, where these volumes are reduced in BDD and

OCD. The finding of widespread reduction in white matter integrity is consistent with most studies in OCD (e.g. Oh, et al., 2012), though not all given the inconsistencies within the OCD data (e.g. Li, et al., 2011). In addition, the fcMRI data was not consistent with OCD data (Harrison, et al., 2012). The three studies in this thesis, taken together, present a mixed picture in terms of similarities and differences to OCD.

One area that we hypothesised might provide compelling evidence for the similarities between OCD and BDD was the thalamus. In particular, given that the thalamus shows increased volumes among a multitude of reduced grey matter volumes in OCD (Atmaca, et al., 2007; Gilbert, et al., 2000), if our data showed a similar pattern this would be of value in terms of the specificity of a neurobiological signature. Our data did not find similarities in thalamic volumes, casting doubt over the similarities between OCD and BDD. Given that the basis of the CSTC hypothesis was findings in OCD related to the thalamus, it also questions the CSTC hypothesis in BDD.

A large OCD study observed that orbitofrontal-striatal dysfunction appeared to be a common pathophysiological finding in OCD independent of OCD patients' major symptoms (Harrison, et al., 2012). The logical extension of this is, if BDD and OCD are related, or indeed if BDD is an OC spectrum disorder, is that BDD would be expected to have this core pathophysiology. However, our data failed to confirm the hypothesised orbitofrontal-striatal differences. Instead, our results showed heightened OFC functional connectivity with amygdala. This data (and the volumetric data showing differences in OFC volumes) indicate that the OFC is important but failed to confirm the functional connectivity differences that are reportedly core to OCD.

Even though the frontostriatal and CSTC models are dominant in OCD literature, there is still some evidence for fear circuitry being of importance, consistent with our findings. For instance, during symptom provocation fronto-amygdala responses have been shown to be important (van den Heuvel, et al., 2004). This, however, to our knowledge has not been shown in resting state function connectivity. Fronto-amygdala circuitry is hardly specific to OCD, with other anxiety disorders like social phobia having similar results (M. Stein, et al., 2002). In fact, fronto-amygdala dysfunction is a common thread among anxiety disorders**.**

OCD itself is a heterogeneous disorder with some symptom dimensions being highly related to BDD. For example, concern with symmetry is relevant to both disorders and conceptually more important to BDD, and there is also a genetic link between this symptom cluster in OCD and BDD (Monzani, et al., 2012). In OCD, Harrison et al. (2012) observed that there was a specific absence of associations between symmetry/ordering symptoms and neural correlates within the cortico-striatal systems that are core to OCD. The author suggests that other, unmeasured, neural systems may be important to this symptom cluster. Indeed, our disparate findings in the precuneus and occipital lobes may relate to this symptom cluster in OCD (and therefore BDD), though to our knowledge this has not been tested.

Research in OCD shows that cognitive measures (Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005b), reduced FA in white matter (Menzies, Williams, et al., 2008) and patterns of grey matter structural abnormalities (Menzies et al., 2007) contribute to an endophenotype of the disorder. Given the genetic link hitherto discussed, and general (but not comprehensive) agreement in our brain imaging results, BDD and OCD may be related. Our evidence suggests that similarities include reduced white matter integrity and reduced OFC and ACC volumes. On the other hand, differences in functional connectivity in cortico-striatal

systems, fear systems at resting state, visual systems and the precuneus might represent pathophysiological distinctions between the disorders.

Indicating the non-specific nature of our findings, amygdala and hippocampus differences have also been found in depression and schizophrenia (Sheline, et al., 1998). Indeed, our connectivity findings in the DTI and fcMRI studies resemble those in social anxiety disorder (Phan, et al., 2009), schizophrenia (Kubicki et al., 2002) and those of individuals with anxious personality traits (Vestergaard, et al., 2011), as much as the results resemble findings in OCD. Therefore, our findings are inconclusive when it comes to a comparison between BDD, OCD and other mental disorders.

What our data does show is that, like OCD, social phobia, and depression, BDD patients have neurobiological abnormalities that are widespread. There is evidence of a generalized neurodegenerative process or a genetically transmitted phenotype, evidenced by reduced total grey matter compared to controls and reduced white matter integrity.

Treatment

Apart from the aetiological and nosology implications, the results of the current thesis also have implications for therapeutic interventions. The most common interventions for BDD currently involve cognitive behaviour therapy (CBT) with an emphasis on exposure and response prevention and/or psychopharmacotherapy (Phillips & Rogers, 2011). This thesis did not intend to make comment on pharmaceutical interventions or their mechanisms of action, instead focussing on how neurobiology interacts with behaviour, and cognitive behavioural therapies.

The support that the current thesis gives to the fear circuitry hypothesis provides a neurobiological basis for the effectiveness of exposure and response prevention treatment. This practice involves purposeful exposure to generally avoided situations (e.g. to avoided social situations), and response (ritual) prevention (e.g. not seeking reassurance, mirror checking) (Phillips & Rogers, 2011). Graded hierarchy exposure is used to overturn cognitive distortion and facilitate habituation. CBT is thought to work by activating the mPFC to down regulate hyperactive amygdala responses, causing fear conditioning extinction. Our data showing differences in the connection between the amygdala and frontal regions supports such treatment, and suggests that this technique is targeting and retraining faulty neural circuits.

There has also been some data that psychological treatments influence white matter integrity. For example, meditation (Tang, et al., 2010) and strategy based exercises (Jang, et al., 2010) can increase FA in healthy controls and may therefore be useful in BDD. Additionally, our findings of abnormalities in visual processing suggest that this may be a useful target for treatment. For instance, specialised training of facial processing and affect recognition has been developed for schizophrenia, with promising results (Wölwer et al., 2005). Such programs could be adapted for use with BDD. In fact, such training may positively interact with existing exposure and response prevention frameworks.

Perhaps the most powerful direct contribution to treatment of the current thesis is the way BDD can be conceptualised and explained to patients. Individuals with BDD fixate on a physical problem and often seek medical intervention. This thesis' provision of "solid" evidence of "physical" abnormities within the brain will help in the communication of the illness to patients. Indeed, the individuals with BDD are known to be difficult to engage in non-physical treatments and it is a major barrier to effective treatment (Phillips, Didie, Feusner, & Wilhelm, 2008). Thus,

having physical brain evidence, with patients with little insight, may help them understand the disorder. Thinking of their problem in terms of an externalized brain disorder may be a useful stepping stone to further insight.

Limitations

Despite the major contribution to the neurobiological knowledge of BDD, and the multiple neuroimaging methods used, the three studies here have limitations. Many of the limitations particular to the imaging modality have been specifically addressed in each paper. This section will address a number of further limitations common within the three studies.

A limitation of this thesis' conclusions is that many of our BDD participants were taking medication at the time of MRI acquisition. This may be problematic as research in OCD has shown that treatment with citalopram influenced DTI values after a period of 12 weeks (Yoo, et al., 2007), although the changes were largely accounted for by symptom reduction. The functional connectivity measurements were the most likely to influenced by medication use, given their state dependent nature.

Another limitation of our sample was the fact that three of the twenty BDD participants were left handed. Although the control group was selected to exactly match the BDD group on handedness, it is acknowledged that having left handed people was a source of heterogeneity within groups. In the general population there is a correlation between handedness and brain lateralization, and among psychiatric samples left handed individuals are over represented (Good, et al., 2001). Thus, if significant brain lateralization affects are a major factor in BDD, as suggested by some past neuroimaging research (e.g. Feusner, et al., 2007), the heterogeneity

within our groups likely made our analysis less sensitive to these differences. Indeed, our research found differences in the left and right hemispheres and no overall hemispheric bias was demonstrated.

While three different imaging modalities have been presented in this thesis, more analysis and methodologies are possible. Of course, there are always many different ways to approach a dataset and volumetric, DTI and fcMRI are but only three. Another gap in this otherwise comprehensive MRI investigation is the lack of fMRI data during behavioural tasks, which can produce compelling support for neurobiological models. Finally, while much of this thesis used OCD as a reference group, no comparison group was used to directly compare BDD to OCD.

Nevertheless, this thesis provides high quality, novel and multi-model neuroimaging data to advance our understanding of BDD. While there are a myriad of techniques to investigate the neurobiological of BDD, this thesis has used three powerful and distinct methods.

Directions for Future Research

This section discuses several directions for future studies in BDD. Many of the limitations highlighted above are currently being addressed within our research group, and further research and analysis is underway. The next logical step would be to include an OCD comparison group to more directly examine the similarities and differences between the disorders. In addition, the T1 data could be used to yield cortical thickness measures that would provide an additional modality to evaluate the integrity of cortical structures and can help differentiate genetic influence from other factors (Winkler, et al., 2010). In addition, tractography could be used to further exploit our DTI data, which can determine the organisation

of white matter pathways, rather than just the strength. A comparison between DTI and resting state fMRI data could also proved useful, as shown in previous research (Honey et al., 2009). In particular, a formal analysis determining if functional connectivity differences are mediated by white matter degradation may be useful in delineating the cause of functional connectivity differences.

In addition, fMRI during behavioural tasks or visual presentation would be of importance. In particular, given our findings of fear circuitry differences, presentation of emotional faces during an fMRI scanning sequence would highlight differential patterns in amygdala and mPFC activation. Presentation of facial stimuli may also help elucidate the facial perception differences highlighted here and in previous studies. Another line of research that may prove beneficial, especially to evaluate the importance of the ACC, is presentation of visual stimuli that represented the aesthetic area of concern. In OCD samples similar paradigms designed to elicit error detection have been used and successfully shown the importance of the ACC (Fitzgerald, et al., 2005; Nieuwenhuis, et al., 2005).

While this thesis has speculated that brain differences are largely a predisposing factor to BDD development rather than a result of it, future research could directly investigate this. There are obvious feasibility problems with evaluating pre-onset versus post-onset brain scans in any large number. An alternative to this would be to compare the brains of those with current BDD diagnosis with those who are in remission. Indeed, the influence of treatment on different brain mechanisms is also of interest.

Conclusion

This thesis aimed to characterise the brain using DTI, T1 and fcMRI, using hypotheses based on neurobiological mechanisms that may underpin BDD. We sought to explain both symptoms, such as an excessive preoccupation with appearance, and phenomenology, such as neuropsychological deficits. We also aimed to evaluate the neurobiological similarities between OCD and BDD, and used OCD literature as a basis to hypothesise about the mechanisms underpinning BDD.

This thesis contributed neuroimaging data of the largest sample size in BDD to date. The data contributed evidence of widespread neurobiological differences between BDD and controls with three different imaging modalities. Specifically, we contributed evidence showing widespread white matter fibre degradation, and found that several frontal and limbic regions had altered functional connectivity compared to control participants. The nature of the findings supplements the converging evidence that BDD may lie on a spectrum of anxiety disorders, and this is evidenced by the findings of aberrant connectivity in fronto-limbic regions involved in regulation and processing of emotion and social cognition. In addition, differences in the visual systems were demonstrated without any formal task. Our volumetric results showed a general reduction in grey matter volumes consistent with OCD and other psychiatric disorders, and highlighted the importance of the OFC and ACC in BDD.

It was speculated that white matter degradation is the core and predisposing factor relevant to BDD, a factor that it has in common with OCD. We also articulated the importance of the fear circuitry and the conditioning mechanisms that may underlie BDD onset, maintenance and remission. Our data was compared to OCD data in the literature, and we concluded that

BDD shares general neurobiological characteristics to OCD, but that the proposed shared CSTC and frontostriatal hypotheses could not be confirmed in BDD.

Postface

"I've been suffering with BDD for about four years now but in the past two years it's become unbearable"

She says to me as we sit down together in the interview room.

"I honestly feel like the ugliest human alive and its ruining me. I feel so much disgust when I catch a glimpse of myself in the mirror."

I write down the word "glimpse" on my notepad, and wonder if this is an expression of the incomplete view of her face, mediated by problems with the integration of the visual systems.

"I just feel so ashamed that other people have to look at me, so I don't go out much. When I'm at home I sit upstairs so my family doesn't have to look at me. I know they think I'm ugly, I can tell, though they don't say it to my face"

"How can you tell they think you're ugly?" I'm hoping she won't misinterpret the question, or my neutral facial expression as judging. I jot down her response, remembering that the amygdala activity caused by sharing her story might spill over into emotional misperceptions.

"The only way I feel bearable to let people see me is when I'm caked in makeup, fake tan, eyelashes and hair extensions and even then I still feel deformed. It has gotten so bad that I won't even answer the front door. When I hear the doorbell I hide upstairs till they have gone."

The mention of the doorbell reminds me of Pavlov's dogs and classical conditioning. I wonder if I played her doorbell sound here she would become anxious. I write a note to remind myself that ringing the doorbell could be a target for exposure and response prevention, and wonder, given the compromised connections between the orbitofrontal cortex and the amygdala, how long it would take for extinction to occur.

I ask, "What have you tried so far to cope with these feelings?"

"Friends have suggested a few different things. I should look at myself in the mirror less, more...whatever. Another told me to go out with the mentality of "who cares what they think". I walked down an empty street and it seemed to work fine but as soon as I saw another person glance in my direction instantly I was thinking oh God they think I'm hideous. So that one failed as well."

Thinking about the inhibitory control the frontal regions have over amygdala reactivity I say, "That was a brave thing to do, walk down the street like that. But the fear was too much. You couldn't just talk yourself out of it. The emotions were too strong and came too quick".

"I constantly compare myself to every other girl I see and I spend most of my time reapplying makeup. I just look in the mirror and try different shades of makeup, but nothing works. I don't even think surgery would help me because my face is that bad."

"It seems like you've tried a few things that haven't worked so far. I wonder if checking in the mirror and putting makeup on gets you into a bit of a cycle?" I suggest, keeping the cortical-striatal-thalamic-cortical circuit in mind.

"Yes, but I can't stop thinking of how I look. Sometimes I try to block out the thoughts but then I get this overwhelming sense that something is wrong."

I nod, "like your brain is sending you this signal that something just isn't right?", thinking about dysfunction in the anterior cingulate cortex and error detection circuits.

"My parents don't know; I am suffering alone. I just hope I will get out of it because I just can't keep going anymore and there is no reason for waking up in the morning. I can't believe it has taken me so long to admit this, but I have to admit it to someone. I have finally decided to get counselling"

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Appendices

Appendix A

Published Literature Review: Body Dysmorphic Disorder: A Review Of Nosology, Cognition And Neurobiology

REVIEW

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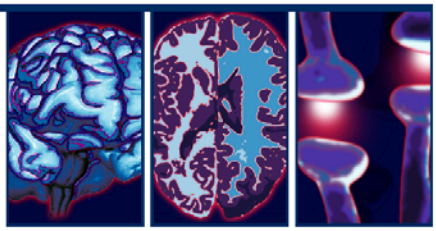

Body dysmorphic disorder: a review of nosology, cognition and neurobiology

Ben G Buchanan[1], Susan L Rossell[2] & David J Castle[†]

Practice points

- Body dysmorphic disorder (BDD) is underdiagnosed, as individuals with BDD are unlikely to reveal their body image concerns unless directly asked. They may, however, seek cosmetic procedures for their perceived defect or psychological treatment for a comorbid condition.
- Common comorbid conditions include depression, social phobia, anorexia nervosa and obsessive–compulsive disorder.
- Obsessive–compulsive disorder and BDD have similar symptoms and research is beginning to show that they also have similar underlying cognitive dysfunctions.
- The delusional subtype of BDD is best considered as a more severe case of BDD with lower levels of insight, rather than a separate subtype.
- Individuals with BDD have visual processing abnormalities including a tendency to process visual information in a piecemeal manner rather than holistically. This indicates that they see things differently and may explain their fixations on slight anomalies in their own appearance.
- Hyperactivity in the limbic system may explain why individuals with BDD feel that they are constantly being negatively judged by others.
- BDD can be successfully treated with cognitive behavioral therapy and medication.

SUMMARY An understanding of the neurocognitive and neurobiological underpinnings of body dysmorphic disorder (BDD) is important in differentiating BDD from related disorders, namely obsessive–compulsive disorder and psychotic disorders. Similar cognitive anomalies in executive function, spatial visual processing and memory (bias to process detailed visual information) have been found in BDD and obsessive–compulsive disorder samples, while schizophrenia patients display more pervasive cognitive deficits. Emotional hyperactivity

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Appendix A

and misinterpretation of emotion in others have been found in BDD, with similar results to obsessive–compulsive disorder samples. Neuroimaging has shown abnormalities in the prefrontal cortex, visual cortex, caudate nucleus and right amygdala in BDD patients. These findings are consistent with the neurocognitive profile. This field of research is in its infancy. However, the bias towards detailed visual analysis may be an important clue when investigating the neurobiological basis of BDD, and could explain why individuals exhibit focused attention on one aspect of their own appearance. Emotional hyperarousal caused by amygdala pathology may reinforce a perception of negative physical appearance.

A degree of concern regarding physical appearance is culturally accepted and even expected; however, for some individuals concern regarding their appearance is excessive and causes them considerable distress. These people may be identified as having body dysmorphic disorder (BDD), which is a mental disorder that includes obsessive–compulsive phenomena and overvalued ideas that may become delusional. This article will discuss the phenomenological similarities between BDD, obsessive–compulsive disorder (OCD) and psychotic disorders and review neuropsychological and brain imaging studies and their possible implications for a neurobiological model of BDD.

Characteristics of BDD

Individuals with BDD frequently describe themselves as unattractive, disfigured, deformed or ugly and are preoccupied with one or more aspect of their appearance that they attest to looking abnormal. The disorder's essential feature, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised (DSM-IV-TR) [1], is a preoccupation with some imagined defect in appearance, or, if a slight physical abnormality is present, that the person has a disproportionate concern regarding the anomaly. Furthermore, individuals with BDD often demonstrate little insight into the fact that their self-perception of repulsiveness is unrealistic, and these beliefs may thus reach delusional proportions.

