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Intranasal oxytocin alters amygdala-temporal resting-state functional connectivity in body dysmorphic disorder: A double-blind placebo-controlled randomized trial

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ABSTRACT

The aetiology of body dysmorphic disorder (BDD) is poorly understood. Recent evidence from functional brain imaging studies suggests that BDD is associated with aberrant task-based functional connectivity and that intranasal oxytocin (OXT) may improve network connectivity in BDD patients. Thus, the aim of this study was to investigate the effect of intranasal OXT on amygdala resting-state functional connectivity (rsFC) in BDD. In a randomized, double-blind, cross-over design, 19 BDD participants and 17 demographically matched healthy control participants received intranasal OXT (24 IU) or placebo prior to resting-state functional magnetic resonance imaging. The left and right amygdala were seeded as regions of interest, and temporal correlations between the amygdalae and all other voxels comprising cortical and subcortical grey matter were investigated. Compared to healthy controls, BDD patients showed greater baseline (placebo) rsFC between the left amygdala and two clusters within the left temporal lobe and one cluster within the superior frontal gyrus which was reversed following OXT administration. The control group also showed significantly greater rsFC between the left amygdala and anterior prefrontal cortex in the OXT session compared to placebo. Whilst preliminary, these findings suggest that BDD patients exhibit abnormal amygdala-temporal connectivity at rest, and OXT might have a role in changing this functional relationship.

1. Introduction

Body dysmorphic disorder (BDD) is a chronic and debilitating psychiatric disorder, with an estimated lifetime prevalence of 1.7–2.4% (Buhlmann et al., 2010; Koran et al., 2008). BDD is characterised by preoccupations and obsessions with perceived abnormalities or “defects” in physical appearance, often conceptualised as an imagined ugliness, resulting in profound distress (American Psychiatric Association, 2013; Buhlmann and Winter, 2011). Current treatment options for BDD encompass pharmacotherapy – mostly with serotonergic antidepressants – and cognitive behavioural therapy (Phillipou et al., 2016). However, current outcome data suggests that up to 60% of patients with BDD have distressing and disabling symptoms despite these treatments (Harrison et al., 2016). Exploration of novel treatments for BDD is therefore warranted. One potential treatment could be the neuropeptide oxytocin (OXT). Accumulating evidence suggests that when given intranasally, OXT might improve social and affective impairments in psychiatric illnesses (Bakermans-Kranenburg and van, 2013), and modulate the activity and functional connectivity of brain regions that underlie these socioemotional impairments (Grace et al., 2018).

Current models of neurobiological dysfunction in BDD have suggested that aberrations in frontostriatal, temporolimbic and visual system brain networks have a key role in the pathophysiology of the disorder (Grace et al., 2017; Li et al., 2013). For example, during face processing tasks, BDD patients abnormally hyper-activate occipital-temporal networks (ventral visual stream pathways; Moody et al., 2015) and hypo activate occipital-precuneus networks (dorsal visual stream pathways; Li et al., 2015a). Behaviourally, BDD patients present with a range of neurocognitive impairments including poor emotion recognition abilities, selective processing of visual information, and a bias to interpret neutral environmental cues as negative (Buhlmann et al., 2004; Monzani et al., 2013; Toh et al., 2017). Integrating this data, the biological mechanisms of BDD might involve feedback loops

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to and from the amygdala, prefrontal cortex and temporal lobe, giving rise to excessive appearance preoccupations and negative appraisal of the self-image (Grace et al., 2017). Of significance, intranasal OXT might have a clinical application in BDD patients by changing the responsiveness of the amygdala. However, no studies to date have investigated the impact of intranasal OXT in brain function in BDD.

Over the past decade, several studies have examined the association between intranasal OXT and resting-state functional brain connectivity in healthy individuals and an array of clinical groups (Ebner et al., 2016; Eckstein et al., 2017; Fan et al., 2014; Koch et al., 2016; Riem et al., 2013; Sripada et al., 2012). Resting-state functional connectivity (rsFC) identifies synchronous activation of spatially remote brain regions in the absence of a task, or "at rest" (van de Ven et al., 2004). Intranasal OXT appears to modulate rsFC in a similar manner to task-based fMRI, with consistent effects on the amygdala (see, for a review; Seeley et al., 2018). For instance, in healthy humans, intranasal OXT has been shown to enhance amygdala rsFC with medial frontal regions (medial prefrontal cortex, mPFC; and anterior cingulate cortex, ACC), as well as posterior cingulate cortex (PCC) to brainstem rsFC (Riem et al., 2013). Increased amygdala-prefrontal connectivity might reflect enhanced attentional control and salience processing, which is hypothesized to regulate cognitive-emotional-somatic integration (Sripada et al., 2012). Furthermore, the mPFC and PCC are hubs of the default mode network (DMN), a large-scale network of brain areas that are typically deactivated during goal-oriented tasks and which form an integrated system for self-referential processing, autobiographical memory and social-reflection processes such as theory of mind (Broyd et al., 2009). Thus, intranasal OXT may restore aberrant rsFC in BDD within regions comprising the amygdala and the DMN, altering responsiveness to internal and external stimuli in psychiatric patients.

