Running title: Neurobiology of BDD

The neurobiology of body dysmorphic disorder: A systematic review and theoretical model.

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Highlights:

- A systematic review of brain structure and function in body dysmorphic disorder (BDD).
- The underlying neuropathophysiology of BDD remains largely untested and unknown.
- We identified the temporal gyrus, limbic system, and prefrontal cortex as important regions in BDD.
- Abnormal structure, activity, and functional connectivity within identified regions may contribute to disordered visual perception and emotional arousal in BDD.
- There is need for future neuroimaging research to test the model discussed.

Abstract

There has been an increase in neuroimaging research in body dysmorphic disorder (BDD), yet little is known about the underlying neurobiological basis of the disorder. We aimed to provide a systematic overview of the literature on the neurobiology of BDD. Two reviewers undertook a search of three electronic research databases: PubMed, PsycINFO, and Google Scholar. The search consisted of synonyms commonly associated with BDD and methods to evaluate brain structure, function, and network organisation. Out of an initial yield of 175 articles, 19 fulfilled inclusion criteria and were reviewed. We identified differences in brain activity, structure, and connectivity in BDD participants in frontostriatal, limbic, and visual system regions when compared to healthy control and other clinical groups. We put forth a neurobiological model of BDD pathophysiology that involves wide-spread disorganisation in neural networks involved in cognitive control and the interpretation of visual and emotional information. This review considers how this model might aid in the development of future research and understanding of BDD.

Keywords: BDD; neuroimaging; MRI; fMRI; EEG; cognition; network organisation; pathophysiology; limbic system; visual system; prefrontal cortex.

1. Introduction

Body dysmorphic disorder (BDD) is a psychiatric illness with relatively unknown aetiology despite reported lifetime prevalence rates of 1.7 – 2.4% (Buhlmann et al., 2010). The disorder is characterised by distress and markedly excessive preoccupation with perceived flaws and defects in physical appearance which are unobservable to others (Castle, Rossell, & Kyrios, 2006; Phillips, Menard, Fay, & Weisberg, 2005). These preoccupations are typically focused on the face, skin, hair, or nose; however, concerns may be reported for any aspect of the body, and often encompass numerous aspects of body image (Veale et al., 1996). The symptom profile of BDD comprises repetitive thoughts, feelings, and compulsive behaviours in response to appearance concerns. The ritualistic nature of this symptom profile has led to the classification of BDD as an Obsessive-Compulsive and Related Disorder (OCRD), alongside obsessive-compulsive disorder (OCD) (American Psychiatric Association, 2013). Quality of life is markedly poor in BDD cohorts with patients exhibiting significant distress, disability, extreme cosmetic surgery, suicidal ideation, and high rates of suicide attempts (DeMarco, Li, Phillips, & McElroy, 1998; Marazziti et al., 2006; Phillips & Menard, 2006b).

Due to the highly sensitive and personal nature of symptoms, BDD often goes undiagnosed or misdiagnosed as another disorder, leading to ineffective care and psychiatric treatment (Phillips, 2004). Perhaps, as a result, despite high rates of prevalence and chronicity, relatively little is known about the underlying neurobiology and aetiological origins of the disorder. In this article, we describe a systematic review of extant neuroimaging research in BDD, and through collation of their findings, we put forward an up-to-date neurobiological model of BDD. Conclusions

drawn from neuroimaging research may inform the development of targeted identification and treatment strategies.

1.1. Objectives

Focusing on neuroimaging and psychophysiological research, we aimed to provide insight into the pathogenic mechanisms of BDD and highlight important directions for future research. We summarised these results in an updated neurobiological model of BDD.

2. Methods

2.1. Search Strategy

Article selection was conducted according to the PRISMA guidelines (Moher, Liberati, Tetzlaff, Altman, & The, 2009; Shamseer et al., 2015; see Supplementary material I). The literature was searched using the PubMed, PsycINFO, and Google Scholar databases, and by additional hand searches through reference lists and specialist OCD and body image journals. The following search terms were used: (“body dysmorphic disorder” OR “body dysmorphia” OR BDD or “body dysmorphic*”) AND (neuro* OR brain OR neurobiology OR neuroimaging) OR (EEG OR electroencephalography OR magnetoencephalography OR MEG OR SPECT OR PET OR “magnetic resonance imaging” OR MRI OR fMRI OR “Diffusion Tensor Imaging” OR functional OR structural OR connectomics OR network). All studies before December 2016 were included.

2.2. Study selection and eligibility criteria

Two authors (SG and RK) screened all titles and abstracts in the electronic databases. Studies were included if they met the following eligibility criteria: (1) the

full-text was published in the English language; (2) used only human participants; (3) the clinical group was diagnosed according to DSM criteria; (4) a healthy control group had to be present; and (5) used clinical populations with BDD and not nonclinical populations with BDD symptoms. Articles were excluded that: (1) used a single case-report; and (2) were reviews or meta-analyses of the literature. Only peer-reviewed original articles were included. A qualitative approach was chosen in place of quantitative methodologies, such as meta-analysis, as the information needed to compute effect sizes was limited due to the small number of neuroimaging investigations available in BDD research to date.

2.3. Risk of bias in individual studies

In observation of PRISMA guidelines, we chose the Cochrane Collaboration tool for examining study bias (Higgins et al., 2011). Two authors (SG and RK) independently conducted quality ratings for the included studies, with discrepancies resolved by discussion.

3. Results

3.1. Study selection

The electronic database search provided a total of 2,037 records, and 1,959 remained after removal of duplicates. After reviewing article titles and abstracts, 1,892 were excluded based on identifying at least one feature of the article that warranted exclusion. A total of 31 articles were selected for full-text review, after which 21 studies were identified for inclusion in this systematic review. A flowchart of this selection process is displayed in **Figure 1**.

Insert Figure 1 about here

3.3. Study characteristics

The following data were extracted from all selected papers: patient characteristics, including sample size, age and gender distribution, handedness, medication use, patient comorbidities; the procedure and design of the relevant neuroimaging technique; and brain regions implicated in the significant findings of the study. All studies were published between 2003 and 2016 and, except for two studies, most studies were performed by three research centres (University of California, Stanford University and Swinburne University/St Vincent's Hospital).

Among the neuroimaging methods available, magnetic resonance imaging (MRI) is the most widely employed in BDD research, with 18 out of the 19 studies utilising functional or structural MRI. Based on the use of structural and morphometric MRI methods, six studies investigated structural brain differences in BDD (**Table 1**). Six studies investigated functional differences using functional MRI (fMRI) or EEG (**Table 2**), and six studies examined functional network organisation and white matter connectivity in BDD using white matter tractography or functional connectivity analysis (**Table 3**). One study examined psychopharmacological characteristics *in vivo* using Single Photon Emission Computed Tomography (SPECT) (**Table 4**). These articles yielded a total of 198 BDD patients, of which three patients (1.5%) were left-handed, 62 patients (32%) were males, and the age range was 18-65 years. The vast majority of patients (79%) were unmedicated and had a comorbid mental disorder, most commonly major depressive disorder, generalised anxiety disorder or dysthymia.

3.2. Risk of bias within studies

Overall, bias in study methodology was low (see Supplementary material II), however, upon review of patient characteristics, there was substantial overlap in the

patient cohort used across all of the included studies: Bohon, Hembacher, Moller, Moody, and Feusner (2012); Feusner, Moody, et al. (2010); Leow et al. (2012) used the same sample; Buchanan et al. (2014); Buchanan et al. (2013); Grace, Buchanan, et al. (2017) used the same sample; Feusner, Townsend, Bystritsky, and Bookheimer (2007); Feusner et al. (2009) Li, Lai, Bohon, et al. (2015); Li, Lai, Loo, et al. (2015) used the same sample; and Arienzo et al. (2013); Feusner et al. (2013) used the same sample.

3.3. Study synthesis

3.3.1. Structural Brain Differences

Table 1 provides detailed methodological information and summarises findings of the six studies that report on structural MRI. Total sample sizes range from 8-49 BDD patients, adding up to a total of 197 individuals, including 101 patients and 96 controls.

Insert Table 1 about here.