Body dysmorphic disorder patients are usually preoccupied with their face or head, and most commonly their skin, hair or nose [2]; they can spend between 3 and 8 h per day thinking about their perceived defects; in fact some individuals report that these thoughts are present continuously [3]. Beliefs about their defects usually carry strong personal meaning, and are often cited as the main reason for personal problems [4], for example, "I cannot get a job because of my nose". Many individuals with BDD give almost exclusive attention to their perceived flaws while ignoring other aspects of their appearance.

Individuals with BDD have impaired psychosocial functioning and quality of life [5]. They may experience prolonged unemployment, severe social isolation and suicidal ideation, with approximately 25% of individuals with BDD attempting suicide [6].

Prevalence rates of BDD are reportedly between 0.7 [7] and 2.4% [8], with similar levels in males and females. It is generally underdiagnosed, as individuals are not likely to reveal their symptoms unless directly questioned about their body image concerns. The secretive nature of BDD, as well as the strongly held belief that they possess a physical defect rather than a psychological problem, means that few individuals with BDD will seek appropriate treatment. They may, however, opt for cosmetic procedures to 'cure' their problem. For example, Veale *et al.* found in their BDD samples that 26% had had one or more cosmetic operations [3]. Furthermore, the vast majority (83% in the study by Phillips *et al.* [9]) of BDD patients experience either no improvement or a worsening of BDD symptoms after surgery. In cosmetic settings, rates of BDD are high: 7% in a sample of cosmetic surgery patients [10] and between 8.8 and 14% in dermatology patients [11,12]. If individuals with BDD do present for psychological treatment it is often for a secondary or associated condition, such as depression, OCD, anorexia nervosa or social anxiety [13–15]. Patients are commonly not diagnosed with BDD until 10–15 years after the onset, which usually occurs in adolescence [16]. The course of the disorder is generally chronic if untreated. If treated with psychological therapy and medication [17], however, the outlook is more optimistic, with nearly 60% achieving remission after 4 years.

Nosology

At present BDD is classified as a somatoform disorder in the DSM-IV-TR. However, it is widely acknowledged that the nosological status of BDD is in need of review [18,19], with the DSM-V Working Group recommending that BDD be reclassified as either an anxiety disorder or an

obsessive–compulsive spectrum disorder [19,101]. There is also debate relating to the delusional subtype of BDD, and how this can best be conceptualized within the BDD classification framework. Currently the delusional variant requires a separate, additional, classification with the delusional disorders.

There is also debate over how BDD relates to other mental disorders. For example, social phobia shares many characteristics with BDD, such as the tendency to feel socially anxious and chronic fear of embarrassment or rejection [20]. In fact, 39% of individuals with BDD have had comorbid lifetime social phobia [20]. While BDD has been compared with many disorders, this article will focus on the issues most salient in the context of the possible reclassification of the disorder within the DSM-V, namely BDD as an obsessive–compulsive spectrum disorder and BDD's delusional variant.

■ BDD as an obsessive–compulsive spectrum disorder

Body dysmorphic disorder shows several similarities to OCD, including:

- Preoccupations that are often described as obsessional, anxiety producing and difficult to control [21];
- Engagement in repetitive and ritualistic behaviors, such as skin picking and checking behaviors, which may take up many hours of the day [22];
- A concern with esthetics such as symmetry [23];
- A tendency to engage in reassurance seeking from others [23];
- Social withdrawal [24].

A number of studies have directly compared BDD to OCD on a broad range of demographic and clinical features, with relatively consistent findings [14,24–26]. Comorbidity studies have tended to focus on the prevalence of BDD in OCD samples. They have shown that 7.7–15.3% of those with OCD meet diagnostic criteria for concurrent BDD [15,23]. The high comorbidity rate may represent a diagnostic overlap or an etiological link. In clinical BDD samples, OCD is a frequent comorbid disorder (41%) [27]. Furthermore, familial studies have demonstrated a familial link between OCD and BDD. Hollander, Cohen and Simeon found that OCD was the most common disorder found in the relatives of 50 BDD participants, with 17% of them having first-degree relatives with OCD [28].

As well as the phenomenological and familial links between OCD and BDD, both disorders have similar treatment responses to serotonergic reuptake inhibitor medications [29,30]. Given these similarities there seems to be a general consensus towards conceptualizing BDD as an obsessive–compulsive spectrum disorder [31], and some neuropsychological studies have set out to measure BDD against OCD to test this conceptualization; this is addressed below.

■ Delusional & nondelusional subtype

A key difference between OCD and BDD, and a topic of debate regarding subtypes of BDD, is the delusional and nondelusional typology. In BDD, obsessions tend to be held with more conviction and less insight than those of OCD [32]. Thus, whilst only 2% of OCD patients were 'delusional', 27% of BDD participants were currently delusional according to the Brown Assessment of Beliefs Scale. Other studies have found a higher rate of delusions in BDD, of between 34 and 60% [33,34]. In contrast to delusions in psychotic disorders such as schizophrenia, delusional beliefs in BDD tend to be nonbizarre and monothematic and generally linked to their perceived flaw. BDD patients also often experience delusions of reference, such as the belief that other people take special notice of the supposed defect, for example, talk about it and mock it [35].

Under the present diagnostic system for BDD in the DSM-IV-TR there is the provision of a secondary diagnosis of a delusional disorder within the delusional disorder group, somatic subtype. This diagnosis is given if beliefs reach delusional intensity, or strong ideas of reference are present. The current psychotic/nonpsychotic dichotomy has been under scrutiny because the separate classification of the types implies that they are, in fact, distinct disorders. However, available evidence suggests that the delusions present in BDD should not be represented as a categorical difference in classification but rather reflect a dimensional intensity of belief [34,36]. To this end, there has been considerable speculation regarding a dimensional approach to the delusional aspect of BDD in development of the DSM-V [18,34,37].

Nevertheless, there are several differences between the subtypes: individuals with delusional BDD experience more impairment in social functioning, more suicide attempts and

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rate of hospitalization, and have more severe BDD symptoms compared with their nondelusional counterparts [33,38]. Delusional subjects also have lower scores on nearly all functioning and quality of life variables. However, there are more similarities than differences between the two subtypes, including age, comorbidity and, most importantly, the core symptomatology of BDD. Moreover, both delusional and nondelusional variants respond similarly to serotonin reuptake inhibitor pharmacotherapy [39]. Thus, the delusional subtype patients could merely have a more severe form of the same core disorder.

Neurocognition

The severe body image distortions that individuals with BDD experience suggest that fundamental cognitive and perceptual abnormalities are involved. Cognitive research has revealed a range of deficits in BDD, including executive function [40,41], selective attention [42], information processing [41,43], recognition of emotion in others [44] and visual processing [45,46].

In the context of the nosological debate surrounding BDD, studies that have directly compared cognition in BDD, OCD and schizophrenia are of particular interest. Hanes compared a BDD group with OCD and schizophrenia groups on executive function tasks [40]. Parallel deficits in BDD and OCD were found, while the schizophrenia group showed more severe and widespread deficits. The author concluded that the cognitive similarities between OCD and BDD imply that the neuroanatomical underpinnings may be similar. In OCD, impairment on one of the same executive function tasks (Stroop color naming) has been shown to be associated with abnormal frontal–striatal and limbic activation [47], although this has not, to our knowledge, been directly investigated in BDD.

Dunai *et al.* demonstrated executive function impairments in BDD patients compared with nonclinical controls, with the BDD group making more errors on a Spatial Working Memory task, and performing more slowly on the Stocking of Cambridge task, which required organization, planning and online manipulation of visual information [41]. Such deficits, on the same tasks, have previously been observed in OCD [48] and schizophrenia [49]. Executive function deficits in BDD, however, were not pervasive, and the BDD group scored similarly to controls on a pattern recognition task and another test of spatial short-term memory, suggesting that spatial memory capacity, motor speed and visual memory are intact.

One of the most cited neuropsychological findings in BDD has been that individuals with BDD process images in a detailed fashion rather than in a more holistic way [43,50]. Deckerbach *et al.* demonstrated disruptions in visual learning when holistic organization of visual information is required rather than detailed analysis [43]; this is also characteristic of OCD [51,52]. Interestingly, holistic visual processing disruption with facial stimuli was shown in schizophrenia by Joshua and Rossell [53], suggesting that BDD, OCD and schizophrenia all have a bias towards detailed visual processing. However, no published studies have directly compared BDD with OCD or schizophrenia in this regard, so any conclusions are only tentative.

In a recent study examining detail bias in BDD [50], participants viewed images of faces that were either upright or inverted. Inverted faces slowed the recognition response time in both BDD and control groups, but individuals with BDD slowed significantly less than controls. Gestalt recognition is disrupted when images are inverted and the smaller response delay for the BDD group suggests they rely on detailed visual analysis, causing less disruption when images are inverted. This detailed analysis bias has also been demonstrated in a study that showed that individuals with BDD were more accurate than controls with dermatological conditions at noticing small differences between facial images [54]. However, there has been some variation in results, with BDD participants in another study showing no difference to OCD and control subjects in their ability to detect slight asymmetry in faces [55].

Other studies of BDD patients have focused on facial emotional recognition. One study compared BDD with OCD on a facial emotion identification task [44] and found that both disorders were associated with difficulties interpreting the emotional facial expressions compared with controls. The BDD group more often misidentified emotional expressions as angry compared with OCD and control subjects. Such emotional misinterpretation has also been shown for nonface general social scenarios [56,57], suggesting a more generalized emotional hyperarousal. In another study requiring matching of faces [58], BDD participants performed similarly to nonclinical controls when the stimulus facial expression was neutral. However, when the stimulus faces were

showing emotion (e.g., sad, happy or angry), BDD participants reacted more slowly and made twice as many mistakes as controls, indicating a tendency to be distracted by emotional cues and a possible hypersensitivity to emotion.

Identification of these emotional biases, coupled with fundamental cognitive abnormalities and deficits in information processing can inform our understanding of the neurobiological abnormalities underpinning BDD. Thus, this review of neurocognition illustrates that individuals with BDD have abnormal ways of processing information and these may be linked to specific brain regions. For example, poor executive functioning is surmised to be a result of abnormalities in the prefrontal cortex [40,41], while memory deficits are thought to involve abnormalities of the medial temporal cortex [43]; and poor facial expression recognition implicates underlying networks involved in facial recognition, including the superior temporal sulcus [59]. More specifically, interpretation biases may implicate an emotional regulation system in the brain, particularly the limbic system [60]. Specific functional neuroimaging experiments will need to be conducted to confirm these interpretations, but there is a coherent emerging story that can now be told. We now turn to neuroimaging studies that have investigated the pathophysiology of BDD. None of these studies have directly compared BDD with other disorders.

Neuroimaging

Both functional and structural imaging has been conducted with BDD patients. Functional imaging has tended to focus on activation levels while the participants engage in visual processing tasks, as their symptomatology is closely related to these systems.

Feusner *et al.* conducted an functional MRI (fMRI) study to explore brain activation in 13 BDD and 12 control participants [46]. The participants were presented with faces that had been digitally manipulated to either have low, normal or high levels of detail. The low spatial frequency was blurred, while the high spatial frequency had exaggerated contour details. Previous research has shown that visual processing of detailed stimuli produces different brain activation to global processing in healthy participants [61,62]. Given that individuals with BDD tend to have a bias toward detail in visual analysis [43,50], patterns of brain activation in response to the three different spatial frequency stimuli were expected to be different to controls. The researchers found two major group differences. First, right amygdala activation was significantly greater in the BDD group for high spatial frequency and low spatial frequency facial pictures, but there were similar levels of activation for the normal resolution pictures. Second, there was more left hemispheric activation in the lateral aspects of the middle and inferior prefrontal cortex in the high and low spatial frequency face presentation for the BDD group, while controls had more right activation. Studies with healthy individuals have demonstrated that left prefrontal cortex activation is associated with local or analytical processing, while the right prefrontal cortex has increased activation for holistic or global processing [63]. The results from this study showing greater activation in the BDD group for brain regions associated with detailed analysis, taken together with the Deckersbach *et al.* study showing a bias for detailed visual information organization, suggest that BDD participants engage in a more piecemeal and detailed analysis of faces compared with healthy individuals [43].

A subsequent study with a similar design aimed to examine brain function particular to visual presentation of BDD participants' own face or a familiar face [64]. The BDD patients (n = 17) demonstrated lower levels of activation in primary and secondary visual cortical areas for low-detail images for their own faces and faces of familiar people, compared with 16 healthy controls. Since the low-detail images require holistic processing, abnormal brain activation may indicate difficulties in processing such information. In addition, this study demonstrated hyperactivity in the left orbitofrontal cortex and bilateral caudate when shown a picture of their unaltered face, compared with the familiar face condition. OCD samples have also demonstrated hyperactivity in these areas [65], supporting their conceptual association. The study also found that frontostriatal activation was correlated with higher levels of obsessive thoughts and compulsive behaviors in the BDD group. These two studies are particularly interesting because the face is the most common area of fixation in BDD. Future research should consider comparing BDD groups based on the area of fixation (facial vs body), as cortical differences may be present. Abnormal cortical activation in BDD patients has also been found for

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visual stimuli, which is unrelated to BDD symptoms. Feusner *et al.* found that, when presented with manipulated images of houses, individuals with BDD showed similar abnormalities in brain activation as when shown faces [66]. This suggests general abnormities in visual processing rather than symptom-specific deficits.

Another brain imaging study used single photon emission computed tomography with six BDD participants [67]. Single photon emission computed tomography imaging uses injected radioactive material to measure blood flow (perfusion) in different areas of the brain. There was no control group in this study, thus the results from brain regions of interest were compared with previously acquired and standardized region-of-interest templates. The study found widespread neurocircuitry abnormalities, including perfusion deficits in bilateral anterior–medial temporal and occipital regions and frontal areas, and asymmetrical perfusion in parietal lobes. Of particular note were the blood flow deficits in the temporal regions, as these regions are associated with body image perception [68]. Ventral areas of the temporal region are known to be involved in face perception, while anterior areas are involved in visual processing [59,69]; both functions have been shown to be abnormal in BDD [43,70]. However, owing to the small sample size and no control group, replications of these findings are needed.

Neuroanatomical differences in BDD were studied by Rauch and colleagues [71]. They conducted a brain structure study using morphometric MRI with eight female BDD participants and the same number of sex-matched controls. They reasoned that studying brain structure could establish a basis for comparison of BDD to other obsessive–compulsive spectrum disorders. Their results showed that there was greater total white matter volume and a left-shifted caudate asymmetry in BDD. These results may explain the selective attentional biases towards detail found in the cognitive studies reviewed previously [43,50,58], as the caudate region is involved in the filtering of new sensory information, learning and memory. The caudate nucleus is also consistently abnormal in OCD samples [72]. Volumetric differences between all other measured brain regions, including the amygdala, thalamas, globus pallidus, hippocampus and putamen, were not significant. However, owing to the female gender bias in the sample and the small sample size, these results should be viewed with caution, as nonsignificant findings may be due to a lack of power and significant findings may be due to sampling error.

In contrast to the all-female sample in the above study, Atmaca *et al.* compared 12 male BDD subjects who were unmedicated with 12 male controls [73]. Greater total white matter volumes were found, confirming the results of Rauch *et al.* [71]. Consistent with fMRI data showing hyperactivity in the orbitofrontal cortex [64], this structural study found that the BDD group had significantly smaller orbitofrontal cortices compared with controls. Furthermore, the study found that the longer the duration of illness the smaller the orbitofrontal cortex volumes, suggesting hypoatrophy caused by hyperactivation. These results may explain the executive function and emotional regulation deficits in BDD. In addition, these results give further support for the conceptual link between OCD and BDD, as similar reductions in volumes have been demonstrated in the orbitofrontal cortex in OCD [74,75].

Feusner and colleagues also undertook a structural imaging study with 12 BDD participants and 12 controls [76]. This study measured specific regions of interest using a manual tracing technique, limiting the brain regions measured to the amygdale, caudate and inferior frontal gyri. This technique is in contrast to the Rauch *et al.* study, which measured more regions with a more automated, although less accurate, process [77], making comparison between their studies difficult. Feusner *et al.* [76] found no significant differences between the groups in terms of volumetric differences in white and gray matter or their regions of interest. However, symptom severity within the BDD group was significantly positively correlated with right amygdala volumes, supporting previous fMRI data of abnormal right amygdala activation [46]. This finding is consistent with current knowledge on amygdala function, as the amygdalae have consistently been shown to be involved with emotional arousal [78] and affective facial recognition [60]. The right amygdala is particularly active in tasks that require the processing of emotional visual information [61]. As individuals with BDD have been shown to have high emotional arousal, biases in affective facial recognition tasks [70] and their primary symptoms involve visual emotional disturbances, the finding of right amygdala structural and functional abnormalities suggests that hyperactive amygdalae might be important in BDD

symptomatology. However, further evidence of amygdala pathology is needed, especially as the Fuesner *et al.* structural study [76] again had a small sample size. In fact, the reported significant correlation between amygdala size and symptom severity may be explained by two outliers among the 12 data points.

Figure 1 shows brain areas that have been shown to be abnormal in BDD. In addition, in terms of general differences between BDD and control brains, increased white matter volumes and leftward shift in hemispheric activation have been consistent findings.

The etiology of BDD

This article has focused on neurocognitive and neurobiological underpinnings of BDD, but these can by no means comprehensively explain the mechanisms by which BDD evolves within certain individuals. For example, certain psychological and sociocultural factors have been shown to be related to the onset of BDD [79,80]: the causal interaction of these factors has been conceptualized well in the cognitive behavioral model of BDD [80,81]. However, neurobiological pathology, as discussed here, represent the most direct factors underlying BDD symptomatology. Such pathology is perhaps influenced by genetic factors and early environmental experiences. Indeed, genetic influences have been shown to be important, with prevalence studies showing higher BDD rates of 5.8–8% among first-degree relatives of those with BDD [5,82]; there is also a genetic link to OCD [28]. Thus, any holistic model of BDD must encompass all of these parameters.