To our knowledge, this is the first resting-state analysis of functional brain networks in BDD, and the first examination of intranasal OXT on rsFC in BDD. Our primary aim was to investigate whether intranasal OXT alters amygdala rsFC in BDD patients compared to healthy controls. We conducted a randomized, placebo-controlled, within-subject resting-state fMRI study in BDD patients and demographically matched healthy control participants. We used a seed based connectivity approach and tested the hypothesis that OXT would restore/reverse rsFC of the left amygdala with the mPFC, precuneus (PCC) and/or temporal lobe in BDD patients relative to the healthy control group. The second aim was to investigate whether the relationship between rsFC under placebo and rsFC under OXT varies as a function of level of BDD symptom severity, depression and social anxiety. This question was addressed using moderation analyses

2. Methods

2.1. Participants

The study included 21 BDD and 23 healthy control participants who participated in a larger trial examining OXT in BDD. We excluded two BDD and six control participants due to data lost to follow-up, technical problems during the MRI acquisition, and excessive head motion. This resulted in a final sample of 19 BDD (mean age ± SD: 29.63 ± 10.60 years; 12 males) and 17 healthy control (mean age ± SD: 29.94 ± 9.16 years; 9 males) participants for our analyses. Group characteristics are shown in Table 1. Recruitment for the BDD group was conducted via referrals from St Vincent's Hospital Body Image clinic in Melbourne, Australia, where clients were identified as having BDD through their clinician and introduced to the research project. Diagnosis was then confirmed by the research team using the Body Dysmorphic Disorder Diagnostic Module (BDD-DM; Phillips et al., 1997). All BDD participants were assessed as having moderate-to-severe BDD symptoms, according to the Yale–Brown Obsessive Compulsive Scale Modified for Body Dysmorphic Disorder (BDD-YBOCS; Phillips et al., 1997). For the BDD patients, degree of conviction and insight into beliefs (i.e., degree of delusionality) were measured using the Brown Assessment of Beliefs Scale (BABS; Eisen et al., 1998).

Table 1
Demographic and psychometric measures.

	BDD (n = 19)	HC (n = 17)	t/χ^2 (34)	p
Demographics				
Gender (M/F)	12/7	9/8	0.39	0.535
Age	29.63 (10.60)	29.94 (9.18)	−0.09	0.926
Estimated IQ	108.95 (9.95)	112.82 (11.32)	−1.09	0.282
Clinical measures				
DCQ	17.63 (3.59)	3.58 (4.15)	12.02	< 0.001
SIAS	41.05 (18.98)	16.88 (12.57)	4.47	< 0.001
DASS Depression	23.42 (17.38)	2.06 (2.67)	5.08	< 0.001
DASS Anxiety	14.11 (10.27)	1.12 (1.90)	5.13	< 0.001
DASS Stress	21.58 (12.24)	3.59 (4.15)	5.85	< 0.001
Hormonal factors			5.65	0.130
Hormonal contraception	5	3		
Luteal	2	2		
Follicular	0	3		
BDD symptomatology				
Age of onset (years)	15.00 (4.52)	–		
Illness duration (years)	5.36 (4.56)	–		
BDD-YBOCS	25.16 (11.27)	–		
BABS	11.11 (6.62)	–		

Note. Data are presented as mean (± SD). HC, healthy control group; BDD, body dysmorphic disorder group; M, male; F = female; DCQ, dysmorphic concern questionnaire; SIAS, Social Interaction Anxiety Scale; DASS, Depression Anxiety Stress Scale; BDD-YBOCS, Yale-Brown Obsessive Compulsive Scale Modified for Body Dysmorphic Disorder; BABS, brown assessment of beliefs scale. IQ was estimated via the Wechsler Test of Adult Reading.

BDD patients were excluded if they had a past or current psychotic disorder, bulimia nervosa, anorexia nervosa, and alcohol or substance abuse history, as assessed by the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). 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 diagnosis (see Table **S1** for additional clinical details of the BDD group).