Of the six studies of brain morphometry in BDD, two found greater total white matter volumes (Atmaca et al., 2010; Rauch et al., 2003), and one found decreased total grey matter (Buchanan et al., 2014). Also, thinner cortical grey matter has been observed within left middle temporal and left inferior parietal gyri (Grace, Buchanan, et al., 2017), and thinner cortical grey matter within the left superior temporal cortex was associated with anxiety in BDD patients compared to healthy controls (Madsen et al., 2015). Further, using volumetric ROI approaches, two studies have found volumetric reductions in orbitofronto-striatal systems, including smaller volumes in the bilateral orbitofrontal cortex (OFC), bilateral anterior cingulate cortex (ACC), left amygdala, bilateral thalamus, and left hippocampus, in BDD cohorts compared to

healthy controls (Atmaca et al., 2010; Buchanan et al., 2014). In contrast to these volumetric reductions in orbitofrontal regions, increased left caudate nucleus volumes have been identified in BDD patients (Rauch et al., 2003), as well as positive associations between BDD symptom severity and increased volumes of the left inferior frontal gyrus (IFG) and right amygdala (Feusner et al., 2009). Overall, these results hint at frontostriatal and corticolimbic abnormalities in BDD.

There are some methodological considerations that need to be noted when interpreting findings across these studies. Firstly, while the data presented here hints at morphometric abnormalities, all but one study included here used low patient numbers (n<20), which are vulnerable to inflated Type I errors. Whereas the largest study by Madsen et al. (2015) included a relatively large patient sample (n=49) and found no volumetric or cortical thickness abnormalities at the group level, and only identified subtle associations of thickness abnormalities with anxiety. Consequently, this suggests that brain morphometric abnormalities in BDD might be subtle, and only occur as a function of clinical variables such as anxiety or symptom severity. Moreover, all studies listed here applied different normalisation techniques while measuring brain volumes. Two studies applied normalisation with intracranial volume (Feusner et al., 2009; Madsen et al., 2015), whereas two normalised to whole brain volume (Atmaca et al., 2010; Buchanan et al., 2014), and two applied no normalisation at all (Grace, Buchanan, et al., 2017; Rauch et al., 2003). Thus, the discrepancy in the normalisation techniques used may have significantly impacted results.

3.3.2. Functional Brain Differences

Table 2 provides the detailed methodological information of the six studies using functional brain imaging. Total sample sizes range from 12-20 BDD patients, adding up to a total of 166 individuals, including 83 patients and 83 controls.

Insert Table 2 about here.

Clinical observations of BDD patients suggest that they focus on minor or perceived flaws in their appearance that are unobservable to others (Monzani et al., 2013). This is supported by neuropsychological data demonstrating abnormal patterns of visual information processing in BDD patients, including the selective recall of details, rather than global features, of visual information from faces and figures (Deckersbach et al., 2000; Feusner, Moller, et al., 2010; Hanes, 1998; Jefferies et al., 2012; Monzani et al., 2013). As a result, fMRI protocols in BDD research have involved altering the spatial frequency of images to examine the processing of visual information within two different visual processing streams: detailed featural information (high spatial frequency; HSF) via ventral visual stream (VVS) pathways, and holistic information (low spatial frequency; LSF) via dorsal visual stream (DVS) pathways.

Three fMRI studies have examined face and object perception in patients with BDD, and found abnormalities in brain function relating to the VVS pathway which might contribute to the excessive processing of details in BDD patients compared to controls (Feusner, Hembacher, Moller, & Moody, 2011; Feusner, Moody, et al., 2010; Feusner et al., 2007). Specifically, while viewing LSF faces of others, BDD patients demonstrated left-sided hyperactivity in several regions within the lateral-temporal-parietal cortices. Whereas, in contrast, the control group indicated a

healthy reliance on detail processing for HSF information, as they demonstrated a similar pattern of activity within the right hemisphere for LSF faces and only activated these regions of the left hemisphere during the processing of HSF information (Feusner et al., 2007). This suggests that BDD participants engage in detail focus analysis of faces, even when only holistic (i.e. LSF) information is available. On the other hand, abnormal activity has also been found beyond primary visual cortex areas, comprising orbitofrontal, temporal, and parietal regions during own-face and image processing, that may represent additional deficits in later stages of visual image construction or top-down effects (Feusner, Moody, et al., 2010; Feusner et al., 2007). Together, this indicates that there is an imbalance in the visual processing streams, with greater reliance on bottom-up contextualization of holistic information of own-faces via magnocellular (DVS) pathways, over top-down visual processing in BDD patients. Behaviourally, this can lead to the inability of BDD patients to view their face as a meaningful whole, leading to the overemphasis of HSF (i.e. fine-detail) information.

In two studies, electrophysiological investigations of evoked response potential (ERPs) involving EEG, have also contributed to the understanding of the processes underlying face and object perception in BDD (Li, Lai, Loo, et al., 2015). During the processing of face and object stimuli, the P100 is evoked by first-order (configural) visual processing localised to V1 and V2 (i.e., early DVS), and N170 is thought to reflect later detailed (featural) processing typically within posterior fusiform regions (i.e., VVS). In BDD patients compared to controls, the amplitude of the N170 component was significantly reduced and was significantly associated with levels of insight (as measured by The Brown Assessment of Beliefs Scale; BABS; Eisen et al., 1998) (Li, Lai, Bohon, et al., 2015; Li, Lai, Loo, et al., 2015). Further, when

examining ERP's alongside fMRI, the same team found relative hypoactivity within early VVS areas for LSF faces and houses (occipital fusiform, temporal occipital fusiform, and lateral occipital cortices), and DVS areas (superior parietal lobule) for LSF houses, corresponding to electrical activity in the N170 component (Li, Lai, Loo, et al., 2015). For HSF houses, the N170 component was associated with later stages in the VVS (the posterior temporal fusiform cortex). Together, this suggests that people with BDD have aberrant early processing of visual information as early as 100ms post-stimuli. For faces, BDD participants demonstrated hypoactivity in DVS regions including the precuneus, lateral occipital cortex for LSF faces (Li, Lai, Loo, et al., 2015). They did not find hypoactivity in the P100 component for faces, which would have been concurrent with abnormalities in later stages of the visual processing stream.

Further, clinical correlates within these functional studies might shed light on the behavioural phenotypes of such neural abnormalities. Firstly, increased activity in the OFC and caudate and visual processing systems have been associated with BDD symptom severity (Feusner, Moody, et al., 2010). Secondly, the amygdala was shown to mediate a significant relationship between anxiety and abnormal right VVS activity during own-face viewing in BDD (Bohon et al., 2012). The involvement of the amygdala presents a novel hypothesis that the limbic system may fail to adequately regulate top-down or bottom-up limbic detail visual processing within the VVS. Thirdly, associations of BDD symptom severity with lower DVS and ventrolateral prefrontal activity might indicate a relationship between BDD symptoms and higher order processing within DVS regions associated with information integration and holistic visual processing (Feusner et al., 2011). Fourthly, decreased structural encoding of faces has been associated with greater perceptual distortions, as

indicated by the association of reduced N170 amplitudes (VVS activity) with the degree of insight (BABS scores) (Li, Lai, Loo, et al., 2015). Taken together, the clinical correlates presented here might reflect dysfunctions in top-down functional pathways from key prefrontal regions through the limbic to the visual system, which may lead to the misattribution of negative emotional experience (i.e., anxiety) to visual information in those with BDD.

Altogether, studies using functional brain imaging (EEG and fMRI) have suggested that there are consistent patterns of altered brain functioning in BDD, with predominant left hemispheric activation during visual processing tasks, as well as a preference for detailed (i.e., VVS) activity over holistic (i.e., DVS) activity. We speculate that these findings may indicate a possible deficit in magnocellular/DVS pathway systems that normally construct a low-resolution holistic template visual information. The inability to integrate parts into wholes may contribute to the distorted perceptions underlying appearance concerns as BDD patients cannot organise visual information into a meaningful whole; that is, they cannot see the “forest through the trees”. Considered within the context of the frontostriatal hypothesis of OCD, which suggests that dysfunction in frontostriatal loops leads to deficits in cognitive and inhibitory functions (Menzies et al., 2008), these results suggests that the clinical presentation of BDD might be more complex and widespread than that of OCD, and warrant the critical inclusion of tasks that probe DVS and VVS processing streams in the design of future functional MRI experiments.