Conclusion

While much is known regarding the phenomenology of BDD, further research is needed into the fundamental cognitive and neurophysiological underpinnings of the disorder. Neuropsychological studies have indirectly implicated certain regions of the brain and contributed to the formulation of a neurobiological paradigm of BDD. Based on this evidence, it is possible that the perceptual distortions experienced by individuals with BDD are caused by a tendency to process detailed visual information rather than configural arrangement. Neuroimaging research to date supports this, showing hyperactivity in the left hemisphere associated with detailed analysis, rather than the right hemisphere-mediated holistic appraisal. The tendency for individuals with BDD to mirror gaze and focus on one aspect of their appearance can be explained through this mechanism. The emotional hyperactivity and misinterpretations experienced in BDD may make individuals with the disorder more likely to interpret slight physical anomalies in a

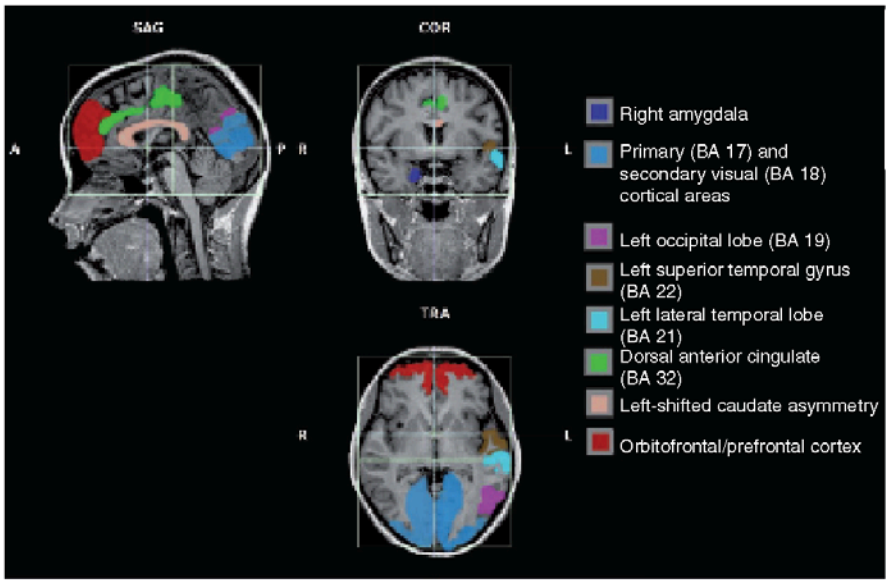

Figure 1. Implicated brain regions in body dysmorphic disorder.

Appendix A

negative manner, exaggerated by the perceived negative evaluation by others. This may involve abnormal functioning of the limbic system including the amygdalae.

In terms of the nosological debate around BDD as an OCD or a delusional disorder, the available data have produced more support for BDD's conceptualization as an obsessive–compulsive spectrum disorder. Similarities to OCD in executive function, visual processing, facial emotion recognition and abnormal patterns of activation in the orbitofrontal cortex have been found. These similarities, however, are largely based on comparison of separate study's findings. Beyond neurocognitive similarities, OCD and BDD still have an important difference in terms of insight, and the delusions present in BDD make classification within an obsessive–compulsive spectrum disorder category problematic. Thus, more data directly comparing BDD with OCD and schizophrenia are needed. Neurocognitive similarities between BDD and schizophrenia should also be directly examined, as comparative neuroimaging studies would help inform the nosological debate.

Future perspective

Over the next decade it is predicted that there will be greater emphasis on untangling the etiological factors important for understanding BDD. This will include an influx of neuroimaging studies examining the integrity of both the structure and function of the brain using MRI and other techniques. There is also scope to employ other technologies, including advanced modern eye tracking. Eye movement abnormalities have frequently been reported in other mental illnesses, including schizophrenia and other anxiety disorders. There is a particular dearth of such investigation in BDD, which is surprising given the extensive literature on visual processing problems.

In addition, the publication of the DSM-V may see BDD placed as an obsessive–compulsive spectrum disorder. However, there will be ongoing debate as to the significance of delusions in BDD and the nosological implications thereof.

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No writing assistance was utilized in the production of this manuscript.

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Appendix A

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■ Website

101 Diagnostic and Statistical Manual of Mental Disorders V
www.dsm.org
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Appendix B Ethics Approval

Ethics Committee Certificate Of Approval

This Is To Certify That

Project No: 111/09

Project Title: A Multimodal Investigation Of Body Dysmorphic Disorder (Bdd)

Principal Researcher: A/Professor Susan Rossell

Participant Information And Consent Form Version: Version 3 **Dated: 11-May-2009**

*Was Considered By The Ethics Committee On **30-Apr-2009** And **Approved** On* **12-May-2009**

It Is The Principal Researcher's Responsibility To Ensure That All Researchers Associated With This Project Are Aware Of The Conditions Of Approval And Which Documents Have Been Approved.

The Principal Researcher Is Required To Notify The Secretary Of The Ethics Committee, Via Amendment Or Progress Report, Of

- Any Significant Change To The Project And The Reason For That Change, Including An Indication Of Ethical Implications (If Any);
- Serious Adverse Effects On Participants And The Action Taken To Address Those Effects;
- Any Other Unforeseen Events Or Unexpected Developments That Merit Notification;
- The Inability Of The Principal Researcher To Continue In That Role, Or Any Other Change In Research Personnel Involved In The Project;
- Any Expiry Of The Insurance Coverage Provided With Respect To Sponsored Clinical Trials And Proof Of Re-Insurance;
- A Delay Of More Than 12 Months In The Commencement Of The Project; And,
- Termination Or Closure Of The Project.

Additionally, The Principal Researcher Is Required To Submit

- A Progress Report On The Anniversary Of Approval And On Completion Of The Project *(Forms To Be Provided)*;

The Ethics Committee May Conduct An Audit At Any Time.

All Research Subject To The Alfred Hospital Ethics Committee Review Must Be Conducted In Accordance With The National Statement On Ethical Conduct In Human Research (2007).

The Alfred Hospital Ethics Committee Is A Properly Constituted Human Research Ethics Committee In Accordance With The National Statement On Ethical Conduct In Human Research (2007).

Appendix C Informed Consent

ALFRED PSYCHIATRY RESEARCH CENTRE

Po Box 315, Prahran 3181, Victoria, Australia
Level 1, Old Baker Building, The Alfred Hospital
Commercial Road, Melbourne 3004, Australia
Tel: 61 (0) 3 9076 6924
Fax: 61 (0) 3 9076 8545

Participant Information and Consent Form: Healthy Controls

Full Project Title: A Multimodal Investigation of Body Dysmorphic Disorder (BDD)

Principal Researcher: Associate Professor Susan Rossell

1. Introduction

You are being invited to take part in this research project. You are being invited because you have expressed interest in response to one of our advertisements, or you are enrolled as part of A/Prof Susan Rossell's voluntary research participant database. You have been approached because you do not have any known mental health problems. The research project aims to further our understanding of body dysmorphic disorder (BDD). It aims to do this by comparing cognitive task performance and brain activation patterns of people with this condition to people with no known mental health problems.

This Participant Information and Consent Form tells you about the research project. It explains what is involved in the research project to help you decide if you want to take part in it.

Please read the information carefully, and ask questions about anything that you don't understand or would like to know more about (contact details for the researchers can be found at the end of this document). Before deciding whether to take part, you might want to talk about it with a relative or friend.

Participation in this research is voluntary. If you don't wish to take part, you do not have to.

If you decide to take part in the research project you will be asked to indicate this by signing the consent section. By signing the consent section you are telling us that you;

- understand what you have read;
- consent to take part in the research project;
- consent to be involved in the procedures described, and;
- consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2. What is the purpose of this research project?

At present, very little research has investigated the causes or maintaining factors involved in BDD. It is the aim of this study to help clarify how this disorder is recognised, classified, and how it should be assessed and treated. Further understanding of BDD should aid in improving treatments and outcomes for those with the disorder.

It is currently thought that people with BDD, obsessive compulsive disorder (OCD), and schizophrenia have problems in the way they perceive and process things, but in different ways. Previous studies have shown that face processing is different in persons with BDD. But no study has comprehensively

investigated other cognitions in BDD like memory and attention. In addition, there is no evidence as to whether brain function and structure is different in BDD. We will collect data to look at this.

The research is a collaborative project involving researchers from a number of universities and specialised clinics. This study is a sub-component of a larger research project investigating cognition and brain structure in a total of 160 people; 40 people with BDD, 40 people with OCD, 40 people with schizophrenia, and 40 people with no known mental health problems. This will enable us to understand how BDD people perform in comparison to (a) other common mental health problems and (b) individuals with no mental health problems. A Monash University Strategic Grant has provided funding for this project.

3. What does participation in this research project involve?

Participation in this research project is divided into two parts:

1. A clinical interview and cognitive assessment session,
2. A brain scanning session using Magnetic Resonance Imaging.

All participants will be asked to complete the first part. This part involves an interview and questionnaires which assess the symptoms of BDD, OCD, and schizophrenia, as well as depression, belief formation, and self evaluation of physical characteristics. It also involves a number of tasks that examine processes like memory, attention and reading. This part of the research is expected to take around 2 hours (including breaks), and will take place at the Alfred Psychiatry Research Centre at the Alfred Hospital, 1st Floor, Old Baker Building, Commercial Road, Prahran, OR, at the Victorian Transcultural Psychiatry Unit at St Vincent's Hospital, Bolte Wing, 14 Nicholson Street, Fitzroy OR, at the Murdoch Research Institute, Medical Imaging Department, Royal Children's Hospital, Flemington Road, Parkville, whichever is most convenient to you.

For the second part of the research, volunteers will be asked to attend a magnetic resonance imaging session at the Murdoch Research Institute, Medical Imaging Department, Royal Children's Hospital, Flemington Road, Parkville. At this venue, participants will perform the facial emotion recognition task whilst researchers use specialised equipment to monitor and record the activation of different parts of their brains. We will also take some detailed pictures of your brain.

You will be given informal feedback as to your performance at all stages of the assessment process, however detailed results will not be provided due to time constraints and the experimental nature of some of the tasks. Instead a newsletter will be sent to you with the research project's findings once it has been completed. You will be reimbursed $20 per hour for your time and to cover any travel expenses incurred as a result of participating in each session of this research project.

4. What are the possible benefits?

There will be no clear immediate benefits to you from your participation; however, possible future benefits to the community may include early identification, intervention, and possible advances in therapeutic treatments for body dysmorphic disorder.

5. What are the possible risks?

There are minimal foreseeable risks involved in participating in this research project. Some people may find filling out questionnaires and performing tasks tiring, however breaks have been incorporated to help relieve this. This part of the research can be completed over several sessions if you require it.

The Magnetic Resonance Imaging (brain scanning) machinery can be noisy, and requires you to be still in a semi-enclosed space for periods of time. Some people may find this claustrophobic or uncomfortable,

however, breaks will be included. This session is a voluntary extra session in the study and you may choose to only participate in the first session if you wish.

The Magnetic Resonance Imaging (MRI) scan uses a very strong magnet to obtain images. There are no x-rays involved. It is a safe and painless procedure.

If you become upset or distressed as a result of your participation in the research, the researcher is able to arrange for counselling or other appropriate support. Any counselling or support will be provided by staff who are not part of the research team.

6. Do I have to take part in this research project?

Participation in any research project is voluntary. If you don't wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw at a later stage. If you do decide to withdraw, please notify a member of the research team.

If you decide to leave the project, the researchers would like to keep the personal and health information about you that has been collected. This will allow them to conduct some preliminary analyses on the data that has already been collected from you. If you don't want them to do this, please tell them before you withdraw.

Your decision to take part or not, or to take part and then withdraw, will not affect your relationship with the researchers or members of your treating team.

7. How will I be informed of the final results of this research project?

A summary of the general findings of this research will be made available to you via either post or email, if you have consented to receive such further communication. These results will potentially be published in appropriate scientific journals and presented at academic conferences. Final results may be expected to be available in 2012.

8. What will happen to the information about me?

Any information obtained in connection with this research project that can identify you will remain confidential and only used for the purpose of this study. It will only be disclosed with your permission, except as required by law.

The data that is collected from you will be de-identified, that is, reference to your identity will be replaced with a code. Data will be stored securely in a locked facility (e.g. locked filing cabinet) or under password protection (if electronic) and will only be accessible by the research team. All data will be stored indefinitely at the Alfred Psychiatry Research Center, in line with standard Alfred policy. Data derived from the present study may also be compared with that from previous research conducted by the same investigators.

In any publication or presentation, information will be provided in such a way that you cannot be identified, except with your permission. All participants will remain anonymous, with results presented as pooled group data only.

9. Can I access researcher information kept about me?

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. Please contact one of the researchers named at the end of this document if you would like to access your information.

Further, in accordance with standard Alfred research policy, the information collected in this study will be retained indefinitely. You must be aware that the information will become de-identified at some point, and access to information about you after this point will not be possible.

10. Is this research project approved?

The ethical aspects of this research project have been approved by the Human Research Ethics Committee at the Alfred Hospital **(pending)**.

This study will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)* produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

11. Consent:

I have read this document and I understand the purposes, procedures, and risks of this research project as described within it.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project, as described.

I understand that I will be given a signed copy of this document to keep.

Do you wish to volunteer to take part in the second session – Magnetic Resonance Imaging (brain scanning) – of this study that is to be conducted on a separate day? Yes ☐ No ☐

Name of participant (printed): _____
Signature: _____ Date: _____

Please provide a postal or email address should you wish for a summary of the general research findings, in the form of a newsletter, or any further scientific communications that arise from our current research, to be made available to you upon completion of the study.
_____

Name of witness to participant's signature (printed): _____
Signature: _____ Date: _____

Declaration by researcher: I have given a verbal explanation of the research project, its procedures and risks, and I believe that the participant has understood that explanation.

Name of researcher (printed): _____
Signature: _____ Date: _____

BDD database

We are seeking permission to enter data from this current study onto a database on BDD. It is hoped by collecting data from a collection of studies on its clinical characteristics, cognitive profile and MRI scans we can learn more about the disorder. You do not have to give permission for your data from this current study to be entered onto this database.

☐ Yes, I agree to enter my data from the current study onto the BDD database.

☐ No, I do not give permission.

12. Who can I contact?

Who you may need to contact will depend on the nature of your query, therefore please note the following:

For further information and appointments:

If you want any further information concerning this research project, or if you have any medical problems, which may be related to your involvement in this study, you may contact the principal researcher, A/Prof **Susan Rossell** on **03 9076 8650**.

For complaints:

If you have any complaints about any aspect of this research project, the way it is being conducted, or have any questions about being a research participant in general, you may contact:

Name: Ms Rowan Frew
Position: Ethics Manager, Research and Ethics Unit
Telephone: 03 9076 3848

ALFRED PSYCHIATRY RESEARCH CENTRE

Po Box 315, Prahran 3181, Victoria, Australia
Level 1, Old Baker Building, The Alfred Hospital
Commercial Road, Melbourne 3004, Australia
Tel: 61 (0) 3 9076 6924
Fax: 61 (0) 3 9076 8545

Participant Information and Consent Form: Patient samples

Full Project Title: A multimodal investigation of body dysmorphic disorder (BDD)

Principal Researcher: Associate Professor Susan Rossell

1. Introduction

You are being invited to take part in this research project. You are being invited because you have expressed interest in this project and your contact details have been forwarded to us (e.g. from your clinician), or alternatively you have expressed interest in response to one of our advertisements, or you are enrolled as part of A/Prof Susan Rossell's voluntary research participant database. This could be because you have been diagnosed with one of the following: body dysmorphic disorder, obsessive compulsive disorder, or schizophrenia. The research project aims to further our understanding of body dysmorphic disorder. It aims to do this by comparing cognitive performance and brain activation patterns of people with this condition to people with obsessive compulsive disorder and schizophrenia.

This Participant Information and Consent Form tells you about the research project. It explains what is involved in the research project to help you decide if you want to take part in it.

Please read the information carefully, and ask questions about anything that you don't understand or would like to know more about (contact details for the researchers can be found at the end of this document). Before deciding whether or not to take part, you might want to talk about it with a relative, friend or you local health worker or clinician.

Participation in this research is voluntary. If you don't wish to take part, you do not have to.

If you decide to take part in the research project you will be asked to indicate this by signing the consent section (below). By signing the consent section you are telling us that you;

- understand what you have read;
- consent to take part in the research project;
- consent to be involved in the procedures described, and;
- consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

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At present, very little research has investigated the causes or maintaining factors involved in body dysmorphic disorder (BDD). It is the aim of this study to help clarify how this disorder is recognized, understood, classified, and how it should be assessed and treated. Further understanding of it should aid in improving treatments and outcomes for those suffering with this disorder.

It is currently thought that people with BDD, obsessive compulsive disorder, and schizophrenia all have problems in the way they perceive certain things, but in different ways.

This research project will involve collecting information from a total of 160 people; 40 people with body dysmorphic disorder, 40 people with obsessive compulsive disorder, 40 people with schizophrenia, and 40 people with no known mental health problems (to act as a point of comparison). The research is a collaborative project involving researchers with different but relevant expertise from a number of universities and specialised clinics. A Monash University Strategic Grant has provided funding for this project.

3. What does participation in this research project involve?

Participation in this research project is divided into two parts:

3. A clinical interview and cognitive assessment session,
4. A brain scanning session using Magnetic Resonance Imaging.

All participants will be asked to complete the first part. This part involves an interview and questionnaires which assess the symptoms of body dysmorphic disorder, obsessivecompulsive disorder, and schizophrenia, as well as depression, belief formation, and selfevaluation of physical characteristics. It also involves a number of tasks that examine processes like memory, attention and reading. This part of the research is expected to take around 2 hours (including breaks), and will take place at the Alfred Psychiatry Research Centre at the Alfred Hospital, 1st Floor, Old Baker Building, Commercial Road, Prahran, OR, at the Victorian Transcultural Psychiatry Unit at St Vincent's Hospital, Bolte Wing, 14 Nicholson Street, Fitzroy, whichever is most convenient to you.