The control group were volunteer members of the public who were recruited through community advertisements and did not meet criteria for a current or lifetime mental illness, had no history of current alcohol/substance abuse or dependence, no known first-degree family history of mental illness, and were naïve to prescription strength medication. All participants completed commonly used standardised clinical measures to assess trait anxiety, depression, social anxiety and body image concern using the Depression Anxiety Stress Scale (DASS; Lovibond and Lovibond, 1995) and the Social Interaction Anxiety Scale (SIAS; Mattick and Clarke, 1998), and the Dysmorphic Concern Questionnaire (DCQ; Mancuso et al., 2010), respectively (see Table 1). In addition, all participants had to be right-handed as confirmed via the Edinburgh Inventory (Oldfield, 1971), between the ages of 18 and 55 years, non-smokers, spoke English as their preferred language and recorded a Wechsler Test of Adult Reading (WTAR) pre-morbid intelligence quotient (IQ) score of > 80. All participants were assessed with the MINI as well as the BDD-DM (Phillips et al., 1997). The exclusion criteria for all participants were a history of neurological disorder, head trauma, endocrinological disorders, current smoking, or metal implants; and for female participants, current breastfeeding or pregnancy.

This trial was approved by the St. Vincent's Hospital Melbourne Drug and Device Human Ethics Committee and participants provided written informed consent in accordance with the Declaration of Helsinki before they took part (General Assembly of the World Medical, A., 2014). This study is registered with the Australian and New Zealand Clinical Trials Registry (ACTR; ACTRN12614000991617).

2.2. Procedure

In a randomized, counterbalanced, double-blind, placebo-controlled within-subjects pharmaco-fMRI design, participants self-administered each a single dose of OXT (24 IU) or placebo (containing all ingredients except for the peptide), corresponding to three puffs of 4 IU each per nostril in alternating order with 45 s between each application. Participants were randomly assigned to each order of study conditions using block randomization in Excel. The dosages were comparable to those used in previous human studies (Grace et al., 2018; Labuschagne et al., 2010), and administered in accordance with standard recommendations for oxytocin nasal administration (Guastella et al., 2013). Pre and post each MRI scan, mood and state-anxiety were assessed using the state measure of the STAI (Spielberger, 1983) and the Visual Analogue Mood Scale (VAMS; Bond and Lader, 1974); see supplementary analyses and Table **S2**. Based on previous pharmacokinetic experiments (Paloyelis et al., 2016; Spengler et al., 2017), the fMRI scanning was commenced at a mean time of 51.87 min (SD = 8.05) post-drug administration. The mean interval between the two fMRI scans was 27.25 days (SD = 9.67 days).

Test sessions were conducted by one member of the research team (SG). Participants were instructed to stay well-hydrated before their visits, but to abstain from caffeine, alcohol and use of analgesic medication on the day of scanning; and from food in the three hours leading up to their scan. All participants were screened to have not taken recreational drugs in the 8 weeks prior to testing. All test sessions took place in the afternoons, starting at an average time of 1:20pm (SD = 66.6 min).

For female participants, we attempted to schedule all scans during the luteal phase of the female menstrual cycle (the last 14 days of the cycle) using participant self-report following procedures described in (Penton-Voak et al., 1999). The second scan occurred approximately 28 days after the first scan (M = 27.25 days, SD = 9.67 days). In one female participant, scheduling conflicts prevented us from re-scanning close to the same cycle point at one month later, so in this situation we opted to re-scan at two months (61 days) later. Of the 16 included female participants, all were pre-menopausal, and χ^2 tests revealed no significant differences between the groups regarding menstrual cycle phase and hormonal contraceptive use ($p =$ 0.130, two-sided, Table 1).

2.3. Imaging data acquisition

Imaging data were collected on a Siemens Avanto 3.0 T Magnetom Tim Trio scanner (Siemens, AG, Erlagen, Germany). T1-weighted images were acquired using an optimized Magnetization-Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence (TE = 2.52 ms, TR = 1900 ms, flip angle = 9°, FoV = 256 mm, 176 sagittal 1-mm slices) that was used for image pre-processing and anatomical reference purposes. Resting-state fMRI was acquired using a $T2_*$-weighted echo-planar imaging sequence (TE = 30 ms, TR = 2 s, flip angle = 80°, 25 transverse slices, voxel size 3.0 × 3.0 × 3.0 mm). Data were acquired for 8 min, resulting in 200 volumes. Each participant was positioned supine in the MRI scanner with their head in a comfortable restraint to reduce movement. Participants were instructed to fixate on a central white cross on a black background, relax, and let their minds wander, but not to fall asleep.