3.3.3. Network Analyses

Table 3 provides the detailed methodological information of six studies examining white matter integrity or functional network topology. Total sample sizes range from 11-20 BDD patients, adding up to a total of 94 individuals, including 45 patients and 49 controls.

Insert Table 3 about here.

3.3.3.1 Structural Network Analyses

Two studies have examined the white matter structure of BDD patients using diffusion-weighted MRI techniques (Buchanan et al., 2013; Feusner et al., 2013), which maps white matter fibre structure through assessing the diffusion of water molecules. Buchanan and colleagues (2013) used tract-based spatial statistics (TBSS; Smith et al., 2006) to measure fractional anisotropy (FA) in BDD patients. Fractional anisotropy is a measure of diffusion within white matter tracts, whereby high FA means high directional diffusion and low FA is associated with disorganisation within the white matter (Smith et al., 2006). The BDD group demonstrated lower FA in white matter tracts that connect the hemispheres and frontal, parietal, occipital and temporal lobes relative to controls (Buchanan et al., 2013).

Feusner and colleagues (2013) used probabilistic tractography to determine connectivity between visual processing, frontostriatal, and limbic systems, as well as TBSS, to conduct exploratory analyses on whole-brain white matter in BDD patients and healthy controls. There were no significant between-group differences in the white matter within the selected structural pathways and no significant group differences in whole-brain white matter (Feusner et al., 2013). However, significant

negative correlations were evident between BABS scores (i.e., insight) and FA in the inferior longitudinal fasciculus (ILF), which connects the temporal and occipital lobes, and positive correlations were evident between BABS scores and mean diffusivity (a measure of overall diffusivity) in the ILF and the forceps major, a connection between the bilateral occipital lobes (Feusner et al., 2013). Thus, clinical symptoms have significant prognostic implications for brain connectivity in BDD.

Further insight into the global network architecture of BDD is found within research applying graph theoretical approaches to network organisation. In graph theory, a network comprises ‘nodes’ or brain regions (e.g., anatomically defined ROIs) and ‘edges’ or connections between the nodes (e.g., white matter tracts). The total possible connections between nodes are represented by a ‘cluster coefficient’ (CC), and the mean of these connections (the mean cluster coefficient; MCC) reflects the global efficiency of information transfer between the network (Bullmore & Sporns, 2009). Arienzo et al. (2013) used diffusion tensor imaging (DTI) tractography and graph-theoretical approaches to analyse the regional and whole brain white matter organisation in BDD. They observed a higher MCC in the BDD sample compared to healthy controls suggesting that BDD pathophysiology might involve an imbalance in network organisation where local networks dominate over global networks, leading to disorganised information transfer and interpretation of information (Arienzo et al., 2013).

In graph theory, a measurement of how central a node is relative to the whole network, is referred to as ‘betweenness centrality’, whereby the fraction of shortest paths that pass through a specific node is measured, and thus, higher values indicate that the node has more ‘influence’ over the flow of information to other nodes (Girvan & Newman, 2002). In BDD, greater edge centrality has been evident

between the anterior temporal and occipital pole nodes, reflecting either the heightened importance of this connection relative to others in the network or heightened information transfer between these nodes (Arienzo et al., 2013). Arienzo and colleagues (2013) postulated that the clinical importance of this connection is evident through the strong positive association of edge betweenness centrality and BDD-YBOCS symptom severity scores, suggesting that as symptoms worsen local connections relative to global connections dominate.

Moreover, communities of nodes that are highly interconnected but have fewer connections outside of the community make up a subsystem known as a 'module' (Bullmore & Sporns, 2009). Zhang and colleagues (2016) used this graph theoretical approach to examine whole-brain tractography network 'modularity' in BDD and anorexia nervosa (AN) patients compared to healthy controls. They found significant modularity in the AN group, and a trend towards abnormal modularity within the BDD group, involving right hemisphere frontal, basal ganglia, posterior cingulate and medial OFC nodes. Notably, compared to healthy controls, both the BDD and AN groups displayed an abnormal inclusion of the medial OFC and excluded the PCC within this module (Zhang et al., 2016). Given that the OFC is central to the frontostriatal network in OCD (Menzies et al., 2008), the authors proposed that these abnormalities within structural network organisation may be associated with obsessions and compulsions in both disorders. However, this remains untested and unclear.

3.3.3.2 Functional Network Analyses

The underlying functional network pathophysiology of BDD is largely unknown. As discussed in the previous section, the use of functional neuroimaging in BDD has provided insight into the possible associative functional activation patterns

within the disorder. However, the dynamic interactions between these nodes of activity are poorly understood.

The characteristics of functional visual system pathways have been examined in BDD patients through multimodal MRI imaging in two studies (Leow et al., 2012; Moody et al., 2015). Leow and colleagues (2012) mapped fMRI activation signals from a previous empirical study (Feusner, Moody, et al., 2010) onto structural DTI pathways within the visual system. The BDD patients underutilised structural connections within several local visual system locations (Leow et al., 2012), which may explain the relative hypoactivation of the lingual gyrus, parahippocampal gyrus, and the precuneus evident in the previous fMRI results (Feusner et al., 2011). This pattern of connectivity underscores aberrant information transfer between primary and secondary occipital regions in BDD (Leow et al., 2012).

A further fMRI study examined the functional connectivity of specialised networks for processing high and low spatial frequency images using psychophysiological interaction analyses, a brain imaging method of estimating the functional connectivity between target brain regions and the rest of the brain (Moody et al., 2015). In a comparison of BDD and AN groups to healthy controls, a unique functional connectivity pattern was observed in the BDD sample, with heightened connectivity in occipitotemporal networks for LSF faces. BDD and AN patients showed similar patterns of functional connectivity in higher-order networks connecting the right fusiform face area, precuneus and posterior cingulate cortex (PCC); however, this finding was greater in the BDD sample. Also, connectivity patterns between BDD and AN groups both demonstrated decreased connections of the insula and the central opercular cortex, which is posited to reflect aberrant introspection and a misattribution to the salience of information (Moody et al., 2015).

Together, connectivity analyses suggest that, while global alterations in brain connectivity may not contribute to BDD pathology, subtle local functional and structural connections, particularly within temporal and limbic regions, might lead to some of the symptoms experienced by these individuals.

3.5. Psychopharmacological Evidence

One study has examined the dopaminergic system *in vivo* in BDD. Vulink and colleagues (2016) found significantly reduced dopamine D2/3-receptor availability in the striatum (caudate nucleus and putamen) in BDD patients and matched healthy controls (**Table 4**). The authors propose that D2/3-receptor binding is involved in the behavioural compulsivity in OCD. Thus poor dopaminergic function within the caudate might underlie some of the behavioural similarities between BDD and OCD. Given that selective serotonin reuptake inhibitors (SSRIs) are the first-line treatment for BDD (Ipser et al., 2009), dopaminergic dysfunction in BDD may be primarily caused by serotonergic deficits leading to secondary dopaminergic alterations.

Insert Table 4 about here.

4. Discussion

To our knowledge, this is the first systematic review regarding the neurobiological basis of BDD. We identified preliminary evidence for neurobiological disturbances in brain activity, structure, and connectivity in BDD patients in frontostriatal, limbic, and visual system regions when compared to healthy control and other clinical groups.

An advantage of this review is that it included a broad range of neuroimaging methods. However, a disadvantage of the studies included is the heterogeneity of the patient groups, study methods, and research questions, which make it difficult to

integrate the findings fully and to make definitive conclusions. Nonetheless, with the abovementioned neuroimaging investigations considered, the underlying pathophysiology of BDD appears to involve several key structural and functional abnormalities.