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You will be given informal feedback as to your performance at all stages of the assessment process, however detailed results will not be provided due to time constraints and the experimental nature of some of the tasks. Instead a newsletter will be sent to you with the research project's findings once it has been completed.

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The Magnetic Resonance Imaging (brain scanning) machinery can be noisy, and requires you to be still in a semi-enclosed space for periods of time. Some people may find this claustrophobic or uncomfortable, however breaks will be included. This session is a voluntary extra session in the study and you may choose only to participate in the first session if you wish.

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If you become upset or distressed as a result of your participation in the research, the researcher is able to arrange for counselling or other appropriate support. Any counselling or support will be provided by staff who are not part of the research team.

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If you decide to leave the project, the researchers would like to keep the personal and health information about you that has been collected. This will allow them to conduct some preliminary analyses on the data that has already been collected from you. If you don't want them to do this, please tell them before you withdraw.

Your decision to take part or not, or to take part and then withdraw, will not affect your relationship with the researchers or members of your treating team.

7. How will I be informed of the final results of this research project?

A summary of the general findings of this research will be made available to you via either post or email, if you have consented to receive such further communication. These results will potentially be published in appropriate scientific journals and presented at academic conferences. Final results may be expected to be available in 2012.

8. What will happen to the information about me?

Any information obtained in connection with this research project that can identify you will remain confidential and only used for the purpose of this study. It will only be disclosed with your permission, except as required by law.

The data that is collected from you will be de-identified, that is, reference to your identity will be replaced with a code. Data will be stored securely in a locked facility (e.g. locked filing cabinet) or under password protection (if electronic) and will only be accessible by the research team. All data will be stored indefinitely at the Alfred Psychiatry Research Center, in line with standard Alfred policy. Data derived from the present study may also be compared with that from previous research conducted by the same investigators.

In any publication or presentation, information will be provided in such a way that you cannot be identified, except with your permission. All participants will remain anonymous, with results presented as pooled group data only.

9. Can I access researcher information kept about me?

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. Please contact one of the researchers named at the end of this document if you would like to access your information.

Further, in accordance with standard Alfred research policy, the information collected in this study will be retained indefinitely. You must be aware that the information will become de-identified at some point, and access to information about you after this point will not be possible.

10. Is this research project approved?

The ethical aspects of this research project have been approved by the Human Research Ethics Committee at the Alfred Hospital **(pending)**.

This study will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)* produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

11. Consent:

I have read this document and I understand the purposes, procedures, and risks of this research project as described within it.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project, as described.

I understand that I will be given a signed copy of this document to keep.

Do you wish to volunteer to take part in the second session – Magnetic Resonance Imaging (brain scanning) – of this study that is to be conducted on a separate day? Yes ☐ No ☐

Name of participant (printed): _____
Signature: _____ Date: _____

Please provide a postal or email address should you wish for a summary of the general research findings, in the form of a newsletter, or any further scientific communications that arise from our current research, to be made available to you upon completion of the study.

_____

Name of witness to participant's signature (printed): _____

Signature: _____ Date: _____

Declaration by researcher: I have given a verbal explanation of the research project, its procedures and risks, and I believe that the participant has understood that explanation.

Name of researcher (printed): _____
Signature: _____ Date: _____

BDD database

We are seeking permission to enter data from this current study onto a database on BDD. It is hoped by collecting data from a collection of studies on its clinical characteristics, cognitive profile and MRI scans we can learn more about the disorder. You do not have to give permission for your data from this current study to be entered onto this database.

☐ Yes, I agree to enter my data from the current study onto the BDD database.

☐ No, I do not give permission.

12. Who can I contact?

Who you may need to contact will depend on the nature of your query, therefore please note the following:

For further information and appointments:

If you want any further information concerning this research project, or if you have any medical problems, which may be related to your involvement in this study, you may contact the principal researcher, A/Prof **Susan Rossell** on **03 9076 8650**.

For complaints:

If you have any complaints about any aspect of this research project, the way it is being conducted, or any questions about being a research participant in general, you may contact:

Name: Ms Rowan Frew
Position: Ethics Manager, Research and Ethics Unit
Telephone: 03 9076 3848

Appendix D Measures

Participant ID number:..... **Date:**.....

Study: BDD Study 111/09

CLINICAL DEMOGRAPHIC INFORMATION

1. Date of Birth: ___ ___-___ ___-___ ___ ___ ___
   Day Month Year

2. Age at start of Study: ____ ____

3. Sex:
   - ❑ Male$_1$
   - ❑ Female$_2$

4. Handedness
   - ❑ Right$_1$
   - ❑ Left$_2$

5. Country of Birth:
   - ❑ Australia$_1$
   - ❑ UK and Ireland$_2$
   - ❑ Europe (including former USSR) $_3$
   - ❑ North America$_4$
   - ❑ Central and South America$_5$
   - ❑ NZ, Pacific islands, PNG$_6$
   - ❑ East Asia (China, Japan, Korea, Taiwan, Hong Kong) $_7$
   - ❑ South East Asia$_8$
   - ❑ Indian subcontinent and other Asia$_9$
   - ❑ Middle East$_{10}$
   - ❑ North Africa$_{11}$
   - ❑ Central and Southern Africa$_{12}$
   - ❑ Other$_{13}$_____

6. Ethnicity:
   - ❑ Caucasian$_1$
   - ❑ African Descent$_2$
   - ❑ Asian$_3$
   - ❑ Hispanic$_4$
   - ❑ Aboriginal or Torres Strait Islander$_5$
   - ❑ Other$_6$_____

7. Primary Language

- ☐ English$_1$
- ☐ Other$_2$_____

8. Marital Status:

- ☐ Single: (Never married)
- ☐ Defacto$_2$
- ☐ Married$_3$
- ☐ Divorced$_4$
- ☐ Separated$_5$
- ☐ Widowed$_6$
- ☐ Other$_7$_____

9. Education:

- ☐ Primary School qualification$_1$
- ☐ Secondary School Qualification$_2$
- ☐ Trade Certificate/apprenticeship$_3$
- ☐ Tafe/Diploma$_4$
- ☐ Undergraduate university degree$_5$
- ☐ Post graduate Degree$_6$
- ☐ Masters/Doctorate/PhD$_7$
- ☐ Other$_8$_____

Total years of Education _____

10. Employment:

- ☐ Unemployed$_1$
- ☐ Employed Full-time$_2$
- ☐ Employed Part-time$_3$
- ☐ Employed Casual$_4$
- ☐ Self Employed$_5$
- ☐ House duties$_6$
- ☐ Student$_7$
- ☐ Retired$_8$

Participant ID number:..... **Date:**.....

Study: BDD Study 111/09

MEDICAL AND PSYCHIATRIC INFORMATION

1. Have you ever suffered from a head injury accompanied by a loss of consciousness that lasted for longer than 5 minutes or required hospitalisation?

- ☐ Yes$_1$
- ☐ No$_2$
- ☐ Do not know$_3$

2. Do you have a neurological or seizure disorder?

- ☐ Yes$_1$
- ☐ No$_2$

If so, please specify:

_____

_____

_____

3. Please list all medications you are currently taking:

Name	*Dosage (per day)*	*Purpose*

4. Do you have a psychiatric diagnosis?

- ☐ Yes$_1$
- ☐ No$_2$

If so, please specify:

_____

_____

_____

5. Age of diagnosis: _____

6. Duration of condition to this point (*years / months*):_____

WTAR Word List

Say, **I will show you some words that I will ask you to pronounce.** Place the WTAR Word Card in front of the examinee. As you point to the card, say, **Beginning with the first word on the list, pronounce each word aloud. Start with this word** (point to Item 1), **and go down this column, one right after the other, without skipping any. When you finish this column, go to the next column** (point to the second column). **Pronounce each word even if you are unsure. Do you understand?** When you are sure that the examinee understands the task, say, **Ready? Begin.**

	Item	Pronunciation	Score (0, 1)		Item	Pronunciation	Score (0, 1)
1.	again	uh-GEHN *or* uh-GAIN		26.	conscientious	kon-chee-EN-shus *or* kon-chee-INCH-us	
2.	address	uh-DRESS *or* AD-dress		27.	homily	HAHM-uh-lee	
3.	cough	kawf *or* kof		28.	malady	MAL-uh-dee	
4.	preview	PREE-vyue		29.	subtle	SUH-tl	
5.	although	awl-THO		30.	fecund	FE-cund *or* FEE-cund	
6.	most	mohst		31.	palatable	PAL-uh-tuh-bul	
7.	excitement	eck-SITE-munt *or* ik-SITE-munt		32.	menagerie	muh-NAJ-uh-ree	
8.	know	noh *or* no		33.	obfuscate	OB-fuh-skate *or* ob-FUH-skate	
9.	plumb	plum		34.	liaison	lee-A-zahn *or* LAY-a-zahn *or* LEE-ah-zahn	
10.	decorate	DEK-uh-rate		35.	exigency	EKS-eh-jen-see *or* ek-ZEE-jen-see	
11.	fierce	firhrss		36.	xenophobia	zen-uh-FO-bee-uh *or* zeen-uh-FO-bee-uh	
12.	knead	need		37.	ogre	OH-gur	
13.	aisle	EYE-l		38.	scurrilous	SKUR-uh-lus *or* SKUH-ruh-lus	
14.	vengeance	VEN-junts *or* VIN-junts		39.	ethereal	ih-THEER-ee-uhl *or* ih-THIR-ee-uhl	
15.	prestigious	pre-STIJ-us *or* pre-STEEJ-us		40.	paradigm	PAIR-uh-dime *or* PAIR-uh-dim	
16.	wreathe	reeTH		41.	perspicuity	pur-spuh-KYEW-uh-tee	
17.	gnat	nat		42.	plethora	PLETH-er-aah	
18.	amphitheater	AM(p)-fuh-the-uh-ter		43.	lugubrious	loo-GOO-bree-us *or* luh-GOO-bree-us *or* loo-GYEW-bree-us	
19.	lieu	loo		44.	treatise	TREET-us	
20.	grotesque	gro-TESK		45.	dilettante	DILL-uh-tahnt	
21.	iridescent	ihr-uh-DESS-unt		46.	vertiginous	vur-TI-jin-us *or* vur-TIJ-uh-nus	
22.	ballet	BA-lay *or* ba-LAY		47.	ubiquitous	you-BIC-wuh-tus *or* you-BIH-kwah-tus	
23.	equestrian	ih-KWESS-tree-un		48.	hyperbole	hi-PUR-buh-lee	
24.	porpoise	POR-pus		49.	insouciant	in-SOO-see-yunt	
25.	aesthetic	ess-THET-ik *or* ees-THET-ik		50.	hegemony	heh-JEM-o-nee *or* he-je-MO-nee	

WTAR Raw Score

WTAR Standard Score

Body Dysmorphic Disorder Diagnostic Module (BDD-DM)

Have you ever been very worried about your appearance in any way?

IF YES: What was your concern? Did you think (body part) was especially unattractive?

What about the appearance of your face, skin, hair, nose, or the shape/ size/other aspect of any other part of your body?

Did this concern preoccupy you? That is, did you think about it a lot and wish you could worry less about it? (Did others say that you were more concerned about (body part) than you should have been?)

What effect has this preoccupation has on your life? (Has it caused you a lot of distress?)

Has your concern had any effect on your friends or family?

(If concern is secondary to Anorexia Nervosa, score *1*)

A. Preoccupation with an imagined defect in appearance. If a slight physical anomaly is present, the person's concern is markedly excessive. **1 2 3**

NOTE: GIVE SOME EXAMPLES EVEN IF PATIENT ANSWERS NO TO THESE QUESTIONS.

Examples include skin concerns (eg. acne, scars, wrinkles, paleness), hair concerns (eg. thinning), or the size or shape of the nose, jaw, lips, etc.

Also consider perceived 'defects' of hands, genitals, or any other body part.

NOTE: LIST ALL BODY PARTS OF CONCERN.

B. Preoccupation causes clinically significant distress OR impairment in social, occupational, or other important areas of functioning. **1 2 3**

NOTE: IF SLIGHT PHYSICAL DEFECT IS PRESENT, CONCERN IS CLEARLY EXCESSIVE.

C. The preoccupation is not better accounted for by another mental disorder (eg. dissatisfaction with body size and shape in Anorexia Nervosa). **1 2 3**

1 = absent ***2 = subthreshold*** ***3 = threshold or true***

To meet DSM-IV criteria for BDD, all questions must receive a score of 3.

Edinburgh Handedness Inventory[1]

Your Initials:_____

Please Indicate With A Check (✓) Your Preference In Using Your Left Or Right Hand In The Following Tasks.

Where The Preference Is So Strong You Would Never Use The Other Hand, Unless Absolutely Forced To, Put Two Checks (✓✓).

If You Are Indifferent, Put One Check In Each Column (✓ | ✓).

Some Of The Activities Require Both Hands. In These Cases, The Part Of The Task Or Object For Which Hand Preference Is Wanted Is Indicated In Parentheses.

Task / Object	Left Hand	Right Hand
1. Writing		
2. Drawing		
3. Throwing		
4. Scissors		
5. Toothbrush		
6. Knife (Without Fork)		
7. Spoon		
8. Broom (Upper Hand)		
9. Striking A Match (Match)		
10. Opening A Box (Lid)		
Total Checks:	Lh =	Rh =
Cumulative Total	Ct = Lh + Rh =	
Difference	D = Rh – Lh =	
Result	R = (D / Ct) × 100 =	
Interpretation: (Left Handed: R < -40) (Ambidextrous: -40 ≤ R ≤ +40) (Right Handed: R > +40)		

[1] Oldfield, R. C. (1971). The Assessment And Analysis Of Handedness: The Edinburgh Inventory. *Neuropsychololgia, 9*, 97-113.

SIAS - Social Interaction Anxiety Scale

For each item, please enter an x in the column to indicate the degree to which you feel the statement is characteristic or true for you. The rating scale is as follows:

0 = Not At All Characteristic Or True Of Me.
1 = Slightly Characteristic Or True Of Me.
2 = Moderately Characteristic Or True Of Me.
3 = Very Characteristic Or True Of Me.
4 = Extremely Characteristic Or True Of Me.

	0	1	2	3	4
I get nervous if i have to speak with someone in authority (teacher, boss, etc.).					
I have difficulty making eye contact with others.					
I become tense if i have to talk about myself or my feelings.					
I find It Difficult To Mix Comfortably With The People I Work With.					
I find It Easy To Make Friends My Own Age.					
I tense up if i meet an acquaintance in the street.					
When mixing socially, i am uncomfortable.					
I feel tense if i am alone with just one other person.					
I am at ease meeting people at parties, etc.					
I have difficulty talking with other people.					
I find It Easy To Think Of Things To Talk About.					
I worry about expressing myself in case i appear awkward.					
I find It Difficult To Disagree With Another's Point Of View.					
I have difficulty talking to attractive persons of the opposite sex.					
I find Myself Worrying That I Won't Know What To Say In Social Situations.					
I am nervous mixing with people i don't know well.					
I Feel i'll Say Something Embarrassing When Talking.					
When Mixing In A Group, I find Myself Worrying I Will Be Ignored.					
I am tense mixing in a group.					
I am unsure whether to greet someone i know only slightly.					

Zung Depression Scale

Please Read Each Statement And Decide How Much Of The Time The Statement Describes How You Have Been Feeling During The Past Several Days.

	A Little Of The Time	Some Of The Time	Good Part Of The Time	Most Of The Time
I Feel Down-Hearted And Blue				
Morning Is When I Feel The Best				
I Have Crying Spells Or Feel Like It				
I Have Trouble Sleeping At Night				
I Eat As Much As I Used To				
I Still Enjoy Sex				
I Notice That I Am Losing Weight				
I Have Trouble With Constipation				
My Heart Beats Faster Than Usual				
I Get Tired For No Reason				
My Mind Is As Clear As It Used To Be				
I Find It Easy To Do The Things I Used To				
I Am Restless And Can't Keep Still				
I Feel Hopeful About The Future				
I Am More Irritable Than Usual				
I Find It Easy To Make Decisions				
I Feel That I Am Useful And Needed				
My Life Is Pretty Full				
I Feel That Others Would Be Better Off If I Were Dead				
I Still Enjoy The Things I Used To Do.				

Body Dysmorphic Disorder Modification of the Yale-Brown Obsessive-Compulsive Scale (BDD-YBOCS)

For each item circle the number identifying the response which best characterises the patient during the **past week**. The patient's specific belief can be incorporated into the question. Optional questions are indicated in parentheses, and instructions to the interviewer are italicised.

---

1. TIME OCCUPIED BY THOUGHTS ABOUT BODY DEFECT

How much of your time is occupied by THOUGHTS about a defect or flaw in your appearance (list body parts of concern)?

0 – None.
1 – Mild (less than 1 hour per day).
2 – Moderate (1 to 3 hours per day).
3 – Severe (greater than 3 and up to 8 hours per day).
4 – Extreme (greater than 8 hours per day).

---

2. INTERFERENCE DUE TO THOUGHTS ABOUT BODY DEFECT

How much do your THOUGHTS about your body defect(s) interfere with your social or work (role) functioning? impaired.

(Is there anything you aren't doing or can't do because of them?)

0 – None.
1 – Mild, slight interference with social, occupational, or role activities, but overall performance not
2 – Moderate, definite interference with social, occupational, or role performance, but still manageable.
3 – Severe, causes substantial impairment in social, occupational, or role performance.
4 – Extreme, incapacitating.

---

3. DISTRESS ASSOCIATED WITH THOUGHTS ABOUT BODY DEFECT

How much distress do your THOUGHTS about your body defect(s) cause you?

Rate 'disturbing' feelings or anxiety that seem to be triggered by these thoughts, not general anxiety or anxiety associated with other symptoms.

0 – None.
1 – Mild, not too disturbing.
2 – Moderate, disturbing but still manageable.
3 – Severe, very disturbing.
4 – Extreme, disabling distress.