2.4. fMRI data preprocessing

Processing and statistical analysis of imaging data were conducted in Statistical Parametric Mapping software (SPM12: Wellcome Trust Centre for Neuroimaging, London, UK) and CONN Functional Connectivity Toolbox (version 16b; http://www.nitrc.org/projects/conn/; Whitfield-Gabrieli and Nieto-Castanon, 2012). Standard pre-processing procedures were employed (using CONN's default pre-processing pipeline), as well as subsequent statistical analyses, on all collected MRI scans. In this pre-processing pipeline, raw functional images were slice-time corrected, realigned (motion corrected), unwarped, and coregistered to each subject's MPRAGE image in accordance with standard algorithms. Images were then normalized to Montreal Neurological Institute (MNI) coordinate space, spatially smoothed (8 mm full-width at half maximum), and resliced to 2 × 2 × 2 mm voxels. The Artifact Detection Tool (ART; http://www.nitrc.org/projects/artifact_detect/) was also used to regress out scans as nuisance covariates in the first-level analysis exceeding 3 SD in mean global intensity and scan-to-scan motion that exceeded 0.5 mm. These were added in addition to covariates for the 6 rotation/translation movement parameters. Prior to analysis, data was de-noised using "aCompCor," an anatomically informed component-based noise correction, to correct for physiological and other sources of noise from white matter and cerebral spinal fluid (Behzadi et al., 2007). The residual BOLD time series was then band-pass filtered (0.008-0.09 Hz). The functional scans of each participant were visually checked for goodness of spatial registration, and for complete brain coverage. These processes did not result in any of the data being removed from the analyses.

2.5. Functional connectivity analysis

In the seed-based analyses, temporal correlations of the resting-state BOLD signal time series were examined between the left and right amygdala seed regions (anatomically derived regions of interest/ROIs from the Automated Anatomical Labelling [AAL] toolbox based on the atlas of (Tzourio-Mazoyer et al., 2002)) and the rest of the brain. Functional connectivity strengths were generated by converting the correlation coefficients to z-values with Fisher's r-to-z transformation. The resultant uncorrected statistical maps representing the voxel-wise strength of functional connectivity to the seed region have been made available on NeuroVault (https://neurovault.org/collections/3666/). During first-level processing, an individual contrast image was created for each participant. A general linear model was applied to examine significant BOLD signal correlation with respect to time between each seed and each voxel. To examine OXT's effects on rsFC in the healthy control group, group level random effects analyses (one-sample and paired t test) were then performed between seed regions and the rest of the brain in the healthy control group only, at a threshold of $p < 0.001$ uncorrected with a minimum cluster size of 150 voxels. Thereafter, whole-brain voxel-wise repeated measures analyses of variance (ANOVAs) were performed to test for main effects of drug (OXT, placebo) and group (BDD, healthy control), and also drug-by-group interactions. For the ANOVAs of left and right amygdala connectivity, cluster-based significance thresholding was used to adjust for multiple comparisons within the search volume. We selected a stringent cluster threshold of $p < 0.05$, family-wise error corrected, with a voxel threshold of $p < 0.001$ and a cluster size of at least 100 voxels. For completeness, any significant main effects that met this threshold are reported. For clusters showing drug-by-group interactions, simple main effects were examined within the CONN Toolbox using a series of *post hoc* paired and independent samples t-tests at $p < 0.05$ (two-tailed).

The connectivity values were also entered into several moderated multiple regression analyses to examine whether clinical symptom severity (DASS depression scores, BDD-YBOCS total scores and SIAS total scores) moderated the relationship of OXT's effect on rsFC of the amygdala in the BDD group. The moderating effect was tested using a multiplicative interaction between placebo rsFC and symptom severity. Assumptions of the linear model were assessed prior to regression analyses and found to be appropriate. The moderator variable (DASS depression scores, BDD-YBOCS total scores, or SIAS total scores) was mean centered prior to computing the interaction. The *post-hoc* analyses were performed in the R statistical environment (version 3.5.3). Analysis scripts and data are available at https://osf.io/dezkt/.