Our findings expand on a current model of BDD neurobiology that considers frontostriatal dysfunction alongside limbic system and visual system abnormalities (Li, Arienzo, & Feusner, 2013), for which clear comparisons can be drawn to models of OCD. To illustrate, the current dominant model of OCD stresses the involvement of orbitofronto-striatal circuitry; including the OFC, caudate, ventral striatum, and thalamus, alongside a more “affective” functional circuit, which comprises the hippocampus, anterior cingulate, and amygdala, all of which are extensively connected with the OFC (Menzies et al., 2008; Saxena & Rauch, 2000). When synthesising the data presented in this review, we draw from these models and consider three broad “systems”, all of which, in unison, may contribute to BDD pathology. Specifically, we speculate that the disturbances in perception, visual attention, and emotion that are evident in BDD patients may be attributable to disturbances in frontostriatal, early visual system, and limbic (amygdala) function, respectively (see **Figure 2**). We discuss these neurobiological systems in detail next. However, we stress that these systems should be considered as part of a large network, as has been depicted in **Figure 2.**

Insert Figure 2 about here

4.1. A Neurobiological Model for BDD Pathophysiology

4.1.1. Detailed processing and visual processing streams

Upon reviewing the neuroimaging data available thus far, the strongest support for neurobiological dysfunction is evident in a discord between the two visual processing streams giving rise to enhanced detail processing in BDD patients. Specifically, available evidence suggests that a “short-cut” exists within the occipitotemporal network (i.e., VVS), where first-order visual information within areas V1 and V2 travels from early visual areas to temporal regions, particularly within the left hemisphere, where heightened detail and structural encoding of visual information occurs (Arienzo et al., 2013; Feusner et al., 2011; Leow et al., 2012; Li, Lai, Bohon, et al., 2015; Li, Lai, Loo, et al., 2015). Additionally, in BDD patients, hypoactivity has been observed within the lateral occipital cortex and the precuneus, which might indicate underutilization of bottom-up processing of second-order visual information within the DVS, leading to deficits in the construction of holistic elements of visual information (Li, Lai, Loo, et al., 2015). Together, imbalances within first and second order visual processing systems suggest that abnormal small-world architecture, with a particular reliance on these systems, might play a major role in BDD pathophysiology. Such findings may explain neuropsychological observations of detail oriented visual-perceptual biases, manifesting behaviourally as enhanced flaw detection in BDD patients.

Inefficiencies within white matter pathways in BDD are indicative of this hypothesis. Specifically, current data suggest that white matter connections between the occipital and temporal cortices via the ILF have a higher relative influence over other neural connections in BDD patients (Arienzo et al., 2013; Feusner et al., 2013). As a result, this dominant structural connectivity between early visual and temporal regions may provide a basis for the heightened functional activity within the VVS (Li, Lai, Bohon, et al., 2015; Li, Lai, Loo, et al., 2015). Additionally, compromised

structural connectivity between the prefrontal, parietal, occipital, and temporal cortices via the SLF may reflect aberrant structural connectivity within DVS pathways, theoretically providing a structural basis for hypoactivity within the DVS (Buchanan et al., 2013).

4.1.2. Frontostriatal systems

Beyond abnormal bottom-up visual processing deficits, available evidence suggests that deficits in frontostriatal and subcortical neural circuitry may contribute to the repetitive and compulsive behaviours seen in BDD. The obsessive and compulsive behaviours in OCD are thought to arise from abnormal signalling between the thalamus, OFC, and caudate (Saxena & Rauch, 2000). Likewise, these regions are implicated in BDD, as hyperactivity and reduced grey-matter volumes have been observed within the bilateral OFC, bilateral caudate, left IFG, left PFC, and right thalamus (Atmaca et al., 2010; Buchanan et al., 2014; Feusner et al., 2011; Feusner, Moody, et al., 2010; Feusner et al., 2007). Further, within frontostriatal-subcortical circuitry, the basal ganglia, and in particular the caudate nucleus, may be particularly relevant to BDD psychopathology through inappropriately mediating motor inhibition and habit formation (DeLong & Georgopoulos, 2011; Knowlton, 2015).

Evidence that the white matter pathway that connects the frontal and occipital regions via the caudate, known as the inferior occipitofrontal fasciculus, operates inefficiently in BDD patients supports this hypothesis (Buchanan et al., 2013). Namely, abnormalities in information transfer within this pathway offer a possible explanation for the hyperactivity evident in frontal regions and the caudate in BDD research, leading to abnormal top-down control from frontal regions on visual information (Feusner et al., 2007). Moreover, cognitive investigations in BDD provide

support for frontostriatal involvement, as individuals with BDD show poorer performance than healthy controls on tasks of executive functioning, including response inhibition and planning (Deckersbach et al., 2000; Dunai et al., 2010; Hanes, 1998). Akin to OCD, poorer performance on these indices might be mediated by abnormalities in frontostriatal networks (Labuschagne, Rossell, Dunai, Castle, & Kyrios, 2013; Menzies et al., 2008). Consequently, we hypothesise that a frontostriatal model of BDD suggests that abnormalities in top-down and bottom-up feedback loops, particularly within orbito-frontostriatal circuitry, give rise to cognitive deficits in executive functions, as well as compulsive behaviours in BDD patients.

4.1.2. Temporolimbic systems

Finally, while substantive evidence is limited, there is support for limbic system dysfunction in BDD. In the context of phenomenology, BDD patients misattribute anxiety and negative emotional valence to their self-percept, as well as have a heightened experience of general anxiety, social anxiety and distress (Didie, Kelly, & Phillips, 2010; Kelly, Dalrymple, Zimmerman, & Phillips, 2013; Phillips, Menard, Fay, & Weisberg, 2005). Evidence from neuroimaging studies has demonstrated abnormal hyperactivation of the right amygdala during visual processing tasks (Feusner et al., 2007), as well as significant positive correlations between right amygdala volumes and BDD symptom severity (Feusner et al., 2009). Further, Bohon et al. (2012) demonstrated that the right amygdala mediates the relationship between anxiety and activation of the VVS for own-face stimuli in BDD patients. We spectulate that the involvement of the amygdala is crucial to BDD pathophysiology, as enhanced top-down signals carrying the emotional valence of stimuli to the visual cortex may result in enhanced visual processing of emotionally salient stimuli, which in turn might contribute to the preference for VVS over DVS

processing discussed above (Bohon et al., 2012). This hypothesis is supported by evidence of reduced directional diffusion in the uncinate fasciculus, which suggests that the connections between frontal and temporal regions via the limbic system (and in particular the amygdala) are compromised (Buchanan et al., 2013) (**Figure 3**). Impoverished connections between frontal and limbic regions may account for hyperactivity within the inferior frontal regions (i.e. the OFC, PFC, and the IFG), which serve important roles in the top-down regulation of the amygdala in the control of negative affect (Buchanan et al., 2014; Feusner et al., 2007; Feusner et al., 2009).

Altogether, the neural abnormalities in BDD cohorts discussed may reflect the heightened bottom-up processing of detailed holistic information from early visual system areas and the VVS, combined with poor top-down control of visual and emotional information from inferior frontal and limbic regions. The integration of such systems is likely impaired by inefficient information transfer across the whole-brain network, leading to the inability to integrate and contextualise visual information effectively. In association with poorer insight (Feusner et al., 2013; Li, Lai, Loo, et al., 2015), this may lead BDD patients to develop delusional beliefs about what they see (Eisen et al., 2004). The model proposed here is largely supported by abnormalities in white matter organisation in BDD cohorts presented in **Figure 3**. Disorganisation and dysfunction within these regions may explain the neuropsychological research in BDD involving difficulties with detailed and global information processing, compulsive behaviours, delusional beliefs, as well as the misattribution of emotional salience to visual information (Buhlmann et al., 2013; Monzani et al., 2013).

Insert Figure 3 about here

4.2. Limitations

The current review is limited primarily to studies that had relatively small sample sizes (n<20) and included substantial overlap of study participants. Further, samples differed regarding the prevalence and types of comorbid psychiatric diagnoses, however, with psychiatric comorbidity in BDD apparently the norm rather than the exception (20-40%) (Gunstad & Phillips, 2003; Phillips, Menard, Fay, & Weisberg, 2005); such samples are representative of the BDD population. Additionally, synthesis of study findings is complicated by differences in the medication status of participants across different studies. Based on these concerns, we recommend that future research includes BDD participants with similar demographic characteristics, psychiatric symptom profiles, and medication status to provide a basis for a more accurate comparison of the neurobiological basis of the disorder.

4.3. Future directions

There is a clear need for further neuroimaging investigations in BDD. While the issues noted with patient samples are difficult to overcome, care should be taken to eliminate the confounding effects of variability of patient characteristics and study methods. In this section, we propose some further methodological considerations that are intended to address these limitations and expand any future understanding of BDD neurobiology.