---

4. RESISTANCE AGAINST THOUGHTS OF BODY DEFECT

How much of an effort do you make to resist these THOUGHTS? [Pause] How often do you try to disregard or turn your attention away from these thoughts as they enter your mind?

Only rate effort made to resist, not success or failure in actually controlling the thoughts. How much patient resists the thoughts may or may not correlate with ability to control them.

0 – Makes an effort to always resist, or symptoms so minimal doesn't need to actively resist.
1 – Tries to resist most of the time.
2 – Makes some effort to resist.
3 – Yields to all such thoughts without attempting to control them but yields with some reluctance.
4 – Completely and willingly yields to all such thoughts.

---

5. DEGREE OF CONTROL OVER THOUGHTS ABOUT BODY DEFECT

How much control do you have over your THOUGHTS about your body defect(s)? How successful are you in stopping or diverting these thoughts?

0 – Complete control, or no need for control because thoughts are so minimal.
1 – Much control, usually able to stop or divert these thoughts with some effort and concentration.
2 – Moderate control, sometimes able to stop or divert these thoughts.
3 – Little control, rarely successful in stopping thoughts, can only divert attention with difficulty.
4 – No control, experienced as completely involuntary, rarely able to even momentarily divert attention.

---

6. TIME SPENT IN ACTIVITIES RELATED TO BODY DEFECT

The next several questions are about the activities/ behaviours you do in relation to your body defect(s).

Read list of activities below to determine which ones the patient engages in.

0 – None.
1 – Mild (less than 1 hour per day).
2 – Moderate (1 to 3 hours per day).
3 – Severe (greater than 3 and up to 8 hours per day).
4 – Extreme (greater than 8 hours per day).

How much time do you spend in ACTIVITIES related to your concern over your appearance [read activities patient engages in]?
Read list of activities (check all that apply)
___ *Checking mirrors/other surfaces*
___ *Grooming activities*
___ *Applying makeup*
___ *Camouflaging with clothing/other cover (rate time spent selecting/changing clothes, not time wearing them)*
___ *Scrutinising others' appearance (comparing)*
___ *Questioning others about/discussing your appearance*
___ *Picking at skin*
___ *Other* _____

---

7. INTERFERENCE DUE TO ACTIVITIES RELATED TO BODY DEFECT

How much do these ACTIVITIES interfere with your social or work (role) functioning?
(Is there anything you don't do because of them?)

0 – None
1 – Mild, slight interference with social, occupational, or role activities, but overall performance not impaired.
2 – Moderate, definite interference with social, occupational, or role performance, but still manageable.
3 – Severe, causes substantial impairment in social, occupational, or role performance.
4 – Extreme, incapacitating.

---

8. DISTRESS ASSOCIATED WITH ACTIVITIES RELATED TO BODY DEFECT

How would you feel if you were prevented from performing these ACTIVITIES? [Pause] How anxious would you become?
Rate degree of distress/frustration patient would experience

0 – None.
1 – Mild, only slightly anxious if behaviour prevented, or only slight anxiety during the behaviour.
2 – Moderate, reports that anxiety would mount but remain manageable if behaviour is prevented, or that anxiety increases but remains manageable during the behaviour.

If performance of the activities were suddenly interrupted. prominent and incapacitating	3 – Severe, prominent and very disturbing increase in anxiety if behaviour is interrupted, or very disturbing increase in anxiety during the behaviour. 4 – Extreme, incapacitating anxiety from any intervention aimed at modifying activity, or anxiety develops during the behaviour.

9. **RESISTANCE AGAINST COMPULSIONS** How much of an effort do you make to resist these ACTIVITIES? *Only rate effort made to resist, not success or failure in* some *actually controlling the activities. How much the patient resists these behaviours may or may not correlate with his/her ability to control them.*	0 – Makes an effort to always resist, or symptoms so minimal doesn't need to actively resist. 1 – Tries to resist most of the time. 2 – Makes some effort to resist. 3 – Yields to almost all of these behaviours without attempting to control them, but does so with reluctance. 4 – Completely and willingly yields to all such behaviours.

10. **DEGREE OF CONTROL OVER COMPULSIVE BEHAVIOUR** How strong is the drive to perform these behaviours? [Pause] How much control do you have over them? voluntary only with overpowering, rarely	0 – Complete control, or control is unnecessary because symptoms are mild. 1 – Much control, experiences pressure to perform the behaviour, but usually able to exercise control over it. 2 – Moderate control, strong pressure to perform behaviour, can control it only with difficulty. 3 – Little control, very strong drive to perform behaviour, must be carried to completion, can delay difficulty. 4 – No control, drive to perform behaviour experienced as completely involuntary and able to even momentarily delay behaviour.

11. **INSIGHT** Is it possible that your defect might be less noticeable or less unattractive than you think it is? [Pause] How convinced are convinced you that [fill in body part] is as unattractive as you think it is? [Pause] Can anyone convince you that it doesn't look so bad? contrary	0 – Excellent insight, fully rational. 1 – Good insight. Readily acknowledges absurdity of thoughts (but doesn't seem completely there isn't something besides anxiety to be concerned about). 2 – Fair insight. Reluctantly admits that thoughts seem unreasonable but wavers. 3 – Poor insight. Maintains that thoughts are not unreasonable. 4 – Lacks insight, delusional. Definitely convinced that concerns are reasonable, unresponsive to evidence.

12. **AVOIDANCE**

Have you been avoiding doing anything, going any place, or being with anyone because of your thoughts or behaviours related to your body defect(s)?
IF YES, then ask: What do you avoid?

0 – No deliberate avoidance.
1 – Mild, minimal avoidance.
2 – Moderate, some avoidance clearly present.
3 – Severe, much avoidance; avoidance prominent.
4 – Extreme, very extensive avoidance; patient avoids almost all activities.

Rate degree to which patient deliberately tries to avoid things such as social interactions or work-related activities. Do not include avoidance of mirrors or avoidance of compulsive behaviours.

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 5.0.0

DSM-IV

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DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel.

M.I.N.I. 5.0.0 (July 1, 2006)

Patient Name:		*Patient Number:*	
Date of Birth:		*Time Interview Began:*	
Interviewer's Name:		*Time Interview Ended:*	
Date of Interview:		*Total Time:*	

	MODULES	TIME FRAME	MEETS CRITERIA	DSM-IV	ICD-10	
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks)	☐	296.20-296.26 Single	F32.x	☐
		Recurrent	☐	296.30-296.36 Recurrent	F33.x	☐
	MDE WITH MELANCHOLIC FEATURES Optional	Current (2 weeks)	☐	296.20-296.26 Single 296.30-296.36 Recurrent	F32.x F33.x	☐ ☐
B	DYSTHYMIA	Current (Past 2 years)	☐	300.4	F34.1	☐
C	SUICIDALITY	Current (Past Month) Risk: ☐ Low ☐ Medium ☐ High	☐			☐
D	MANIC EPISODE	Current	☐	296.00-296.06	F30.x-F31.9	☐
		Past	☐			
	HYPOMANIC EPISODE	Current	☐	296.80-296.89	F31.8-F31.9/F34.0	☐
		Past	☐			
E	PANIC DISORDER	Current (Past Month)	☐	300.01/300.21	F40.01-F41.0	☐
		Lifetime	☐			
F	AGORAPHOBIA	Current	☐	300.22	F40.00	☐
G	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month)	☐	300.23	F40.1	☐
H	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	☐	300.3	F42.8	☐
I	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	☐	309.81	F43.1	☐
J	ALCOHOL DEPENDENCE	Past 12 Months	☐	303.9	F10.2x	☐
	ALCOHOL ABUSE	Past 12 Months	☐	305.00	F10.1	☐
K	SUBSTANCE DEPENDENCE (Non-alcohol)	Past 12 Months	☐	304.00-.90/305.20-.90	F11.1-F19.1	☐
	SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months	☐	304.00-.90/305.20-.90	F11.1-F19.1	☐
L	PSYCHOTIC DISORDERS	Lifetime	☐	295.10-295.90/297.1/	F20.xx-F29	☐
		Current	☐	297.3/293.81/293.82/ 293.89/298.8/298.9		
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Lifetime	☐	296.24/296.34/296.44	F32.3/F33.3/ ☐	
		Current	☐	296.24/296.34/296.44	F30.2/F31.2/F31.5 F31.8/F31.9/F39 ☐	
M	ANOREXIA NERVOSA	Current (Past 3 Months)	☐	307.1	F50.0	☐
N	BULIMIA NERVOSA	Current (Past 3 Months)	☐	307.51	F50.2	☐
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current	☐	307.1	F50.0	☐

O	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	☐	300.02	F41.1	❐
P	ANTISOCIAL PERSONALITY DISORDER Optional	Lifetime	☐	301.7	F60.2	❐

Which problem troubles you the most? Indicate your response by checking the appropriate check box(es).

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization for lay interviewers for ICD-10). The results of these studies show that the M.I.N.I. has acceptably high validation and reliability scores, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. is divided into **modules** identified by letters, each corresponding to a diagnostic category.

•At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a **gray box**.

•At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAPITALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « **bold** » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them (➡) indicate that one of the criteria necessary for the diagnosis(es) is not met. In this case, the interviewer should go to the end of the module, circle « **NO** » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, question H6).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either Yes or No. Clinical judgment by the rater should be used in coding the responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that <u>each dimension</u> of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).

<u>Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I.</u> The M.I.N.I. Plus has questions that investigate these issues.

For any questions, suggestions, need for a training session, or information about updates of the M.I.N.I., please contact :

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A. MAJOR DEPRESSIVE EPISODE

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

A1	Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks?	NO	YES
A2	In the past two weeks, have you been much less interested in most things or much less able to enjoy the things you used to enjoy most of the time?	NO	YES
	IS **A1** OR **A2** CODED **YES?** ➡	NO	YES

A3 **Over the past two weeks, when you felt depressed or uninterested:**

a	Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by ±5% of body weight or ±8 lbs. or ±3.5 kgs., for a 160 lb./70 kg. person in a month)? IF YES TO EITHER, CODE YES.	NO	YES *
b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES
c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day?	NO	YES *
d	Did you feel tired or without energy almost every day?	NO	YES
e	Did you feel worthless or guilty almost every day?	NO	YES
f	Did you have difficulty concentrating or making decisions almost every day?	NO	YES
g	Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead?	NO	YES

ARE **5** OR MORE ANSWERS (**A1**-**A3**) CODED **YES**?

NO **YES ***

MAJOR DEPRESSIVE EPISODE, CURRENT

IF PATIENT HAS CURRENT MAJOR DEPRESSIVE EPISODE CONTINUE TO A4, OTHERWISE MOVE TO MODULE B:

A4	a	During your lifetime, did you have other episodes of two weeks or more when you felt depressed or uninterested in most things, and had most of the problems we just talked about? ➡	NO	YES
	b	In between 2 episodes of depression, did you ever have an interval of at least 2 months, without any depression and any loss of interest?		

NO **YES**

MAJOR DEPRESSIVE EPISODE, RECURRENT

* If patient has Major Depressive Episode, Current, use this information in coding the corresponding questions on page 5 (A6d, A6e).

MAJOR DEPRESSIVE EPISODE WITH MELANCHOLIC FEATURES (optional)

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE **NO**, AND MOVE TO THE NEXT MODULE)

IF THE PATIENT CODES POSITIVE FOR A CURRENT MAJOR DEPRESSIVE EPISODE (**A3 = YES**), EXPLORE THE FOLLOWING:

A5	a	During the most severe period of the current depressive episode, did you lose almost completely your ability to enjoy nearly everything?	NO	YES
	b	During the most severe period of the current depressive episode, did you lose your ability to respond to things that previously gave you pleasure, or cheered you up? **IF NO:** When something good happens does it fail to make you feel better, even temporarily?	NO	YES
		IS EITHER **A5a** OR **A5b** CODED **YES**?	➡ NO	YES

A6		**Over the past two week period, when you felt depressed and uninterested:**		
	a	Did you feel depressed in a way that is different from the kind of feeling you experience when someone close to you dies?	NO	YES
	b	Did you feel regularly worse in the morning, almost every day?	NO	YES
	c	Did you wake up at least 2 hours before the usual time of awakening and have difficulty getting back to sleep, almost every day?	NO	YES
	d	IS **A3c** CODED **YES** (PSYCHOMOTOR RETARDATION OR AGITATION)?	NO	YES
	e	IS **A3a** CODED **YES** FOR ANOREXIA OR WEIGHT LOSS?	NO	YES
	f	Did you feel excessive guilt or guilt out of proportion to the reality of the situation?	NO	YES

ARE **3** OR MORE **A6** ANSWERS CODED **YES**?

NO	**YES**
Major Depressive Episode **with** ***Melancholic Features Current***	

B. DYSTHYMIA

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE **NO**, AND MOVE TO THE NEXT MODULE)

IF PATIENT'S SYMPTOMS CURRENTLY MEET CRITERIA FOR MAJOR DEPRESSIVE EPISODE, DO NOT EXPLORE THIS MODULE.

B1		Have you felt sad, low or depressed most of the time for the last two years?	➡ NO	YES
B2		Was this period interrupted by your feeling OK for two months or more?	NO	➡ YES
B3		**During this period of feeling depressed most of the time:**		
	a	Did your appetite change significantly?	NO	YES
	b	Did you have trouble sleeping or sleep excessively?	NO	YES
	c	Did you feel tired or without energy?	NO	YES
	d	Did you lose your self-confidence?	NO	YES
	e	Did you have trouble concentrating or making decisions?	NO	YES
	f	Did you feel hopeless?	NO	YES
		ARE **2** OR MORE **B3** ANSWERS CODED **YES**?	➡ NO	YES
B4		Did the symptoms of depression cause you significant distress or impair your ability to function at work, socially, or in some other important way?		

NO **YES**

DYSTHYMIA
CURRENT

C. SUICIDALITY

In the past month did you:

				Points
C1	Suffer any accident? IF NO TO C1, SKIP TO C2; IF YES, ASK C1a,:	NO	YES	0
C1a	Plan or intend to hurt yourself in that accident either passively or actively? IF NO TO C1a, SKIP TO C2: IF YES, ASK C1b,:	NO	YES	0
C1b	Did you intend to die as a result of this accident?	NO	YES	0
C2	Think that you would be better off dead or wish you were dead?	NO	YES	1
C3	Want to harm yourself or to hurt or to injure yourself?	NO	YES	2
C4	Think about suicide?	NO	YES	6

IF YES, ASK ABOUT THE INTENSITY AND FREQUENCY OF THE SUICIDAL IDEATION:

Frequency		Intensity	
Occasionally	❒	Mild	❒
Often	❒	Moderate	❒
Very often	❒	Severe	❒

→ Can you control these impulses and state that you will not act on them while in this program? Only score 8 points if response is NO. NO YES 8

C5	Have a suicide plan?	NO	YES	8
C6	Take any active steps to prepare to injure yourself or to prepare for a suicide attempt in which you expected or intended to die?	NO	YES	9
C7	Deliberately injure yourself without intending to kill yourself?	NO	YES	4
C8	Attempt suicide? Hoped to be rescued / survive ❒ Expected / intended to die ❒	NO	YES	10

In your lifetime:

C9	Did you ever make a suicide attempt?	NO	YES	4

IS AT LEAST **1** OF THE ABOVE (EXCEPT C1) CODED **YES**?

NO **YES**

IF YES, ADD THE TOTAL NUMBER OF POINTS FOR THE ANSWERS (C1-C9) CHECKED 'YES' AND SPECIFY THE LEVEL OF SUICIDE RISK AS INDICATED IN THE DIAGNOSTIC BOX:

MAKE ANY ADDITIONAL COMMENTS ABOUT YOUR ASSESSMENT OF THIS PATIENT'S CURRENT AND NEAR FUTURE SUICIDE RISK IN THE SPACE BELOW:

SUICIDE RISK CURRENT

1-8 points	Low	❒
9-16 points	Moderate	❒
≥ 17 points	High	❒

D. (HYPO) MANIC EPISODE

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

D1	a	Have you **ever** had a period of time when you were feeling 'up' or 'high' or 'hyper' or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.) IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY 'UP' OR 'HIGH' OR 'HYPER', CLARIFY AS FOLLOWS: By 'up' or 'high' or 'hyper' I mean: having elated mood; increased energy; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behavior. IF NO, CODE NO TO **D1b**: IF **YES** ASK:	NO	YES
	b	Are you currently feeling 'up' or 'high' or 'hyper' or full of energy?	NO	YES
D2	a	Have you **ever** been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified? IF NO, CODE NO TO **D2b**: IF **YES** ASK:	NO	YES
	b	Are you currently feeling persistently irritable?	NO	YES
		➡ IS **D1a** OR **D2a** CODED **YES**?	NO	YES

D3 IF **D1b** OR **D2b** = **YES**: EXPLORE THE **CURRENT** AND THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE
IF **D1b** AND **D2b** = **NO**: EXPLORE ONLY THE MOST SYMPTOMATIC **PAST** EPISODE

During the times when you felt high, full of energy, or irritable did you:

		Current Episode		Past Episode	
a	Feel that you could do things others couldn't do, or that you were an especially important person? IF YES, ASK FOR EXAMPLES. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. ❒ No ❒ Yes	NO	YES	NO	YES
b	Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES	NO	YES
c	Talk too much without stopping, or so fast that people had difficulty understanding?	NO	YES	NO	YES
d	Have racing thoughts?	NO	YES	NO	YES
e	Become easily distracted so that any little interruption could distract you?	NO	YES	NO	YES
f	Become so active or physically restless that others were worried about you?	NO	YES	NO	YES
g	Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?	NO	YES	NO	YES

		Current Episode		Past Episode	
				➡	
D3 (SUMMARY): ARE **3** OR MORE **D3** ANSWERS CODED **YES** (OR **4** OR MORE IF **D1a** IS **NO** (IN RATING PAST EPISODE) AND **D1b** IS NO (IN RATING CURRENT EPISODE)? RULE: ELATION/EXPANSIVENESS REQUIRES ONLY THREE D3 SYMPTOMS WHILE IRRITABLE MOOD ALONE REQUIRES **4** OF THE **D3** SYMPTOMS. VERIFY IF THE SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD.		NO	YES	NO	YES
D4	Did these symptoms last at least a week **and** cause significant problems at home, at work, socially, or at school, **or** were you hospitalized for these problems?	NO	YES	NO	YES
		↓	↓	↓	↓
	THE EPISODE EXPLORED WAS A:	❒ *HYPOMANIC EPISODE*	❒ *MANIC EPISODE*	❒ *HYPOMANIC EPISODE*	❒ *MANIC EPISODE*

IS **D4** CODED **NO**?