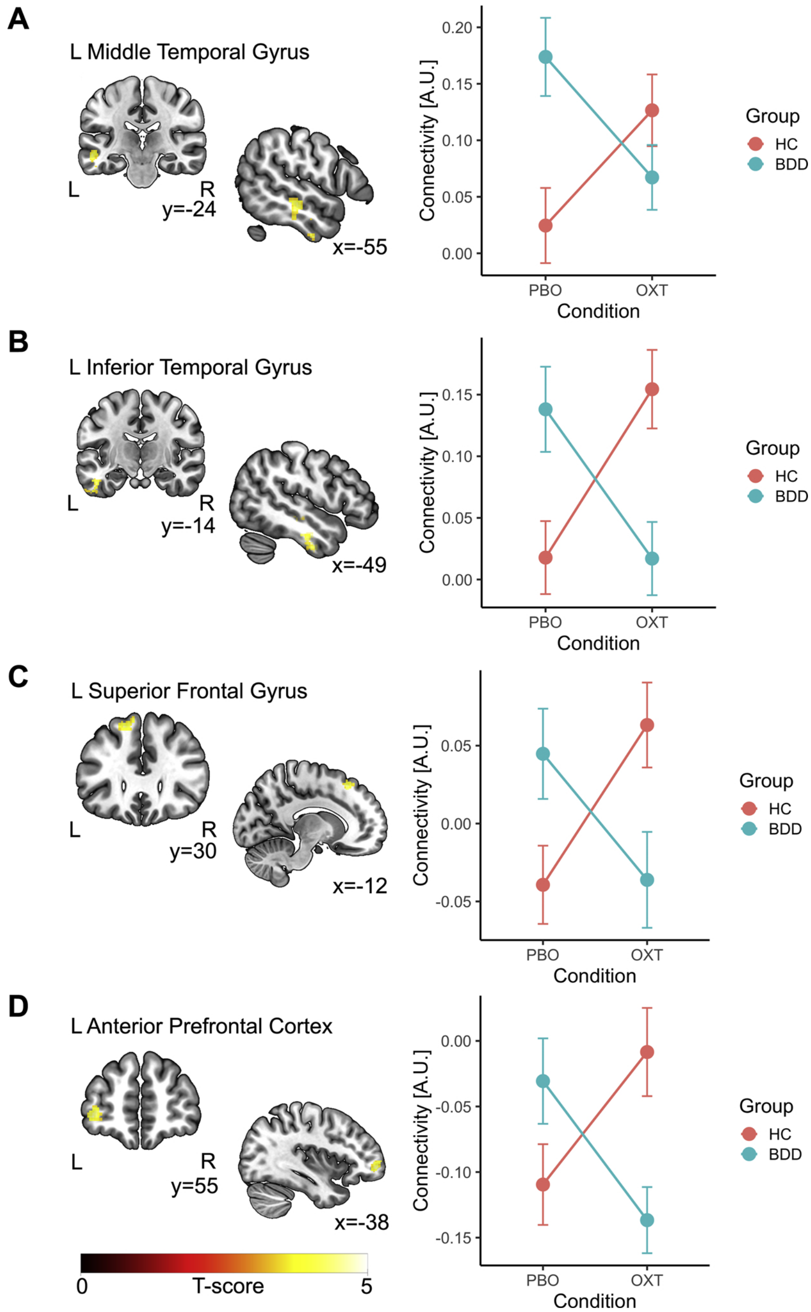

Fig. 1. Resting-state functional connectivity showing drug-by-group interactions exhibited from left amygdala to left MTG (A); left amygdala to ITG (B); left amygdala to left superior frontal gyrus (C); and left amygdala to left frontal pole (D) connectivity. Data were presented as mean ± SEM. Abbreviations: L, left; BDD, body dysmorphic disorder group; HC, healthy control group; OXT, oxytocin; PBO, placebo.

3. Results

3.1. Group and drug analyses

For the right amygdala there were no significant drug, group, or drug-by-group effects observed in rsFC with any clusters in the rest of the brain. For the left amygdala, our rsFC analyses revealed a drug-by-group interaction with the left middle temporal gyrus (MTG; MNI[-56, -26, -16], pFWE-corr = 0.008; Fig. 1**a**; Table 2). Simple main effect analysis revealed that under placebo, the BDD group exhibited significantly greater left amygdala to left MTG rsFC compared to the healthy control group ($t(34) = 3.09$, $p = 0.003$), and under OXT controls exhibited greater MTG-amygdala connectivity, but this was non-significant ($t(34) = 1.39$, $p = 0.172$). Specifically, OXT (> placebo) decreased left amygdala to left MTG rsFC in the BDD group, whereas it increased in the healthy control group such that group differences evident in the placebo session were not observed in the OXT session.