Firstly, limbic involvement in BDD neurobiology is unsubstantiated. The inclusion of tasks that probe limbic system function, such as tasks of face emotion perception, will aid in addressing corticolimbic system involvement in BDD pathology. In support, behavioural face emotion recognition deficits have been consistently found in BDD patients (Buhlmann et al., 2006; Buhlmann et al., 2004;

Buhlmann, McNally, Wilhelm, & Florin, 2002). Importantly, the inhibition of negative affect is thought to involve the functional disassociation of corticolimbic responses, leading to activation within the dorsal anterior cingulate and the prefrontal cortex, as well as the attenuation of limbic structures (Aron, 2007; Phan et al., 2005). On the other hand, in disorders such as autism in which pathological dysfunction in visual and emotion perception is common, visual processing is tightly linked to the amygdala (Pessoa & Adolphs, 2010). Emotion regulation via the limbic system is particularly relevant to BDD, as the inability to down-regulate visual and emotion processes may lead to the misattribution of emotional valence to visual information, that is, anxiety and other “negative” feelings may be directed towards the self-image.

Secondly, insight into the functional architecture of BDD comes solely from task-based activations during visual processing task paradigms. It would be beneficial to examine resting-state functional networks and default mode network (DMN) connectivity to see if these deficits persevere beyond tasks involving visual processing. Available evidence suggests DMN dysfunction in BDD. Namely, there is relative deactivation of regions of the DMN including the medial PFC, precuneus, posterior cingulate and inferior parietal lobule (Feusner et al., 2011). Alternatively, poor integration of small-world, as well as system-wide functional brain networks are particularly relevant in BDD pathology, as abnormalities in these systems are a feasible explanation for the perceptual biases evident in the disorder. The examination of whole-brain resting-state, functional, and structural network analyses in large samples will be instrumental in elucidating neurobiological markers of BDD.

Thirdly, there is evidence that a genetic component contributes to the aetiology of BDD. For example, a study examining family history found that 20% of BDD participants had a first degree relative with BDD (Phillips, Menard, Fay, &

Weisberg, 2005). Further, twin studies of healthy adults have reported rates of up to 64% genetic overlap of dysmorphic concern with obsessive compulsive behaviours (Monzani, Rijsdijk, Iervolino, et al., 2012), BDD is more common in first-degree relatives of OCD probands (Bienvenu et al., 2000; Bienvenu et al., 2012), and genome-wide OCRD association studies suggest that environmental factors, such as appearance-related teasing, may be pertinent in developing BDD specifically (Monzani et al., 2014). At this stage, however, it is unknown if this inherited vulnerability leads to the brain differences discussed here, and none thus far have associated genetic receptor function with functional or structural neurobiology in BDD cohorts. Given the similarities of BDD to OCD in phenomenology and heredity, the approach to future neurobiological research may do well to use integrated genetic and neurobiological models. Specifically, future studies could make reference to the neurobiological models of OCD (Menzies et al., 2008) as a starting point. Such models encompass environmental and genetic risk factors leading to epigenetic modifications within serotonergic, dopaminergic, and glutamatergic systems that in turn may play a crucial role in the functioning of the cortico-striato-thalamo-cortical circuit, leading to the phenotypic presentation of OCD (Pauls, Abramovitch, Rauch, & Geller, 2014).

Indeed, the limited evidence thus far suggests that similar systems may be dysfunctional in BDD. Decreased serotonin receptor binding density has been observed in a study of OCRDs, which included six BDD patients (Marazziti et al., 1999), and trend associations have been observed in serotonin and GABA-ergic genes in BDD (Vulink et al., 2016). Further, a preliminary candidate gene study implicated serotonergic and GABA-ergic systems in BDD through trend associations of respective genotypes (Phillips et al., 2015). However, these studies use small

samples and report trend effects, and as such, further research needs to directly investigate neurotransmitter systems in BDD patients to delineate the nature of disturbances within specific pathways, as has been examined in OCD cohorts (Pauls et al., 2014; Shin et al., 2014). In sum, while a single genome-wide association study of OCRDs has been published (Monzani et al., 2014), more work is needed to elucidate the aetiology and pathology of BDD. This work should include studies of genetic and epigenetic factors contributing to BDD, we well as incorporating these genes into neuroimaging and treatment response studies, much like what has been done in OCD and schizophrenia (Pauls et al., 2014). Available BDD research is limited to cross-sectional examinations, making it hard to determine cause-and-effect for relationships among clinical symptoms and brain abnormalities. Understanding neural and epigenetic changes pre- and post-treatment will lead to the development of informed and sophisticated models of BDD, imperative for guiding the development of targeted future treatments (see, Rossell, Harrison, & Castle, 2015, for a detailed review).

Finally, a noticeable trend within the BDD neuroimaging research to date is that clinical symptoms play a large mediating role in brain differences (e.g., Feusner et al., 2009; Madsen et al., 2015). Overall, these findings indicate that the nature of the brain differences in BDD relative to controls do not necessarily appear at the group level, but increase as a function of symptom presentation and severity. If using diagnostic groups of BDD patients, we recommend that future study designs consider the symptom presentation of the BDD patient cohort, perhaps grouping participants via the absence or presence of particular symptoms, such as those who present with delusional or non-delusional subtypes. Alternatively, we propose that future research into BDD and its related disorders should focus on behavioural

phenotypes, such as behavioural compulsions or body related perceptual distortions, or other psychological constructs like social anxiety, self-referential thinking, and trauma- or shame- related constructs, instead of rigid disorder-specific examinations, as has been proposed in the NIMH Research Domain Criteria (RDoC) framework (Insel, 2013). Of note, a general visual processing phenotype of psychiatric disorders involving distorted self-perception has been suggested by research comparing BDD and AN (Li et al., 2015a). Moving from reductionist approaches of neurobiology to integrative neural system models of psychiatric nosology, through mapping the environmental, pharmacological, cognitive, neural circuit, and genetic aspects of BDD and related disorders may lead to targeted treatment approaches that address symptoms across a range of DSM disorders.

5. Conclusion

BDD is a complex disorder that, like other psychiatric disorders, arises from a complex interplay of environmental factors, genetic predispositions, and neurobiological disturbances. Overall, we hypothesise that the neurobiological contributions of BDD involve systems of detailed visual processing, cognitive control, and emotion processing. Specifically, we speculate that the brain network is disturbed such that overactive detailed processing occurs early in the visual processing stream, which leads to the creation of distorted visual images (which in the case of BDD patients is some aspect of the self-image). Heightened salience and emotional valence are then attributed to this distorted visual image through inappropriate down-regulation from frontal and limbic regions. Also, orbito-frontostriatal loops inadequately regulate motor outputs which are attributed to the visual percept, leading to the engagement of BDD patients in compulsive behaviours

relating to the self-image, such as mirror checking or skin picking. Finally, inefficiencies in the structural architecture of the whole-brain network, impedes information integration between such systems, leading to a reliance on local systems working alone rather than in unison, which would otherwise provide context to the visual images and mediate these processes.

Further work involving neural connectivity, genetic, and pharmacological approaches that address specific symptoms or phenotypes will help to elucidate the aetiology and pathophysiology of BDD. We advocate for a future approach that emphasises the use of disorder-specific phenotypes rather than diagnostic categories, such as obsessions and compulsions. Alternatively, if using diagnostic groups of BDD participants, future research should use clinical participants with similar demographic characteristics, psychiatric symptom profiles, and medication status to provide a basis for a more accurate comparison of the neurobiological characteristics of the disorder. Such advances in our understanding of the underlying neurobiology of BDD is important in the determination of the treatment relevant aspects of BDD.

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Figure 1. PRISMA flow diagram of the article screening and selection process. Article selection was conducted in accordance with PRISMA guidelines for reporting systematic reviews (Moher et al., 2009).