SPECIFY IF THE EPISODE IS CURRENT OR PAST.

NO	**YES**
HYPOMANIC EPISODE	
CURRENT	❒
PAST	❒

IS **D4** CODED **YES**?

SPECIFY IF THE EPISODE IS CURRENT OR PAST.

NO	**YES**
MANIC EPISODE	
CURRENT	❒
PAST	❒

E. PANIC DISORDER

(➡ MEANS : CIRCLE NO IN E5, E6 AND E7 AND SKIP TO F1)

E1	a	Have you, on more than one occasion, had spells or attacks when you **suddenly** felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	➡ NO	YES
	b	Did the spells surge to a peak within 10 minutes of starting?	➡ NO	YES
E2		At any time in the past, did any of those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner?	➡ NO	YES
E3		Have you ever had one such attack followed by a month or more of persistent concern about having another attack, or worries about the consequences of the attack or did you make a significant change in your behavior because of the attacks (e.g., shopping only with a companion, not wanting to leave your house, visiting the emergency room repeatedly, or seeing your doctor more frequently because of the symptoms?	NO	YES
E4		**During the worst spell that you can remember:**		
	a	Did you have skipping, racing or pounding of your heart?	NO	YES
	b	Did you have sweating or clammy hands?	NO	YES
	c	Were you trembling or shaking?	NO	YES
	d	Did you have shortness of breath or difficulty breathing?	NO	YES
	e	Did you have a choking sensation or a lump in your throat?	NO	YES
	f	Did you have chest pain, pressure or discomfort?	NO	YES
	g	Did you have nausea, stomach problems or sudden diarrhea?	NO	YES
	h	Did you feel dizzy, unsteady, lightheaded or faint?	NO	YES
	i	Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body?	NO	YES
	j	Did you fear that you were losing control or going crazy?	NO	YES
	k	Did you fear that you were dying?	NO	YES
	l	Did you have tingling or numbness in parts of your body?	NO	YES
	m	Did you have hot flushes or chills?	NO	YES
E5		ARE BOTH **E3,** AND **4** OR MORE **E4** ANSWERS, CODED **YES**?	NO	YES *PANIC DISORDER LIFETIME*
		IF YES TO E5, SKIP TO E7.		
E6		IF **E5** = **NO,** ARE ANY E4 ANSWERS CODED **YES**?	NO	YES *LIMITED SYMPTOM ATTACKS LIFETIME*
		THEN SKIP TO **F1.**		
E7		In the past month, did you have such attacks repeatedly (2 or more) followed by persistent concern about having another attack?	NO	YES *PANIC DISORDER CURRENT*

F. AGORAPHOBIA

F1	Do you feel anxious or uneasy in places or situations where you might have a panic attack or the panic-like symptoms we just spoke about, or where help might not be available or escape might be difficult: like being in a crowd, standing in a line (queue), when you are alone away from home or alone at home, or when crossing a bridge, traveling in a bus, train or car?	NO YES

IF **F1** = **NO**, CIRCLE **NO** IN **F2**.

F2	Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?	NO YES *AGORAPHOBIA CURRENT*

IS **F2** (CURRENT AGORAPHOBIA) CODED **NO**

and

IS **E7** (CURRENT PANIC DISORDER) CODED **YES**?

NO **YES**

PANIC DISORDER without Agoraphobia CURRENT

IS **F2** (CURRENT AGORAPHOBIA) CODED **YES**

and

IS **E7** (CURRENT PANIC DISORDER) CODED **YES**?

NO **YES**

PANIC DISORDER with Agoraphobia CURRENT

IS **F2** (CURRENT AGORAPHOBIA) CODED **YES**

and

IS **E5** (PANIC DISORDER LIFETIME) CODED **NO**?

NO **YES**

AGORAPHOBIA, CURRENT without history of Panic Disorder

G. SOCIAL PHOBIA (Social Anxiety Disorder)

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

G1	In the past month, were you fearful or embarrassed being watched, being the focus of attention, or fearful of being humiliated? This includes things like speaking in public, eating in public or with others, writing while someone watches, or being in social situations.	➡ NO	YES
G2	Is this social fear excessive or unreasonable?	➡ NO	YES
G3	Do you fear these social situations so much that you avoid them or suffer through them?	➡ NO	YES
G4	Do these social fears disrupt your normal work or social functioning or cause you significant distress?		

SUBTYPES

Do you fear and avoid 4 or more social situations?

If YES Generalized social phobia (social anxiety disorder)

If NO Non-generalized social phobia (social anxiety disorder)

NOTE TO INTERVIEWER: PLEASE ASSESS WHETHER THE SUBJECT'S FEARS ARE RESTRICTED TO NON-GENERALIZED ("ONLY 1 OR SEVERAL") SOCIAL SITUATIONS OR EXTEND TO GENERALIZED ("MOST") SOCIAL SITUATIONS. "MOST" SOCIAL SITUATIONS IS USUALLY OPERATIONALIZED TO MEAN 4 OR MORE SOCIAL SITUATIONS, ALTHOUGH THE DSM-IV DOES NOT EXPLICITLY STATE THIS.

EXAMPLES OF SUCH SOCIAL SITUATIONSTYPICALLY INCLUDE INITIATING OR MAINTAINING A CONVERSATION, PARTICIPATING IN SMALL GROUPS, DATING, SPEAKING TO AUTHORITY FIGURES, ATTENDING PARTIES, PUBLIC SPEAKING, EATING IN FRONT OF OTHERS, URINATING IN A PUBLIC WASHROOM, ETC.

NO **YES**

SOCIAL PHOBIA
(Social Anxiety Disorder)
CURRENT

GENERALIZED ❒

NON-GENERALIZED ❒

H. OBSESSIVE-COMPULSIVE DISORDER

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

H1	In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? (For example, the idea that you were dirty, contaminated or had germs, **or** fear of contaminating others, **or** fear of harming someone even though you didn't want to, **or** fearing you would act on some impulse, **or** fear or superstitions that you would be responsible for things going wrong, **or** obsessions with sexual thoughts, images or impulses, **or** hoarding, collecting, **or** religious obsessions.) (DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)	NO YES ↓ SKIP TO **H4**
H2	Did they keep coming back into your mind even when you tried to ignore or get rid of them?	NO YES ↓ SKIP TO **H4**
H3	Do you think that these obsessions are the product of your own mind and that they are not imposed from the outside?	NO YES **obsessions**
H4	In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, arranging things, or other superstitious rituals?	NO YES **compulsions**
	IS **H3** OR **H4** CODED **YES**?	➡ NO YES
H5	Did you recognize that either these obsessive thoughts or these compulsive behaviors were excessive or unreasonable?	➡ NO YES
H6	Did these obsessive thoughts and/or compulsive behaviors significantly interfere with your normal routine, your work or school, your usual social activities, or relationships, or did they take more than one hour a day?	**NO** **YES** ***O.C.D. CURRENT***

I. POSTTRAUMATIC STRESS DISORDER (optional)

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

I1	Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else? EXAMPLES OF TRAUMATIC EVENTS INCLUDE: SERIOUS ACCIDENTS, SEXUAL OR PHYSICAL ASSAULT, A TERRORIST ATTACK, BEING HELD HOSTAGE, KIDNAPPING, FIRE, DISCOVERING A BODY, SUDDEN DEATH OF SOMEONE CLOSE TO YOU, WAR, OR NATURAL DISASTER.	➡ NO	YES
I2	Did you respond with intense fear, helplessness or horror?	➡ NO	YES
I3	During the past month, have you re-experienced the event in a distressing way (such as, dreams, intense recollections, flashbacks or physical reactions)?	➡ NO	YES

I4	**In the past month:**			
	a	Have you avoided thinking about or talking about the event ?	NO	YES
	b	Have you avoided activities, places or people that remind you of the event?	NO	YES
	c	Have you had trouble recalling some important part of what happened?	NO	YES
	d	Have you become much less interested in hobbies or social activities?	NO	YES
	e	Have you felt detached or estranged from others?	NO	YES
	f	Have you noticed that your feelings are numbed?	NO	YES
	g	Have you felt that your life will be shortened or that you will die sooner than other people?	NO	YES
		ARE **3** OR MORE **I4** ANSWERS CODED **YES**?	➡ NO	YES
I5	**In the past month:**			
	a	Have you had difficulty sleeping?	NO	YES
	b	Were you especially irritable or did you have outbursts of anger?	NO	YES
	c	Have you had difficulty concentrating?	NO	YES
	d	Were you nervous or constantly on your guard?	NO	YES
	e	Were you easily startled?	NO	YES
		ARE **2** OR MORE **I5** ANSWERS CODED **YES**?	➡ NO	YES

I6 During the past month, have these problems significantly interfered with your work or social activities, or caused significant distress?

NO	YES
POSTTRAUMATIC STRESS DISORDER CURRENT	

J. ALCOHOL ABUSE AND DEPENDENCE

(➡ MEANS: GO TO DIAGNOSTIC BOXES, CIRCLE **NO** IN BOTH AND MOVE TO THE NEXT MODULE)

		➡	
J1	**In the past 12 months**, have you had 3 or more alcoholic drinks within a 3 hour period on 3 or more occasions?	NO	YES

J2 **In the past 12 months**:

a	Did you need to drink more in order to get the same effect that you got when you first started drinking?	NO	YES
b	When you cut down on drinking did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms or to avoid being hungover, for example, "the shakes", sweating or agitation? IF YES TO EITHER, CODE YES.	NO	YES
c	During the times when you drank alcohol, did you end up drinking more than you planned when you started?	NO	YES
d	Have you tried to reduce or stop drinking alcohol but failed?	NO	YES
e	On the days that you drank, did you spend substantial time in obtaining alcohol, drinking, or in recovering from the effects of alcohol?	NO	YES
f	Did you spend less time working, enjoying hobbies, or being with others because of your drinking?	NO	YES
g	Have you continued to drink even though you knew that the drinking caused you health or mental problems?	NO	YES

ARE **3** OR MORE **J2** ANSWERS CODED **YES**?

NO **YES***

* IF YES, SKIP J3 QUESTIONS, CIRCLE N/A IN THE ABUSE BOX AND MOVE TO THE NEXT DISORDER. DEPENDENCE PREEMPTS ABUSE.

ALCOHOL DEPENDENCE
CURRENT

J3 **In the past 12 months:**

a	Have you been intoxicated, high, or hungover more than once when you had other responsibilities at school, at work, or at home? Did this cause any problems? (CODE YES ONLY IF THIS CAUSED PROBLEMS.)	NO	YES
b	Were you intoxicated more than once in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES
c	Did you have legal problems more than once because of your drinking, for example, an arrest or disorderly conduct?	NO	YES
d	Did you continue to drink even though your drinking caused problems with your family or other people?	NO	YES

ARE **1** OR MORE **J3** ANSWERS CODED **YES**?

NO **N/A** **YES**

ALCOHOL ABUSE
CURRENT

K. NON-ALCOHOL PSYCHOACTIVE SUBSTANCE USE DISORDERS

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

Now I am going to show you / read to you a list of street drugs or medicines.

			➡	
K1	a	**In the past 12 months**, did you take any of these drugs more than once, to get high, to feel better, or to change your mood?	NO	YES

CIRCLE EACH DRUG TAKEN:

Stimulants: amphetamines, "speed", crystal meth, "crank", "rush", Dexedrine, Ritalin, diet pills.

Cocaine: snorting, IV, freebase, crack, "speedball".

Narcotics: heroin, morphine, Dilaudid, opium, Demerol, methadone, codeine, Percodan, Darvon, OxyContin.

Hallucinogens: LSD ("acid"), mescaline, peyote, PCP ("angel dust", "peace pill"), psilocybin, STP, "mushrooms", "ecstasy", MDA, MDMA, or ketamine ("special K").

Inhalants: "glue", ethyl chloride, "rush", nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers").

Marijuana: hashish ("hash"), THC, "pot", "grass", "weed", "reefer".

Tranquilizers: Quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown, GHB, Roofinol, "Roofies".

Miscellaneous: steroids, nonprescription sleep or diet pills. Any others?

SPECIFY MOST USED DRUG(S): _____

	CHECK ONE BOX
ONLY ONE DRUG / DRUG CLASS HAS BEEN USED	☐
ONLY THE MOST USED DRUG CLASS IS INVESTIGATED.	☐
EACH DRUG CLASS USED IS EXAMINED SEPARATELY (PHOTOCOPY K2 AND K3 AS NEEDED)	☐

b SPECIFY WHICH DRUG/DRUG CLASS WILL BE EXPLORED IN THE INTERVIEW BELOW IF THERE IS CONCURRENT OR SEQUENTIAL POLYSUBSTANCE USE: _____

K2 **Considering your use of (NAME THE DRUG / DRUG CLASS SELECTED), in the past 12 months:**

	a	Have you found that you needed to use more (NAME OF DRUG / DRUG CLASS SELECTED) to get the same effect that you did when you first started taking it?	NO	YES
	b	When you reduced or stopped using (NAME OF DRUG / DRUG CLASS SELECTED), did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable, or depressed)? Did you use any drug(s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better?	NO	YES
		IF **YES** TO EITHER, CODE **YES**.		
	c	Have you often found that when you used (NAME OF DRUG / DRUG CLASS SELECTED), you ended up taking more than you thought you would?	NO	YES
	d	Have you tried to reduce or stop taking (NAME OF DRUG / DRUG CLASS SELECTED) but failed?	NO	YES
	e	On the days that you used (NAME OF DRUG / DRUG CLASS SELECTED), did you spend substantial time (>2 HOURS), obtaining, using or in recovering from the drug, or thinking about the drug?	NO	YES

f Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use? NO YES

g Have you continued to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it caused you health or mental problems? NO YES

ARE **3** OR MORE **K2** ANSWERS CODED **YES**?

SPECIFY DRUG(S): _____

***** IF YES, SKIP K3 QUESTIONS, CIRCLE N/A IN THE ABUSE BOX FOR THIS SUBSTANCE AND MOVE TO THE NEXT DISORDER.
DEPENDENCE PREEMPTS ABUSE.

NO **YES ***

SUBSTANCE DEPENDENCE
CURRENT

Considering your use of (NAME THE DRUG CLASS SELECTED), in the past 12 months:

K3 a Have you been intoxicated, high, or hungover from (NAME OF DRUG / DRUG CLASS SELECTED) more than once, when you had other responsibilities at school, at work, or at home? Did this cause any problem? NO YES

(CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)

b Have you been high or intoxicated from (NAME OF DRUG / DRUG CLASS SELECTED) more than once in any situation where you were physically at risk (for example, driving a car, riding a motorbike, using machinery, boating, etc.)? NO YES

c Did you have legal problems more than once because of your drug use, for example, an arrest or disorderly conduct? NO YES

d Did you continue to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it caused problems with your family or other people? NO YES

ARE **1** OR MORE **K3** ANSWERS CODED **YES**?

SPECIFY DRUG(S): _____

NO **N/A** **YES**

SUBSTANCE ABUSE
CURRENT

L. PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE **YES** ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. BEFORE CODING, INVESTIGATE WHETHER DELUSIONS QUALIFY AS "BIZARRE".

DELUSIONS ARE "BIZARRE" IF: CLEARLY IMPLAUSIBLE, ABSURD, NOT UNDERSTANDABLE, AND CANNOT DERIVE FROM ORDINARY LIFE EXPERIENCE.

HALLUCINATIONS ARE SCORED "BIZARRE" IF: A VOICE COMMENTS ON THE PERSON'S THOUGHTS OR BEHAVIOR, OR WHEN TWO OR MORE VOICES ARE CONVERSING WITH EACH OTHER.

		Now I am going to ask you about unusual experiences that some people have.			BIZARRE
L1	a	Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? NOTE: ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING.	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES ➡**L6**
L2	a	Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking?	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES ➡**L6**
L3	a	Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES ➡**L6**
L4	a	Have you ever believed that you were being sent special messages through the TV, radio, or newspaper, or that a person you did not personally know was particularly interested in you?	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES	YES ➡**L6**
L5	a	Have your relatives or friends ever considered any of your beliefs strange or unusual? INTERVIEWER: ASK FOR EXAMPLES. ONLY CODE **YES** IF THE EXAMPLES ARE **CLEARLY** DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS L1 TO L4, FOR EXAMPLE, SOMATIC OR RELIGIOUS DELUSIONS OR DELUSIONS OF GRANDIOSITY, JEALOUSY, GUILT, RUIN OR DESTITUTION, ETC.	NO	YES	YES
	b	**IF YES OR YES BIZARRE:** do they currently consider your beliefs strange?	NO	YES	YES
L6	a	Have you ever heard things other people couldn't hear, such as voices? HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS **YES** TO THE FOLLOWING:	NO	YES	
		IF YES: Did you hear a voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO		YES
	b	**IF YES OR YES BIZARRE TO L6a:** have you heard these things in the past month? HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS **YES** TO THE FOLLOWING: Did you hear a voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO	YES	YES ➡**L8b**

L7 a Have you ever had visions when you were awake or have you ever seen things other people couldn't see? NO YES
CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.

b **IF YES:** have you seen these things in the past month? NO YES

CLINICIAN'S JUDGMENT

L8 b IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS? NO YES

L9 b IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR? NO YES

L10 b ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING THE INTERVIEW? NO YES

L11 a ARE 1 OR MORE « a » QUESTIONS FROM L1a TO L7a CODED **YES OR YES BIZARRE** AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT OR RECURRENT)
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT OR PAST) CODED **YES**? NO →L13 YES

IF NO TO L11 a, CIRCLE NO IN BOTH 'MOOD DISORDER WITH PSYCHOTIC FEATURES' DIAGNOSTIC BOXES AND MOVE TO L13.

b You told me earlier that you had period(s) when you felt (depressed/high/persistently irritable).