We also observed a drug-by-group interaction in rsFC between the left amygdala and a cluster within the left inferior temporal gyrus (ITG; MNI[-48, -18, -26], pFWE-corr = 0.007; Fig. 1**c**; Table 2). Simple main effects analysis revealed that under placebo, the BDD group exhibited significantly greater left amygdala to left ITG rsFC compared to the healthy control group ($t(34) = 2.61$, p 0.013); and under OXT the connectivity of these clusters was reversed as controls exhibited significantly greater rsFC than patients ($t(34) = 3.16$, $p = 0.003$). There was decreased left amygdala to left ITG rsFC in the BDD group following OXT (> placebo) whereas it decreased in the healthy controls.

Significant drug-by-group interactions outside *a priori* temporal lobe

Table 2
Whole-brain voxel wise ANOVA of Resting-State Functional Connectivity of the Left Amygdala.

Region	H	Coordinates			Peak	Cluster		
		x	y	z	*t* Value	K	*p* uncorrected	*p* FWE-corr
Drug-by-group interaction								
Middle Temporal Gyrus, posterior	L	−56	−26	−16	4.31	137	< 0.001	0.008
Inferior Temporal Gyrus, posterior	L	−48	−18	−26	4.60	138	< 0.001	0.007
Superior Frontal Gyrus	L	−14	−28	52	4.92	136	< 0.001	0.008
Anterior Prefrontal Cortex/Frontal Pole	L	−38	54	−4	4.56	116	< 0.001	0.019

Note. Significance threshold at $p < 0.001$ (uncorrected) with a cluster extent threshold of $k \geq 68$. Abbreviations: H, hemisphere; k = cluster size; FWE = family-wise error. Italics represent *a priori* areas of interest for significant drug-by-group interaction, corrected for multiple comparisons.

regions were also identified in rsFC of the left amygdala with the left superior frontal gyrus (SFG; MNI[-14, -28, 52], *p*FWE-corr = 0.008; Table 2**; Figure S1a**). Simple main effects analysis revealed that under placebo, the BDD group had greater left amygdala to left SFG rsFC (t (34) = 2.17, $p =$ 0.037), and under OXT the relationship was reversed such that control group exhibited greater left amygdala to left SFG rsFC than the BDD group (t(34) = 2.39, $p =$ 0.022). OXT (> placebo) significantly decreased left-amygdala to left SFG rsFC in the BDD group, whereas it significantly increased in the healthy control group. Similarly, a significant drug-by-group interaction in rsFC of the left amygdala with the left frontal pole/ anterior prefrontal cortex was observed (aPFC; MNI[-38, 54, -4], *p*FWE-corr = 0.019; Table 2**; Figure S1b**). Simple main effects revealed that under placebo, the BDD group had greater left amygdala to left aPFC connectivity than the control group which did not meet significance (t(34) = 1.75, $p =$ 0.089), and under OXT the control group exhibited greater left amygdala-aPFC rsFC than the BDD group (t(34) = 3.09, $p =$ 0.004). OXT (> placebo) significantly increased left amygdala to left aPFC rsFC in the BDD group, whereas it significantly increased in the healthy control group such that group differences were observed in the OXT session that were not evident in the placebo session.

3.2. Healthy control analyses

Within the healthy control group, results showed that both the right and left amygdala exhibited similar patterns of connectivity under placebo and OXT (**See Supplementary Table S3**), both exhibiting connectivity with the bilateral cerebellum, middle temporal gyrus, frontal pole, precentral gyrus, and anterior cingulate gyrus. For the right amygdala, there was no significant main effect of drug (OXT vs. placebo; **Table S3**). For the left amygdala, there was a significant main effect of drug, with healthy controls exhibiting greater left amygdala to right superior frontal gyrus (MNI[8, 12, 70], *p*FWE-corr < 0.001, peak t value = 4.01, k = 160; **Table S3**; **Figure S1**) connectivity in the OXT session than in the placebo session.

3.3. Moderation analyses

We conducted a series of moderated multiple regression analyses to examine whether level of BDD symptom severity (BDD-YBOCS total scores), depression (DASS depression scores), and social anxiety (SIAS total scores) moderated the effect of OXT on amygdala rsFC with the clusters identified in our main analyses. rsFC at placebo and mean-centered BDD-YBOCS scores were entered at the first stage, and the multiplicative interaction between these variables was entered at the second stage. As shown in **Table S4**, the moderated multiple regression for level of BDD symptom severity, depression or social anxiety did not reveal a significant interaction term for left amygdala connectivity with the left MTG, the left ITG, left frontal pole, or the left SFG. This indicates that symptom severity within the BDD group was not a significant moderator of the relationship between the effect of OXT (vs. placebo) on rsFC of the left amygdala.