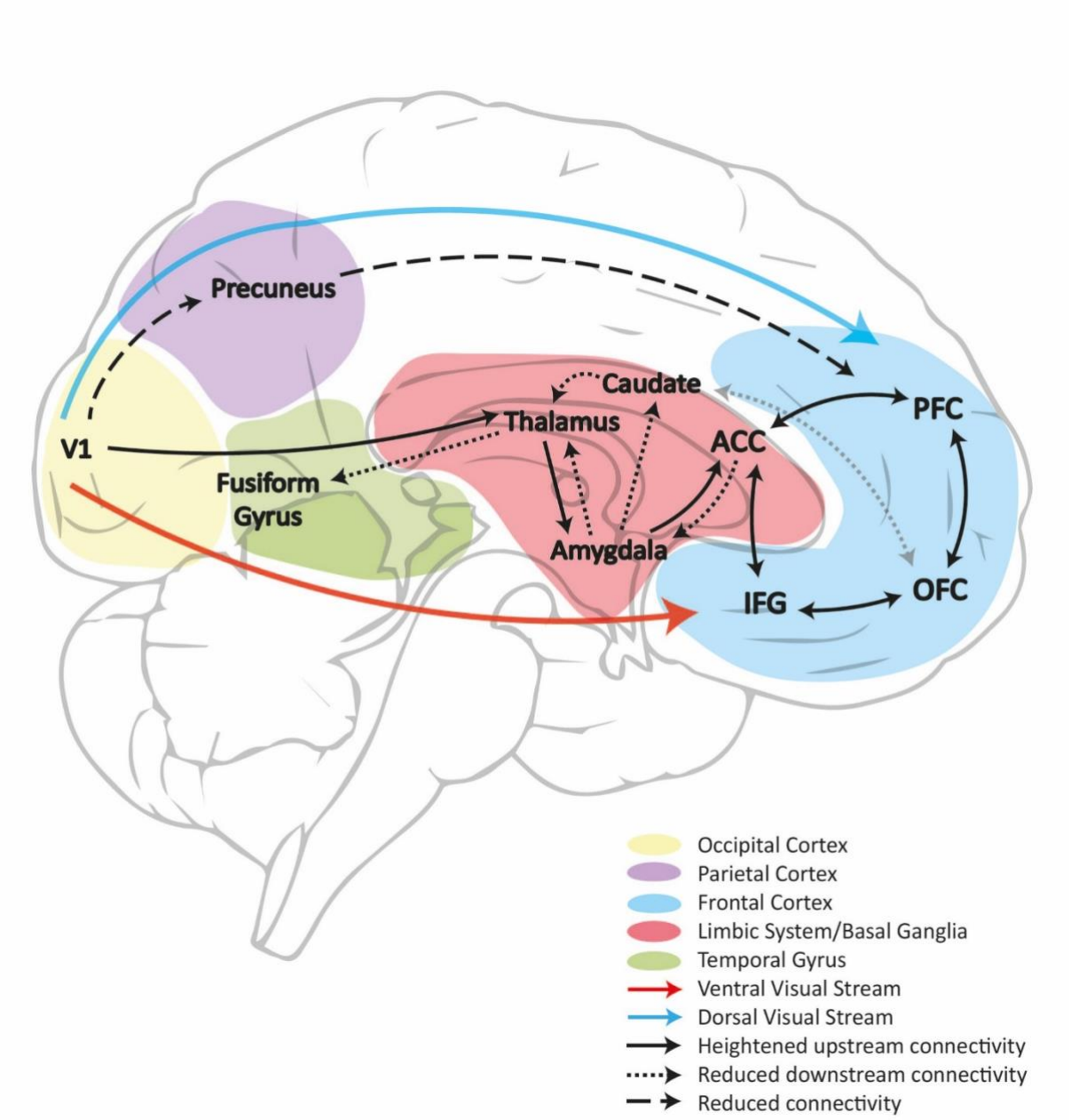

Figure 2. Schematic representation of frontostriatal, corticolimbic and visual system areas that have been implicated in the pathophysiology of BDD through structural and functional imaging investigations. Key brain regions thought to be involved include early visual system areas (e.g., V1), the precuneus, the prefrontal cortex (PFC), the orbitofrontal cortex (OFC), the inferior frontal gyrus (IFG), the anterior cingulate cortex (ACC), the amygdala, the thalamus, the caudate, and the anterior fusiform gyrus.

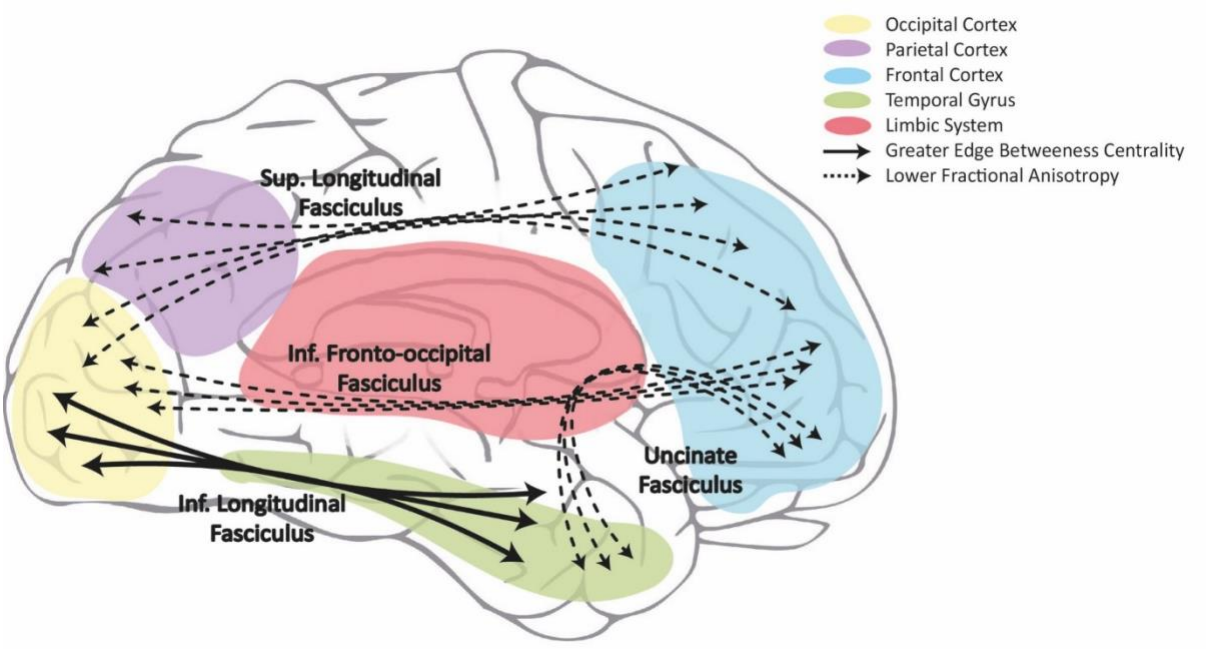

Figure 3. Schematic representation of the structural white matter networks that have been implicated in the pathophysiology of BDD through DTI investigations. Here, connections between the occipital and temporal regions, via the inferior longitudinal fasciculus, have been shown to have a higher 'influence' over other connections. Poor structural connections have been evident between occipital, parietal, and frontal regions via the superior longitudinal fasciculus; and between the inferofrontal and anterotemporal regions via the uncinate fasciculus. Poor structural connections have been identified between the hemispheres via the corpus callosum and forceps major, connecting the occipital lobes (not pictured).