Were the beliefs and experiences you just described (SYMPTOMS CODED YES FROM **L1**a TO **L7**a) restricted exclusively to times when you were feeling depressed/high/irritable?

IF THE PATIENT EVER HAD A PERIOD OF AT LEAST 2 WEEKS OF HAVING THESE BELIEFS OR EXPERIENCES (PSYCHOTIC SYMPTOMS) WHEN THEY WERE NOT DEPRESSED/HIGH/IRRITABLE, CODE NO TO THIS DISORDER.

IF THE ANSWER IS NO TO THIS DISORDER, ALSO CIRCLE NO TO L12 AND MOVE TO L13

NO	YES
	MOOD DISORDER WITH *PSYCHOTIC FEATURES*
	LIFETIME

L12 a ARE 1 OR MORE « b » QUESTIONS FROM L1b TO L7b CODED **YES OR YES BIZARRE** AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT)
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT) CODED **YES**?

IF THE ANSWER IS YES TO THIS DISORDER (LIFETIME OR CURRENT), CIRCLE NO TO L13 AND L14 AND MOVE TO THE NEXT MODULE.

NO	YES
	MOOD DISORDER WITH *PSYCHOTIC FEATURES*
	CURRENT

L13 ARE 1 OR MORE « b » QUESTIONS FROM L1b TO L6b, CODED **YES BIZARRE**?

OR

ARE 2 OR MORE « b » QUESTIONS FROM L1b TO L10b, CODED **YES** (RATHER THAN **YES BIZARRE**)?

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO **YES**

PSYCHOTIC DISORDER
CURRENT

L14 IS **L13** CODED **YES**

OR

ARE 1 OR MORE « a » QUESTIONS FROM L1a TO L6a, CODED **YES BIZARRE**?

OR

ARE 2 OR MORE « a » QUESTIONS FROM L1a TO L7a, CODED **YES** (RATHER THAN **YES BIZARRE**)

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

NO **YES**

PSYCHOTIC DISORDER
LIFETIME

M. ANOREXIA NERVOSA

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

M1	a	How tall are you?	❑ ft ❑❑ in. ❑❑❑ cm.	
	b.	What was your lowest weight in the past 3 months?	❑❑❑ lbs. ❑❑❑ kgs.	
	c	IS PATIENT'S WEIGHT EQUAL TO OR BELOW THE THRESHOLD CORRESPONDING TO HIS / HER HEIGHT? (SEE TABLE BELOW)	➡ NO	YES

In the past 3 months:

M2		In spite of this low weight, have you tried not to gain weight?	➡ NO	YES
M3		Have you intensely feared gaining weight or becoming fat, even though you were underweight?	➡ NO	YES
M4	a	Have you considered yourself too big / fat or that part of your body was too big / fat?	NO	YES
	b	Has your body weight or shape greatly influenced how you felt about yourself?	NO	YES
	c	Have you thought that your current low body weight was normal or excessive?	NO	YES
M5		ARE 1 OR MORE ITEMS FROM **M4** CODED **YES**?	➡ NO	YES
M6		FOR WOMEN ONLY: During the last 3 months, did you miss all your menstrual periods when they were expected to occur (when you were not pregnant)?	➡ NO	YES

FOR WOMEN: ARE **M5 AND M6** CODED **YES**?

FOR MEN: IS **M5** CODED **YES**?

NO **YES**

ANOREXIA NERVOSA
CURRENT

HEIGHT / WEIGHT TABLE CORRESPONDING TO A BMI THRESHOLD OF 17.5 KG/M^2

Height/Weight														
ft/in	4'9	4'10	4'11	5'0	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10
lbs.	81	84	87	89	92	96	99	102	105	108	112	115	118	122
cm	145	147	150	152	155	158	160	163	165	168	170	173	175	178
kgs	37	38	39	41	42	43	45	46	48	49	51	52	54	55

Height/Weight					
ft/in	5'11	6'0	6'1	6'2	6'3
lbs.	125	129	132	136	140
cm	180	183	185	188	191
kgs	57	59	60	62	64

The weight thresholds above are calculated using a body mass index (BMI) equal to or below 17.5 kg/m^2 for the patient's height. This is the threshold guideline below which a person is deemed underweight by the DSM-IV and the ICD-10 Diagnostic Criteria for Research for Anorexia Nervosa.

N. BULIMIA NERVOSA

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

N1	In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?	➡ NO	YES
N2	In the last 3 months, did you have eating binges as often as twice a week?	➡ NO	YES
N3	During these binges, did you feel that your eating was out of control?	➡ NO	YES
N4	Did you do anything to compensate for, or to prevent a weight gain from these binges, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications?	➡ NO	YES
N5	Does your body weight or shape greatly influence how you feel about yourself?	➡ NO	YES
N6	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	NO ↓ Skip to N8	YES
N7	Do these binges occur only when you are under (_____lbs./kgs.)? INTERVIEWER: WRITE IN THE ABOVE PARENTHESIS THE THRESHOLD WEIGHT FOR THIS PATIENT'S HEIGHT FROM THE HEIGHT / WEIGHT TABLE IN THE ANOREXIA NERVOSA MODULE.	NO	YES

N8 IS **N5** CODED **YES** AND IS EITHER **N6** OR **N7** CODED **NO**?

NO **YES**

BULIMIA NERVOSA
CURRENT

IS **N7** CODED **YES**?

NO **YES**

ANOREXIA NERVOSA
Binge Eating/Purging Type
CURRENT

O. GENERALIZED ANXIETY DISORDER

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE **NO**, AND MOVE TO THE NEXT MODULE)

O1	a	Have you worried excessively or been anxious about several things over the past 6 months?	NO ➡	YES
	b	Are these worries present most days?	NO ➡	YES
		IS THE PATIENT'S ANXIETY RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?	NO	YES ➡
O2		Do you find it difficult to control the worries or do they interfere with your ability to focus on what you are doing?	NO ➡	YES
O3		FOR THE FOLLOWING, CODE **NO** IF THE SYMPTOMS ARE CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT.		
		When you were anxious over the past 6 months, did you, most of the time:		
	a	Feel restless, keyed up or on edge?	NO	YES
	b	Feel tense?	NO	YES
	c	Feel tired, weak or exhausted easily?	NO	YES
	d	Have difficulty concentrating or find your mind going blank?	NO	YES
	e	Feel irritable?	NO	YES
	f	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES

ARE **3** OR MORE **O3** ANSWERS CODED **YES**?

NO	**YES**
GENERALIZED ANXIETY DISORDER **CURRENT**	

P. ANTISOCIAL PERSONALITY DISORDER (optional)

(➡ MEANS : GO TO THE DIAGNOSTIC BOX AND CIRCLE NO.)

P1 **Before you were 15 years old, did you:**

a	repeatedly skip school or run away from home overnight?	NO	YES
b	repeatedly lie, cheat, "con" others, or steal?	NO	YES
c	start fights or bully, threaten, or intimidate others?	NO	YES
d	deliberately destroy things or start fires?	NO	YES
e	deliberately hurt animals or people?	NO	YES
f	force someone to have sex with you?	NO	YES
	ARE **2** OR MORE **P1** ANSWERS CODED **YES**?	NO ➡	YES

DO NOT CODE **YES** TO THE BEHAVIORS BELOW IF THEY ARE EXCLUSIVELY POLITICALLY OR RELIGIOUSLY MOTIVATED.

P2 **Since you were 15 years old, have you:**

a	repeatedly behaved in a way that others would consider irresponsible, like failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself?	NO	YES
b	done things that are illegal even if you didn't get caught (for example, destroying property, shoplifting, stealing, selling drugs, or committing a felony)?	NO	YES
c	been in physical fights repeatedly (including physical fights with your spouse or children)?	NO	YES
d	often lied or "conned" other people to get money or pleasure, or lied just for fun?	NO	YES
e	exposed others to danger without caring?	NO	YES
f	felt no guilt after hurting, mistreating, lying to, or stealing from others, or after damaging property?	NO	YES

ARE **3** OR MORE **P2** QUESTIONS CODED **YES**?

NO	YES
	ANTISOCIAL PERSONALITY DISORDER **LIFETIME**

THIS CONCLUDES THE INTERVIEW

Appendix E

Appendix E

Published Paper: Brain Connectivity in Body Dysmorphic Disorder Compared with Controls: A Diffusion Tensor Imaging Study

Appendix E

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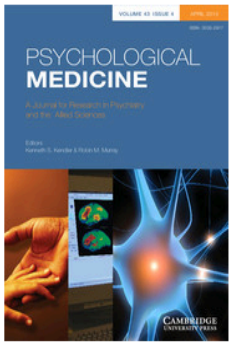

Brain connectivity in body dysmorphic disorder compared with controls: a diffusion tensor imaging study

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ORIGINAL ARTICLE

Brain connectivity in body dysmorphic disorder compared with controls: a diffusion tensor imaging study

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Background. Several neuroimaging studies have investigated brain grey matter in people with body dysmorphic disorder (BDD), showing possible abnormalities in the limbic system, orbitofrontal cortex, caudate nuclei and temporal lobes. This study takes these findings forward by investigating white matter properties in BDD compared with controls using diffusion tensor imaging. It was hypothesized that the BDD sample would have widespread significantly reduced white matter connectivity as characterized by fractional anisotropy (FA).

Method. A total of 20 participants with BDD and 20 healthy controls matched on age, gender and handedness underwent diffusion tensor imaging. FA, a measure of water diffusion within a voxel, was compared between groups on a voxel-by-voxel basis across the brain using tract-based spatial statistics within the FSL package.

Results. Results showed that, compared with healthy controls, BDD patients demonstrated significantly lower FA ($p<0.05$) in most major white matter tracts throughout the brain, including in the superior longitudinal fasciculus, inferior fronto-occipital fasciculus and corpus callosum. Lower FA levels could be accounted for by increased radial diffusivity as characterized by eigenvalues 2 and 3. No area of higher FA was found in BDD.

Conclusions. This study provided the first evidence of compromised white matter integrity within BDD patients. This suggests that there are inefficient connections between different brain areas, which may explain the cognitive and emotion regulation deficits within BDD patients.

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Key words: Body dysmorphic disorder, diffusion tensor imaging, neuroimaging, obsessive–compulsive spectrum, white matter.

Introduction

Body dysmorphic disorder (BDD) is a mental disorder characterized by a preoccupation with an imagined defect in physical appearance, or if a slight abnormality is present, the concern about it is excessive. Individuals with BDD often engage in repetitive and ritualistic behaviours, including skin picking, camouflaging their supposed defect, and checking their appearance in the mirror. The prevalence of BDD is approximately 1.8% in community self-report samples (Buhlmann *et al.* 2010), with slightly higher prevalence among females. Individuals with BDD have impaired psychosocial functioning and quality of life (Phillips *et al.* 2005*b*), they may experience prolonged unemployment, severe social isolation and suicidal ideation, with approximately 25% of individuals with BDD attempting suicide (Phillips *et al.* 2005*a*; Buhlmann *et al.* 2010). Many individuals with primary BDD also fulfil the criteria for other mental disorders, including social phobia (Coles *et al.* 2006), major depression (Phillips *et al.* 2007*a*) and obsessive–compulsive disorder (OCD) (Stewart *et al.* 2008). The high level of co-morbidity may represent conceptual similarities between BDD and other disorders or aetiological links.

The severe body image distortions that individuals with BDD experience suggest that fundamental

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cognitive and perceptual abnormalities are involved. Indeed, neuropsychological research has revealed a range of deficits in BDD, including in executive function (Hanes, 1998; Dunai *et al.* 2009; Labuschagne *et al.* 2011), selective attention (Buhlmann *et al.* 2002), information processing, verbal and non-verbal memory (Deckersbach *et al.* 2000; Dunai *et al.* 2009), recognition of emotion in others (Buhlmann *et al.* 2004) and visual processing (Feusner *et al.* 2007, 2010*a*). The combination of deficits in response inhibition, combined with heightened attention to threatening stimuli compared with controls, has suggested that frontal–striatal circuits may be important in BDD (Buchanan *et al.* 2011).

Several neuroimaging studies have directly investigated structural and functional brain abnormalities in BDD. To date, these investigations have focused primarily on grey matter structures. The right amygdala has been shown to have increased activation in response to visual stimuli in a functional magnetic resonance imaging (fMRI) study (Feusner *et al.* 2007), while structural MRI techniques have shown that right amygdala volume correlates to symptom severity (Rauch *et al.* 2003; Feusner *et al.* 2009). Other abnormalities in areas related to emotion processing, such as the cingulate cortex (Atmaca *et al.* 2010), suggest that there are deficits in the limbic system. The orbitofrontal cortex has been shown to be reduced in volume compared with controls using structural MRI (Atmaca *et al.* 2010), and an fMRI study found hyperactive activation in the same area (Feusner *et al.* 2010*b*). Furthermore, neuropsychological (Dunai *et al.* 2009) research has shown deficits in cognitive functioning that may be related to the orbitofrontal cortex. Consistent with BDD symptomatology centred around visual stimuli, occipital lobe activation has been found to be different from that of controls (Feusner *et al.* 2010*b*). Less consistent abnormalities have been shown in the caudate nucleus (Atmaca *et al.* 2010), and temporal lobes (Carey *et al.* 2004), which could possibly be associated with memory dysfunction found in BDD samples (Deckersbach *et al.* 2000).

BDD and OCD are often compared as they share symptomatology (McKay *et al.* 1997; Stewart *et al.* 2008). There is a high co-morbidity rate (Stewart *et al.* 2008) between these disorders, they have comparable demographic characteristics (Frare *et al.* 2004), and have a genetic overlap (Monzani *et al.* 2012). In terms of neurobiology, abnormalities of the caudate nucleus (Rauch, 2000; Whiteside *et al.* 2004) and orbitofrontal cortices (Atmaca *et al.* 2010; Rotge *et al.* 2010) are common to both disorders. However, neuroimaging data are well replicated in OCD but scarce in BDD, and no study has directly compared the two disorders using neuroimaging techniques.

Diffusion tensor imaging (DTI) is a neuroimaging technique developed to examine the integrity of white matter tracts. Recent methodological advances in DTI have motivated a growing interest in disconnection models proposing that white matter structural connectivity modulates symptoms in various mental disorders. In OCD samples there are at least nine separate studies that have reported DTI data, whereas this technique has not yet been reported on in a BDD sample. Within OCD samples DTI has found abnormalities in the fronto-striatal neural pathway, the corpus callosum, superior longitudinal fasciculus as well as a generalized disorganization among neural tracts (Garibotto *et al.* 2010; Bora *et al.* 2011).

Within DTI analysis, fractional anisotropy (FA) is the most widely used measurement, and represents the normalized standard deviation of three tensor eigenvalues. In white matter the movements of water molecules are restricted by various tissue components (e.g. myelin sheath or membranes), so that diffusion is reported to be anisotropic (Basser *et al.* 1994; Basser & Pierpaoli, 1996). FA reflects the degree of directionality (anisotropy) within a voxel. High FA suggests that there is highly directional diffusion such as that seen in white matter fibre tracts, and low FA values are associated disorganized white matter (Mori *et al.* 2005). This technique, therefore, can allow investigators to examine the neural organization of white matter, which reflects the efficiency of how different parts of the brain communicate with each other.

This study has two main aims: (1) to investigate whether white matter abnormalities exist within a BDD cohort by comparing them with healthy controls; and (2) to characterize the biological abnormalities underlying the disorder, using FA. Given that OCD shares nosological links with BDD, our hypotheses were partly based on the reported OCD white matter abnormalities (although it is acknowledged that there is some inconsistency in the OCD literature). In addition the neuropsychological deficits and grey matter differences reported within BDD samples were used to inform our hypothesis that white matter integrity may be compromised in BDD. Specifically, it was hypothesized that the BDD sample would have widespread significantly reduced FA, including in the corpus callosum, superior longitudinal fasciculus, and inferior fronto-occipital fasciculus. Past neuroimaging studies (Feusner *et al.* 2009, 2010*b*) have suggested a relationship between structural and functional abnormalities and BDD symptom severity. Thus, the relationship between symptoms severity and FA was also investigated in this study. In addition, FA was correlated with current anxiety and depression scores to help investigate the influence of these co-occurring symptoms on white matter integrity.

Appendix E

Table 1. *Demographic and clinical variables*

	BDD	Controls	Group comparison[a]
Demographic characteristics			
Mean age, years (S.D.)	34.6 (11.5)	31.9 (11.4)	$p=0.45$
Mean length of education, years (S.D.)	14.9 (2.4)	16.3 (3.0)	$p=0.11$
Mean WTAR IQ estimate (S.D.)	106 (10.7)	110 (6.5)	$p=0.13$
Handedness, *n*			
Left	3	3	
Right	17	17	
Gender, *n*			
Male	6	6	
Female	14	14	
Clinical variables			
Mean BDD severity, BDD-YBOCS (S.D.)	24.9 (9.6)	–	
Mean duration of illness, years (S.D.)	10.8 (6.9)	–	
Mean depression, Zung (S.D.)	46.0 (11.3)	23.3 (8.7)	$p<0.05$
Mean social anxiety, SIAS (S.D.)	41.7 (18.0)	17.1 (4.2)	$p<0.05$

BDD, Body dysmorphic disorder; S.D., standard deviation; WTAR, Wechsler Test of Adult Reading; IQ, intelligence quotient; BDD-YBOCS, Yale–Brown Obsessive Compulsive Scale Modified for Body Dysmorphic Disorder; Zung, Zung Self-rating Depression Scale; SIAS, Social Interaction Anxiety Scale.

[a] Degrees of freedom=38.