4. Discussion

This study constitutes, to our knowledge, the first examination of resting-state connectivity in BDD patients during an acute dosage of intranasal OXT, with a focus on amygdala to whole-brain rsFC. We observed a drug-by-group interaction for rsFC between the left amygdala and clusters localised within the left MTG, left ITG, left SFG and left anterior PFC. This was consistent with our hypothesis of OXT's influence on the rsFC of the left amygdala with the temporal lobe. However, our hypothesis of intranasal OXTs modulation of the rsFC between the left amygdala and mPFC and precuneus was not supported. We found no significant group differences or interactions with drug (OXT vs. placebo) in the right amygdala rsFC. In our secondary analyses, we found no moderating effect of OXT on the change in rsFC between the left amygdala and the left MTG, left ITG, left SFG and left anterior PFC, and our clinical symptoms.

Under placebo, the BDD group demonstrated significantly increased left amygdala to left MTG rsFC, which was reversed following intranasal OXT such that group differences were no longer evident. The MTG is a key area within the ventral visual stream, which is hyperactive in BDD cohorts during visual processing tasks (Feusner et al., 2011, 2010; Feusner et al., 2007; Li et al., 2015a, b). The left amygdala to left ITG rsFC showed a similar drug by group effect, with connectivity being reversed in the placebo and OXT sessions. Together, this suggests that OXT is having a consistent modulating effect of the rsFC between the left amygdala and left temporal lobe. In our previous neurobiological model of BDD (Grace et al., 2017), we hypothesized that enhanced ventral visual stream (i.e., temporal lobe) versus dorsal visual stream processing, particularly within the left hemisphere, might be a precipitating and/or maintaining factor in BDD, resulting in a bias to process visual information in detail rather than as a meaningful whole. Increased left amygdala to temporal lobe connectivity at baseline may contribute to the increased salience and emotional processing of visual imagery via the amygdala (Pessoa and Adolphs, 2010). We therefore speculate that intranasal OXT could help to treat the fine-detail appearance predilections observed in BDD by de-coupling the amygdala and temporal lobe. The therapeutic efficacy of OXT in BDD could therefore be relevant in visual retraining paradigms that aim to shift attentional biases in BDD patients (Beilharz et al., 2017).

We also demonstrated changes to rsFC in the BDD group under OXT that were localised almost entirely to the left hemisphere. This result is consistent with the findings of previous fMRI studies in BDD that have demonstrated abnormalities in brain function localised to the left hemisphere during face processing tasks (Feusner et al., 2010, 2007). Previous authors have hypothesized that left-hemispheric involvement in face processing reflects a bias to rely on greater detailed encoding of visual information in BDD (Feusner et al., 2010). Thus, the present results suggest that a greater reliance on left-hemisphere processing in BDD patients persists in the resting brain.

The results showed that under OXT the control group showed increased coupling of left amygdala with the left aPFC and superior frontal gyrus compared with the BDD group. The aPFC is required during social interactions to inhibit emotionally driven responses (Volman et al., 2011). We hypothesize that this finding demonstrates OXT-induced recruitment of relevant social cognitive brain regions in healthy controls, which is not seen in BDD participants. Likewise, an analysis of the healthy control group alone revealed a significant treatment effect of OXT increasing the functional coupling of the left amygdala and the right superior frontal gyrus. This finding is unique as previous rsFC research in healthy controls has identified OXT induced rsFC of the bilateral amygdala with regions such as the dorsal ACC, precuneus, and mPFC (see, Grace et al., 2018; Seeley et al., 2018, for reviews).

The amygdala plays a role in social cognition and attention processing as a core region of the salience network (Adolphs, 2010), featuring a high density of OXT and dopamine receptors (Gimpl and Fahrenholz, 2001). It is hypothesized that OXT shapes behaviour through changes to social information processing by acting on the amygdala and prefrontal cortex (Bethlehem et al., 2013). A recent study found intranasal OXT induced decreases in regional cerebral blood flow (rCBF) in the left amygdala and anterior cingulate cortex which likely represents the direct nose-to-brain transport of OXT (Martins et al., 2019). Speculatively, the current pattern of findings suggests that OXT is entering the brain and acting on the amygdala to influence activity in other brain regions in both BDD patients and healthy controls. Though, our lack of behavioural outcomes preclude any hypotheses regarding the effect of OXT on behaviour in the BDD patient sample.