Table 1. Characteristics of structural MRI studies in BDD

Study	Participants (n)	M/F	Age	Handedness (L/R)	Characteristics of sample	Method	Regions Implicated (BDD < HC)	Volumes (cm^3) BDD	Volumes (cm^3) Controls	*p*-value
Grace et al. (2016)	20 BDD	6/14	34.6±11.5	3/17	**Medication:** Seroquel (*n*=5), escitalopram (*n*=4), duloxetine (*n*=2), desvenlafaxine (*n*=2), diazepam (*n*=2), paroxetine (*n*=1), mirtazapine (*n*=1), lorazepam (*n*=1), methylphenidate (*n*=1), sodium valproate (*n*=1), and clomipramine (*n*=1) **Comorbidity** (*n*= not stated): SAD, MDD	3T MRI	Left inferior parietal lobe thickness	Not stated	Not stated	.001
	20 HC	6/14	31.9±11.4	3/17			Left middle parietal lobe thickness	Not stated	Not stated	.001
Madsen et al. (2015)	49 BDD	12/37	26.43±7.79	0/49	**Medication:** Psychoactive free for 8 weeks prior to study **Comorbidity:** None (*n*=23); Agoraphobia (*n*=1); Dysthymia (n=1); Dysthymia, GAD (*n*=2); GAD (*n*=5); MDD (*n*=9); GAD, MDD (*n*=6); GAD, MDD, social phobia (*n*=1); SAD (*n*=2)	3T MRI	Left superior temporal cortex	Not stated	Not stated	0.10***
	44 HC	14/30	25.34±7.80	0/44						
Buchanan et al. (2014)	20 BDD	6/14	34.6±11.5	3/17	**Medication:** Seroquel (*n*=5), escitalopram (*n*=4), duloxetine (*n*=2), desvenlafaxine (*n*=2), diazepam (*n*=2), paroxetine (*n*=1), mirtazapine (*n*=1), lorazepam (*n*=1), methylphenidate (*n*=1), sodium valproate (*n*=1), and clomipramine (*n*=1) **Comorbidity** (*n*= not stated): SAD, MDD	3T MRI	Right OFC	11.8±1.1	13.3±1.5	.002
	20 HC	6/14	31.9±11.4	3/17			Left thalamus	6.99±0.82	7.50±0.70	.040
							Right thalamus	7.15±0.77	7.64±0.58	.028
							Left ACC	4.43±0.67	5.10±0.81	.007
							Left hippocampus	4.19±0.32	4.44±0.36	.025
							Left amygdala	1.59±0.19	1.70±0.14	.049
Atmaca et al. (2010)	12 BDD	12/0	26.8±4.8	0/12	**Medication:** No history of use of lifetime psychoactive medication **Comorbidity:** No	1.5T MRI	Total White Matter	452.32±36.63	388.90±40.43	.044
	12 HC	12/0	28.2±5.7	0/12			Right OFC	10.93±1.72	14.18±2.29	.039
							Left OFC	11.18±1.95	14.77±2.54	.028
							Right ACC (covaried with age)	1.64±0.30	1.93±0.40	.029
							Left ACC (covaried with age)	1.52±0.25	1.89±0.34	.020
							Left Thalamus	5.83±0.77	5.20±0.48	.080
Feusner et al. (2009)	12 BDD	2/10	28.7±10.0	0/12	**Medication**: All participants psychoactive free for 3 weeks and fluoxetine for 5 weeks prior to study **Comorbidity:** Dysthymia (*n*= 1), MDD (*n*= 2), GAD (*n*= 2)	3T MRI	Left Amygdala	0.94±0.18	0.951±0.22	.47**
	12 HC	2/10	31.2±11.8	0/12			Right Amygdala	0.94±0.13	0.90±0.18	.33*
							Left IFG	11.95±2.16	11.88±2.24	.47*

Rauch et al. (2003)	8 BDD 8 HC	0/8 0/8	37.6±10.3 30.5±8.7	0/8 0/8	**Medication:** Unmedicated but SSRI history (*n*=2), Psychotropic naïve (*n*=4), fluoxetine (*n*=2) **Comorbidity:** Social Phobia (*n*=3) , MDD (*n*=2) , Bulimia (*n*=2), Panic Disorder (*n*=2), Agoraphobia (*n*=1), Dysthymia (*n*=1)	1.5T MRI	Total Cerebrum Total White Matter Caudate (left laterality)	1094.83±54.52 458.67±40.40 0.032±0.044	1032.48 ±51.49 406.46±30.61 -0.031±0.070	.034 .011 .048

Note. Data represented as mean±SD. Comorbidity indicates whether participants included in the study were listed as having comorbid disorders. BDD-YBOCS = BDD version of the Yale-Brown Obsessive-Compulsive Disorder Scale, HAM-D = Hamilton Depression Rating Scale, MDD = major depressive disorder, GAD = generalized anxiety disorder, SAD = social anxiety disorder, FFA = fusiform face area, ACC = anterior cingulate cortex, OFC = orbitofrontal cortex, IFG = inferior frontal gyrus.
Regions included are those that reached a significance level of $p<.10$ or has significant symptom correlations; * indicates a significant relationship between volumes and BDD-YBOCS; ** indicates a significant relationship with BDD-YBOCS and HAM-D depression score; ***indicated a significant relationship with HAM-A anxiety scores. BDD-YBOCS, BDD version of the Yale-Brown Obsessive-Compulsive Disorder Scale; HAM-D, Hamilton Depression Rating Scale. HAM-A, Hamilton Anxiety Rating Scale.

Table 2. Characteristics of functional MRI and EEG studies in BDD

Study	Participants (n)	M/F	Age	Handedness (L/R)	Characteristics of the sample	Imaging Modality	Research Design	Results
fMRI Studies								
Moody et al. (2015)	20 BDD 20 HC 20 AN	5/15 3/17 2/18	21.5±3.5 23.3±4.6 22.3±4.4	0/20 0/20 0/20	Medication: BDD (*n*=1): type not stated AN (*n*=1): type not stated Comorbidity: BDD: MDD (*n*=8); MDD & GAD (*n*=1); dysthymia (*n*=1), agoraphobia (*n*=1); MDD & social phobia (*n*=1); MDD, GAD, & social phobia (*n*=1). AN: GAD (*n*=2); MDD (*n*=2); MDD & GAD (*n*=2); dysthymia (*n*=1)	fMRI	*Block design* **Stimuli**: Face matching task; neutral faces; NSF, HSF or LSF. **Control condition:** Grey ovals and circles	**BDD > HC:** Greater connectivity between left anterior occipital face area and right FFA Greater LSF connectivity between right FFA and right and left precuneus, right posterior cingulate cortex and left lingual gyrus. **BDD < HC:** Lower LSF connectivity between right FFA and left insula, putamen, thalamus and central opercular cortex. **BDD > AN:** Greater connectivity between left anterior occipital face area and right FFA
Bohon et al. (2012)	17 BDD 16 HC	9/8 8/8	29.18±7.4 27.38±5.3	0/17 0/16	Medication: Psychoactive free for 8 weeks prior to study Comorbidity: Dysthymia (*n*=1), MDD (*n*=1), GAD (*n*=2), GAD & MDD (*n*=4), GAD & Dysthymia (*n*=2)	fMRI	*Event-related design* **Stimuli:** Participants own face, a familiar face, or oval images; indicate when image disappears from screen. **Control condition**: Grey ovals	**BDD > HC:** **Symptom Correlations:** Linear relationship between amygdala activity and VVS (ROI defined as occipital fusiform gyrus, temporal occipital fusiform cortex, posterior occipital fusiform cortex). Quadratic relationship between anxiety scores and right VVS (activity for own face (strongest in the FFA).
Feusner et al., (2011)	14 BDD 14 HC	0/12 0/12	28.1±7.3 26.9±5.1	0/12 0/12	Medication: Psychoactive free for 8 weeks prior to study Comorbidity: MDD (*n*=1), GAD (*n*=2), GAD & MDD (*n*=4), GAD & Dysthymia (*n*=2)	fMRI	*Block design* **Stimuli:** Houses at HSF, LSF, or NSF. Control Condition: Rectangles and squares of similar size to houses.	**BDD < HC:** LSF Images: parrahippocampal gyrus, lingual gyrus and precuneus **BDD > HC:** HSF images: Left frontal pole, right paracingulate gyrus, left superior frontal gyrus & right anterior cingulate gyrus **Symptom Correlations:** Symptom severity * lower dorsal occipital activity and ventrolateral prefrontal regions