Method

Participants

Two cohorts were recruited comprising 20 individuals with BDD and 20 (after one exclusion) healthy controls, aged between 19 and 64 years. The BDD participants were recruited from the St Vincent's Hospital Body Image Clinic, Melbourne, Australia. Recruitment was conducted via referrals from this clinic, where clients were identified as having BDD and introduced to the research project. Participants gave their informed consent and diagnosis was then confirmed using the Body Dysmorphic Disorder Diagnostic Module (BDD-DM) and symptom severity was recorded using the Yale–Brown Obsessive Compulsive Scale Modified for Body Dysmorphic Disorder (BDD-YBOCS; Phillips *et al.* 1997). BDD patients were excluded if they had a past or current psychotic disorder, OCD, bulimia nervosa, anorexia nervosa, alcohol or substance abuse history, intellectual/cognitive impairment, metal implants or neurological disturbance. Furthermore, BDD participants were excluded if they had a co-morbid mental disorder that was considered to be their primary diagnosis, ensuring that all individuals in the patient sample had BDD as their primary concern. Because primary diagnosis can be difficult to delineate when there is co-morbid OCD, individuals with OCD were excluded, whereas individuals who also fulfilled the criteria of social phobia or major depression were allowed if BDD was clearly assessed as their primary diagnosis. As BDD shows very high rates of psychiatric co-morbidity (Phillips *et al.* 2007*b*) our exclusion criterion was calibrated to obtain a highly representative sample.

Healthy control participants were sourced from a voluntary healthy research database, comprising members of the public. The control group had no personal or family history of a mental disorder and met the same exclusion criteria outlines for the BDD group. All participants had a Wechsler Test of Adult Reading pre-morbid intelligence quotient (IQ) score of >80, and all participants had English as their preferred language. Of the participants, one control was excluded after MRI acquisition due to incidental brain pathology and is not presented in any of the data tables.

Participants were assessed with the Mini-International Neuropsychiatric Interview (MINI; Sheehan *et al.* 1998) to evaluate the presence or absence of other mental disorders. Handedness was assessed with the Edinburgh Inventory, and social anxiety and depression were measured by the Social Interaction Anxiety Scale (SIAS) (Brown *et al.* 1997) and the Zung Self-rating Depression Scale (Zung, 1965), which has been shown to be sensitive to the clinical severity of depression in psychiatric samples (Biggs *et al.* 1978). Group comparisons were computed using independent-samples *t* tests at $p=0.05$. Demographic and clinical data are displayed in Table 1.

The two participant groups were well matched on age, gender, education, estimated IQ and handedness. The clinical data indicate that mean BDD severity was in the 'moderate' range which is defined as scores between 16 and 30 on the BDD-YBOCS (Phillips *et al.* 1997). Scores below 15 indicate 'mild' BDD symptoms and scores from 31 to 48 are defined as 'severe' symptoms. At the time of MRI acquisition our sample comprised two participants in the mild range, 13 with moderate symptoms and five in the severe range.

The depression scores as measured by the Zung Self-rating Depression Scale indicated that the BDD sample had a higher level of depressive symptoms compared with controls. On average the BDD group fell in the subclinical range of depressive symptoms, defined as a score below 50 (Zung, 1965). A score between 50 and 59 on the scale represents mild depression, between 60 and 69 indicates moderate symptoms and above 70 indicates severe symptoms (Zung, 1965). The SIAS scores showed that the BDD sample had a moderate level of social anxiety symptoms; less than people diagnosed with social phobia but higher than other anxiety disorders (Peters, 2000), which is typical of BDD samples (Coles *et al.* 2006). Assessment with the MINI showed that four BDD participants fulfilled the diagnostic criteria for current major depressive disorder or dysthymia, and five had current agoraphobia or social phobia, showing that our sample was representative of a typical BDD profile (Coles *et al.* 2006). Areas of aesthetic concern for our sample were generally the face, skin and hair. All but two members of the BDD sample were taking psychoactive medication: five where taking seroquel, four escitalopram, two duloxetine, two desvenlafaxine, two diazepam, and one each paroxetine, mirtazapine, lorazepam, methylphenidate, sodium valproate or clomipramine.

MRI acquisition

Participants were scanned using a 3 T scanner (Siemens Magnetom TrioTim, Germany) at the Murdoch Childrens Research Institute (Royal Children's Hospital, Melbourne, Australia). The DTI scanning sequence was conducted as a component of a 1 h long scan. The scanner acquired an isotropic DTI sequence for FA estimations (number of directions= 60, *b* value=2000s/m^2, slice thickness= 2.5 mm). Data were transferred to a Linux workstation for image processing and analyses.

FA analysis

Tract-based spatial statistics (TBSS) developed by Smith *et al.* (2006) was used to create a mean FA skeleton that was representative of our 40 participants. TBSS uses non-linear registration to create a template for FA comparisons that allows voxelwise analysis of multi-subject diffusion data. The TBSS module in the FSL package (http://www.fmrib.ox.ac.uk/fsl/) was used to compute statistics. A two-sample *t* test was conducted using the randomize tool, which tests the *t* value at each voxel against a null distribution generated from 5000 random permutations of group membership. The output contained statistical maps corrected for multiple comparisons ($p<0.05$) using threshold-free cluster enhancement. This method has a high level of sensitivity to true differences while minimizing false positives by avoiding the specification of a subjective cluster-forming threshold (Smith & Nichols, 2009). Specific white matter areas were defined using integrated white matter atlases within FSL: the ICBM-DTI-81 White-Matter Labels Atlas and the JHU White-Matter Tractography Atlas, both developed in the Laboratory of Brain Anatomical MRI at Johns Hopkins University (USA).

In addition, a Pearson product-moment correlation analysis at $p<0.05$ was performed between voxelwise FA and symptom severity as measured by the BDD-YBOCS, Zung Self-rating Depression Scale and SIAS.

Results

FA

The BDD patients exhibited widespread significant reductions in corrected FA values compared with controls. Table 2 shows decreased FA values in BDD divided into anatomical regions, and shows areas of significant increase in eigenvalues 2 and 3. There were no significant differences between BDD and controls on eigenvalue 1.

Table 2 shows that there are widespread white matter differences in BDD. Since FA is a composite of eigenvalues 1, 2 and 3 and there was no differences on eigenvalue 1, the majority of FA reductions can be accounted for by an increase of radial diffusivity as represented by eigenvalues 2 and 3.

Correlation analysis

The correlation analysis found that there was no significant correlation between BDD symptom severity scores and corrected FA in any voxel within the BDD sample. Likewise, there was no significant correlation between depression scores and FA in the BDD group. In the BDD group, social anxiety scores were found to correlate negatively with corrected FA values on the left superior longitudinal fasciculus (x=−38, y=2, z=22) at $p<0.05$. There was no correlation between depression and anxiety in any voxel in the control group.

Discussion

As far as we are aware, this is the first study to examine white matter differences within a BDD sample using DTI. Additionally, this study had the largest BDD sample in a neuroimaging study to date, and our sample was thoroughly screened to ensure that BDD was the primary condition and that it was

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Table 2. *Areas of decreased FA and increased eigenvalue 2 and 3 values in BDD*

x	y	z	FA: *p*	Eigenvalue 2: *p*	Eigenvalue 3: *p*	Anatomical region
−39	−47	22	<0.05	<0.05	<0.05	Superior longitudinal fasciculus (left)[a]
40	−44	19	<0.05	N.S.	<0.05	Superior longitudinal fasciculus (right)[a,b]
−37	−53	0	<0.05	<0.05	<0.05	Posterior thalamic radiation (left)[b]
13	44	−16	<0.05	<0.05	<0.05	Uncinate fasciculus (right)[b]
31	42	3	<0.05	<0.05	<0.05	Inferior fronto-occipital fasciculus (right)[a]
−28	31	12	<0.05	<0.05	N.S.	Inferior fronto-occipital fasciculus (left)[a]
−42	−29	−7	<0.05	<0.05	N.S.	Inferior longitudinal fasciculus (left)[a]
−1	−11	25	<0.05	<0.05	<0.01	Body of corpus callosum[b]
18	−37	30	<0.05	<0.05	<0.05	Splenium of corpus callosum (right)[b]
−9	29	11	<0.05	<0.05	<0.05	Genu of the corpus callosum[b], or forcepts minor left[a]
9	29	10	<0.05	N.S.	N.S.	Genu of the corpus callosum[b], or forcepts minor (right)[a]
−8	−5	11	<0.05	N.S.	N.S.	Anterior thalamic radiation (left)[a]
9	−31	−23	<0.05	N.S.	N.S.	Corticospinal tract (right)[a]
−28	−20	−7	<0.05	N.S.	N.S.	Fornix or stria terminalis (cannot be resolved with resolution)[b]

FA, Fractional anisotropy; BDD, body dysmorphic disorder; N.S., not significant.
[a] Area identified using the JHU White-Matter Tractography Atlas.
[b] Area identified using the ICBM-DTI-81 White-Matter Labels Atlas.

representative of the patient population (Phillips *et al.* 2007*a*). Importantly, this study provides preliminary evidence of neural abnormalities in BDD; specifically, evidence for a widespread loss of integrity in white matter connectivity.

Consistent with the hypothesis that we would find similar reductions in FA in BDD as has been shown in OCD (Szeszko *et al.* 2005; Garibotto *et al.* 2010), we found reduced FA in the corpus callosum, superior longitudinal fasciculus, and inferior fronto-occipital fasciculus, bilaterally. The widespread FA reductions in our BDD sample can be accounted for through increases in radial diffusivity rather than reduced eigenvalue 1. Of the 12 areas identified in Table 2 as having significantly reduced FA, nine can be accounted for by eigenvalues 2 and 3. Indeed a comparison between Figs. 1 and 2 shows that mean diffusivity was more widespread than FA differences. This suggests loss of integrity in the white matter whereby attenuated white matter pathways allow water diffusion in directions that are not consistent with overall white matter directionality. Reduced FA has been shown in other work to be driven by myelin abnormalities which is largely under genetic control (Menzies *et al.* 2008). Therefore, neurodevelopment irregularities leading to abnormal myelination may be important to the predisposition to BDD. Reduced FA due to increased radial diffusivity has also been found in OCD (Bora *et al.* 2011).

While the loss of white matter integrity was widespread, it is worth considering the impact of specific neural pathways on BDD cognition. For example, reduced FA in the corpus callosum indicates attenuated interhemispheric communication. This may explain the neuropsychological research in BDD that has shown difficulties with integration of detailed and global information processing (Deckersbach *et al.* 2000; Feusner *et al.* 2010*a*). Moreover, white matter operating inefficiently may explain the Stroop task difficulties associated with BDD (Hanes, 1998), as reduced FA and other neurobiological correlates in frontostriatal–limbic regions have been shown to relate to performance on the Stroop and planning tasks in geriatric depression and OCD (van den Heuvel *et al.* 2005; Murphy *et al.* 2007). Furthermore, reduced FA in the bilateral superior longitudinal fasciculi suggests that connectivity between the prefrontal, parietal, occipital and temporal regions (Makris *et al.* 2005) may be compromised.

The reduced FA in the uncinate fasciculus is of particular interest because it is a major white matter fibre tract that connects the inferofrontal and anterotemporal cortices, and it travels over the lateral nuclei of the amygdala. Thus, lower FA within this tract suggests compromised fronto-amygdala structural connectivity in BDD. In the context of BDD, this is interesting when considering that frontal regions such as the orbitofrontal cortex serve important roles in top-down regulation of amygdala reactivity to control negative affect and mediate threat perception (Ochsner *et al.* 2002; Barrett *et al.* 2007).

It is clear from past research that there are grey matter differences in BDD patients compared with non-psychiatric controls, but how these interact with the white matter abnormalities reported here remains speculative. Volumes of the right amygdala and the

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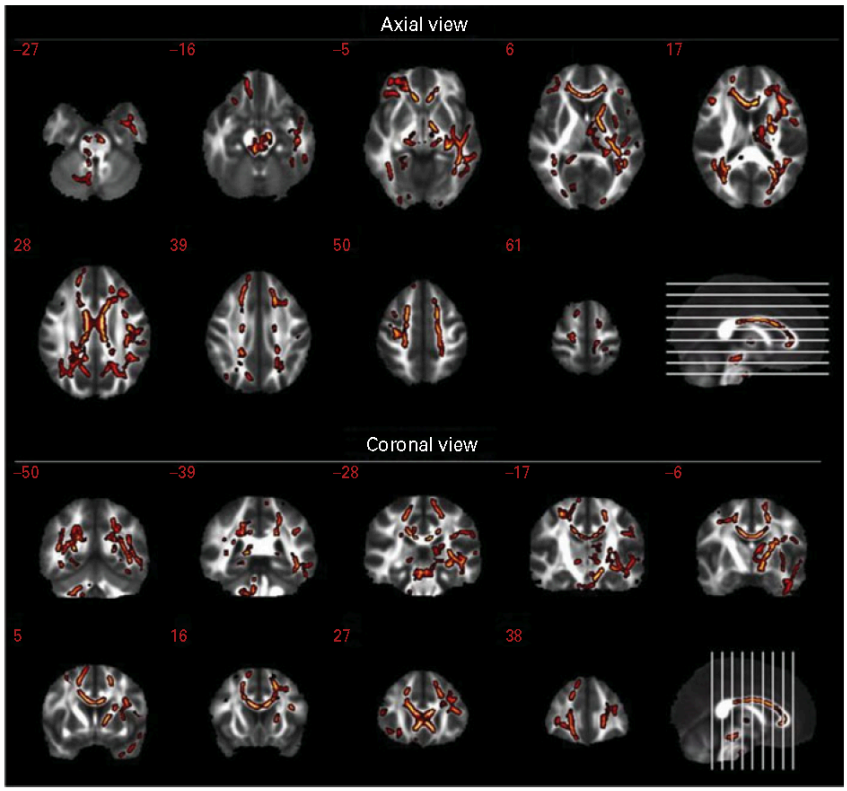

Fig. 1. Statistically significant fractional anisotropy reductions in body dysmorphic disorder sample compared with controls. Numbers in red represent distance (mm) from the anterior commissure.

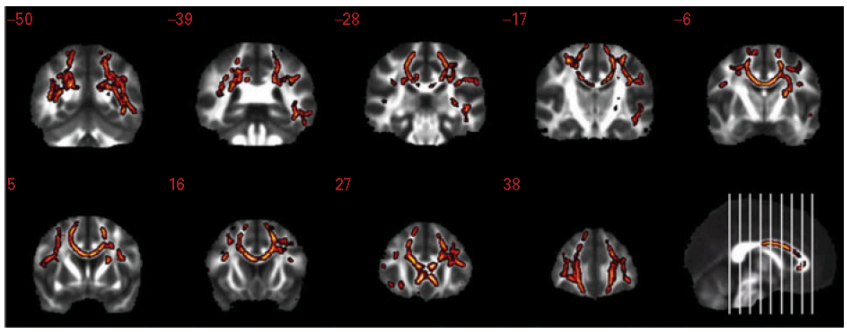

Fig. 2. Statistically significant mean diffusivity increases in body dysmorphic disorder sample compared with controls, coronal view. Numbers in red represent distance (mm) from the anterior commissure.

inferior frontal gyrus have been shown to correlate with current BDD symptom severity (Feusner *et al.* 2009), suggesting that differences in these grey matter structures are the most proximal contributor to symptoms, while white matter differences can be considered as a more distal, or perhaps predisposing, factor in BDD.

Our examination of whether BDD symptom severity correlated with FA was not significant, despite such a correlation being found in OCD samples (Garibotto *et al.* 2010). Given that we had a large range of symptom severity and a sample size that was able to provide robust correlation results, our non-significant results suggest that BDD has a distinct neurobiological makeup that is state-independent. Such a finding suggests important trait-related white matter abnormalities in BDD. This result would need to be replicated; further research could establish if these brain differences are present in an individual whether or not illness is active, and provide preliminary evidence

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for a BDD phenotype that is perhaps related to the emerging phenotype considered important in OCD (Menzies *et al.* 2008).

The results showing a significant negative correlation between social anxiety scores and FA in the left superior longitudinal fasciculus are interesting, considering that the main measure of BDD symptom severity (the BDD-YBOCS) was not significantly correlated. It is possible that our social anxiety measure was sensitive to an important feature of BDD that our main symptom severity rating scale was not. Indeed, social anxiety can be seen as a important factor within BDD symptomatology and is best conceptualized as an expression of higher BDD symptoms rather than a separate problem of social phobia (Coles *et al.* 2006). The finding that there was no correlation between depression scores and FA in any voxel indicated that the FA differences among the two groups can be accounted for by the diagnosis of BDD independent from depression ratings. Indeed, this finding taken together with the non-significant contribution of BDD symptoms to FA suggests that state-based symptoms scores bear less importance to white matter than state-independent diagnosis.

The parallels that have been drawn between OCD and BDD in terms of clinical features (Stewart *et al.* 2008) are yet to be robustly supported using DTI imaging techniques. In fact, to date, the nine DTI studies in OCD have yielded inconsistent results, with both local FA increases and decreases reported (e.g. Menzies *et al.* 2008; Bora *et al.* 2011, Lochner *et al.* 2012). The inconsistent data in OCD and the preliminary evidence of widespread FA decreases provided by the current study in BDD should be supplemented by future studies to help determine biological similarities and differences between the two disorders.

A limitation of this study is that nearly all of our BDD participants were taking medication at the time of MRI acquisition. This may be problematic as treatment is likely to have reduced the severity of BDD symptoms, thereby possibly influencing FA. However, as white matter integrity is generally considered state independent, current BDD symptomatology is unlikely to have significantly influenced the results. At the time of MRI acquisition two of the BDD participants were rated as having mild BDD symptoms on the BDD-YBOCS, although an active diagnosis of BDD was still confirmed using the BDD-DM.

In conclusion, we believe this to be the first study to examine white matter integrity in a BDD sample. The main contribution of our data is that they provide evidence that individuals with BDD have compromised white matter fibres, reflected by changes in fibre directionality as indicated by eigenvalues 2 and 3. This reduced connectivity among different regions of the brain is widespread in nature and is not related to symptom severity.

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Declaration of Interest

None.

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