We identified no group or treatment effects on rsFC of the mPFC or PCC with the amygdala in contrast with previous OXT research (Dodhia et al., 2014; Ebner et al., 2016; Kovacs and Keri, 2015; Riem et al., 2013; Sripada et al., 2012). However, such studies were restricted to ROI-to-ROI analyses or specifically seeded the mPFC or PCC. We chose an unbiased amygdala ROI-to-whole-brain approach which may have impacted our ability to detect default-mode connectivity changes. Future studies would do well to additionally seed key default mode hubs (mPFC/PCC) or run group independent component analyses in BDD patients to interrogate this further.

There are several caveats to consider before OXT can be a clinical treatment for BDD. The dosage of 24 IU of OXT used in the present study is most commonly used in studies of intranasal OXT brain effects (Grace et al., 2018) and may be the most effective dosage in healthy adults (Spengler et al., 2017), yet lower dosages may be more efficacious in psychopathology (Quintana et al., 2016). In a review of OXT's effect on resting-state brain networks, Seeley et al. (2018) report that OXT has the most pronounced effect in clinical samples with greater social cognitive or self-referential dysfunction. However, in conditions like BDD, heightened self-referential processing might be maladaptive (Seeley et al., 2018). One could interrogate both salience and introspective processes by investigating large-scale resting-state brain networks (Menon, 2011), as has been examined in healthy subjects following OXT treatment (Brodmann et al., 2017). For instance, self-referential processes are thought to be processed via the DMN, which is anchored in the PCC and mPFC (Greicius et al., 2003). We propose that future extensions and replications of this work use multidose and repeated administration paradigms paired with careful measurement of behavioural outcomes to systematically identify the therapeutic efficacy of OXT in BDD.

The findings of this study must be considered in the context of several limitations. First, the rsFC analysis protocol in the current study does not allow for an interpretation of the direction of effect. That is, we predict that the amygdala is downregulating heightened processing within the temporal lobe, yet, we cannot test this hypothesis with our dataset. Second, we may have not detected effects for some statistical comparisons because of the modest sample size in the present study ($N = 36$). We did not perform an a priori power analysis, and it is statistically not informative to perform post hoc power calculations (Hoenig and Heisey, 2001). Future studies should perform a priori power calculations to ensure sufficient power to detect smaller magnitude within-group and between-group effects (e.g., gender) in the analyses (Mumford, 2012). Third, our small sample size limited our ability to detect and analyse for confounding effects of psychotropic medication on the current findings. Thus, the involvement of drug naive patients would be advantageous to disentangle possible medication effects on neurobiological function. While we observed no moderating effect of depression and social anxiety on rsFC changes, the BDD group had several comorbid psychiatric diagnoses which may have influenced the results as the effects of OXT seem to be mediated by different clinical factors (see; Cochran et al., 2013; for a review). However, for BDD patients, depression and anxiety co-occur in more than half of diagnosed cases (Gunstad and Phillips, 2003), and concealment of symptoms and avoidance of social situations is common (Phillips et al., 2017). As a result, many studies to date have had sample sizes of $n < 20$ BDD participants (Grace et al., 2017). It is argued that the sample size obtained within the present study is representative of the population and a worthy contribution to the literature. Future research is recommended to replicate and empirically investigate the impact that these individual differences may have on the current results.

In conclusion, this study is among the first to examine the effect of intranasal OXT on brain function in BDD patients. We found preliminary evidence showing that BDD participants demonstrated heightened left amygdala to left MTG and left ITG rsFC at rest, which was reversed following an acute dosage of intranasal OXT. Speculatively, intranasal OXT might restore attention and salience processing of fine-detail visual information processed within the ventral visual stream. Although more research in larger samples is warranted, by modulating amygdala-temporal functional connectivity, intranasal OXT might facilitate treatment of visual and attentional biases in BDD patients. Future studies in BDD patients should confirm whether intranasal OXT can have beneficial therapeutic effects in BDD patients, for instance, by acting as a treatment adjunct and thereby increasing the efficacy of available cognitive behavioural treatments.

Conflicts of interest

The authors report no biomedical financial interests or potential conflicts of interest.

Author contributions are as follows

SG, SR and IL were involved in the conceptualization of the work and experimental design; DC provided financial support for the oxytocin sprays and BDD participant referrals from his Body Image clinic; SG conducted the experiments and analyzed the neuroimaging data; SG drafted the manuscript with assistance from IL and SR. All authors revised the manuscript and approved the final version. The authors would also like to acknowledge BDD patient referrals from Dr Ben Buchanan and Dr Ryan Kaplan, and the comments provided on the statistical analyses presented in the manuscript from Dr Juan Dominguez.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2019.05.022.

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