Feusner et al. (2010)	17 BDD 16 HC	9/8 8/8	29.18±7.4 27.38±5.3	0/17 0/16	Medication: Psychoactive free for 8 weeks prior to study Comorbidity: Dysthymia (*n*=1), MDD (*n*=1), GAD (*n*=2), GAD & MDD (*n*=4), GAD & Dysthymia (*n*=2)	fMRI	*Event-related design* **Stimuli:** own-face or familiar face shown at NSF, LSF, and HSF; indicate when image disappears from screen **Control Condition:** Oval images (stimuli aversiveness measured)	**BDD > HC:** left OFC and bilateral caudate for own face versus familiar face **BDD < HC:** left occipital cortex activity (left intracalcarine cortex, occipital pole, left lingual gyrus, left OFG) for LSF for own-face versus oval **Symptom Correlations:** NSF own-face vs familiar face; Symptom severity * positive activity in right OFC, right caudate, right precentral and postcentral gyri, right dorsal occipital cortex Symptom severity * positively associated with activity in the bilateral caudate and left OFC Own face vs oval; BDD symptom severity negatively associated with left dorsal occipital cortex and right lateral cortex Aversiveness ratings higher in BDD; Frontostriatal activity covaried with aversiveness ratings (frontostriatal activity and visual cortex) BDD-YBOCS explained most variability in the right occipital lobe, precentral and postcetralgyrus, caudate, and the ACC
Feusner et al. (2007)	12 BDD 13 HC	2/10 2/11	28.7±10.0 31.3±11.3	0/12 0/13	Medication: Psychoactive free for 8 weeks prior to study Comorbidity: Dysthymia (*n*=1), MDD (*n*=1), GAD (*n*=2), GAD & Dysthymia (*n*=2)	fMRI	*Block design* **Stimuli:** Face matching task; neutral faces; NSF, HSF or LS. **Control condition:** Grey circles and ovals	**BDD > HC:** HSF Task: left middle, inferior, and temporal gyri activation LSF Task: left intraparietal sulcus; the left IFG; left superior temporal gyrus; right precentral and postcentral gyri; right middle and superior frontal gryri; bilateral dorsal ACC NSF Task: left superior temporal gyrus, left IFG, left insula **BDD < HC:** NSF task: bilateral cuneus, left middle occipital gyrus
EEG and fMRI Studies								
Li et al. (2015a)	15 BDD 15 HC 15 AN	2/13 2/13 2/13	24.93±5.15 22.07±3.85 23.6±3.46	Not stated	Medication: Psychoactive free for 8 weeks prior to study. Comorbidity: Dysthymia (*n*=3), MDD (*n*=4), GAD (*n*=1), panic disorder (*n*=1), SAD (*n*=1)	EEG and fMRI; joint independent component analyses.	*Event-related design* **Stimuli:** Face matching task; faces and houses at HSF, LSF or NSF. **Control condition:** Circles/ovals (faces), squares/rectangles (houses).	**BDD>HC:** Hyperactivity in posterior fusiform cortex (VVS) linked to N170 for HSF houses. **BDD < HC:** Hypoactivity in primary VVS (occipital fusiform, temporal occipital fusiform, and lateral occipital cortices) and secondary DVS (superior parietal lobule) visual systems for LSF houses. **AN & BDD < HC:** Hypoactivity in dorsal visual system linked to N170 for LSF faces **Correlational analyses:** Increased N170 activation for HSF houses associated with lower face attractiveness ratings
Li et al. (2015b)	20 BDD 20 HC	2/18 2/18	24.60±5.13 22.55±4.02	Not stated	Medication: Psychoactive free for	EEG	**Stimuli:** Face matching task; faces and houses at HSF, LSF or NSF.	**BDD < HC:**

	20 AN	2/18	23.40±3.22	8 weeks prior to study Comorbidity (*n*= not stated): Dysthymia, MDD, GAD, panic disorder, social phobia, GAD	**Control condition:** circles/ovals (faces), squares/rectangles (houses).	BDD group had lower N170 amplitude than controls for NSF images. **Symptom correlations:** Positive correlation between BABS scores and N170 amplitude for NSF and LSF faces.

Note. Data represented as mean±SD. HSF = high spatial frequency, LSF = low spatial frequency, NSF = normal spatial frequency (i.e. unaltered), BDD-YBOCS = BDD version of the Yale-Brown Obsessive-Compulsive Disorder Scale, BABS = Brown Assessment of Belief Scale, HAM-D = Hamilton Depression Rating Scale, AN = anorexia nervosa, MDD = major depressive disorder, GAD = generalized anxiety disorder, SAD = social anxiety disorder, FFA = fusiform face area, ACC = anterior cingulate cortex, OFC = orbitofrontal cortex, IFG = inferior frontal gyrus.

Table 3. Characteristics of connectivity studies in BDD included in the review

Study	Participants (n)	M/F	Age	Handedness (L/R)	Patient Characteristics	Imaging	Regions Implicated (BDD vs HC)	Symptom correlations
Zhang et al. (2016)	29 BDD 31 HC 24 AN	4/25 6/25 1/23	23.17±4.98 20.90±3.91 21.33±4.54	0/29 0/31 0/24	Medication: Psychoactive free for 8 weeks prior to study Comorbidity (*n*= not stated): Dysthymia, MDD, GAD, panic disorder, social phobia, GAD	Diffusion weighted MRI: network modularity	Right ACC abnormally not utilised in network. OFC and PCC abnormally included (trend – did not reach significance)	
Arienzo et al. (2013)	14 BDD 16 HC	7/7 8/8	26.7±4.9 27.3±5.3	0/14 0/16	Medication: Psychoactive free for 8 weeks prior to study Comorbidity: GAD (*n*=2), MDD (*n*=1), GAD, MDD & Dysthymia (*n*=3)	DTI: probe whole brain regional white matter organisation and relate to symptoms	Higher MCC Edge betweenness centrality between temporal and occipital pole nodes	Symptom severity associated with shorter paths in the ILF
Buchanan et al. (2013)	20 BDD 20 HC	6/14 6/14	34.6±11.5 31.9±11.4	3/17 3/17	Medication: Seroquel (*n*=5), escitalopram (*n*=4), duloxetine (*n*=2), desvenlafaxine (*n*=2), diazepam (*n*=2), paroxetine (*n*=1), mirtazapine (*n*=1), lorazepam (*n*=1), methylphenidate (*n*=1), sodium valproate (*n*=1) , and clomipramine (*n*=1) Comorbidity (*n*= not stated): SAD, MDD	DTI: white matter connectivity measured by FA	Lower FA in the; SLF, inferior fronto-occipital fasciculus, and the corpus callosum, uncinate fasciculus	Negative correlation between social anxiety scores and FA in the SLF
Feusner et al. (2013)	14 BDD 16 HC	7/7 8/8	26.7±4.9 27.3±5.3	0/14 0/16	Medication: Psychoactive free for 8 weeks prior to study Comorbidity: GAD (*n*=2), MDD (*n*=1), GAD, MDD & Dysthymia (*n*=3)	Diffusion weighted MRI: Estimations of white matter microstructure measured by FA, MD, cl, &cp	ILF &FM	Poor insight negatively correlated with FA and cl and positively correlated with MD &FM in the ILF
Leow et al. (2012)	11 BDD 13 HC	Not specified	Not specified	0/11 0/13	Medication: Psychoactive free for 8 weeks prior to study Comorbidity (*n*= not stated): Dysthymia, MDD, GAD	Diffusion weighted MRI: FSH mapping fMRI signals	Underutilised structural connections between left ICC and left lingual gyrus; the right ICC and right lingual gyrus; right temporal occipital fusiform cortex and right temporal fusiform cortex, posterior division; left ICC and right precuneus cortex; right ICC and left cuneal cortex; and right parahippocampal gyrus, posterior division and right temporal occipital fusiform cortex.	

							Relative hyperactivity in lingual gyrus, precuneus, and the parrahippocampal gyrus

Note. Data represented as mean±SD. FA = fractional anisotropy, MD = Mean diffusivity, cl = linear anisotropy, cp = planar anisotropy, ILF = inferior longitudinal fasciculus, FM = Forceps Major, SLF = superior longitudinal fasciculus, MCC = mean cluster coefficient (high MCC = greater local efficiency for more information transfer of a network), ICC = intracalcarine cortex, DTI = Diffusion Tensor Imaging, FSH = structural hierarchical mapping.

Table 4. Characteristics of psychopharmacological studies in BDD included in the review

Study	Participants (n)	M/F	Age	Handedness (L/R)	Patient Characteristics	Imaging	Regions Implicated (BDD vs HC)
Vulink et al. (2016)	12 BDD 12 HC	9/3 9/3	28.4±6.6 27.9±6.3	0/12 0/12	Medication: Psychoactive free for 1 month prior to study Comorbidity: Social phobia (*n*= 3)	Measurement of $D_{2/3}$ BP_{ND} with SPECT using a selective radiolabelled D2/3 receptor antagonist	Significantly lower dopamine $D_{2/3}$ receptor binding in the striatum (caudate nucleus and Putamen)