Psychiatry Research 289 (2020) 112962

Contents lists available at ScienceDirect

Psychiatry Research

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

Greater history of traumatic event exposure and PTSD associated with comorbid body dysmorphic disorder in a large OCD cohort

Jorge Valderrama[a,b], Stella Kim Hansen[a], Carlos Pato[a,b,1], Katharine Phillips[d], James Knowles[e], Michele T. Pato[a,b,c,*]

[a] Institute for Genomic Health, SUNY Downstate Medical Center, Brooklyn, NY, USA
[b] Department of Psychiatry, SUNY Downstate Medical Center, Brooklyn, NY, USA
[c] College of Medicine, SUNY Downstate Medical Center, Brooklyn, NY, USA
[d] Department of Psychiatry, New York-Presbyterian Hospital and Weill Cornell Medical College, New York, NY, USA
[e] Department of Cell Biology, SUNY Downstate Medical Center, Brooklyn, NY, USA

ARTICLE INFO

Keywords:
Trauma
Body image
Comorbidity
Anxiety
Depression

ABSTRACT

The present study examined whether or not there are differential rates of traumatic event exposure and presumed Post-Traumatic Stress Disorder (PTSD) between individuals with OCD without comorbid presumed BDD (OCD-Non-BDD) and individuals with OCD with comorbid presumed BDD (OCD + BDD) within a large cohort of OCD participants ($N = 605$). Individuals in the OCD + BDD group had significantly higher rates of endorsing at least one lifetime traumatic event and presumed PTSD than individuals with OCD-Non-BDD. Additionally, individuals in the OCD + BDD group with comorbid presumed PTSD had significantly higher rates of major depressive disorder (MDD) and presumed panic disorder (PD). A logistic regression analysis revealed that presumed PTSD significantly predicted the presence of BDD symptoms among individuals who experienced at least one lifetime traumatic event in our sample. These findings suggest that individuals in the OCD + BDD group were more likely to have experienced a traumatic event in their lives, to experience presumed PTSD, and to have MDD and presumed PD than individuals in the OCD-Non-BDD group. Clinical implications and possible mechanistic pathways from trauma exposure to OCD and BDD symptomatology are discussed.

1. Introduction

Extensive research has indicated a relationship between traumatic life events and psychopathology, including mood disorders, anxiety disorders, and psychotic disorders (Norman et al., 2012; Carr et al., 2013; Morgan et al., 2016). However, relatively few studies have examined the association between trauma and obsessive-compulsive disorder (OCD) and body dysmorphic disorder (BDD), an OCD related disorder (DSM-5-American Psychiatric Association, 2013). Further, whether or not there are differential rates in exposure to a lifetime traumatic event between individuals with OCD with comorbid BDD (OCD + BDD) and individuals with OCD without comorbid BDD (OCD-Non-BDD) has yet to be examined. The present study sought to address this research gap by examining whether or not there is a difference between these groups in rates of experiencing a lifetime traumatic event while also examining differences in presumed PTSD rates among trauma-exposed individuals.

Both OCD and BDD are characterized by obsessive thoughts and

* Corresponding author.
E-mail address: michele.pato@downstate.edu (M.T. Pato).

[1] **GPC OCD Cohort**:
Erika L. Nurmi, MD, PhD a, Humberto Nicolini, MD, PhD b, Nuria Lanzagorta b, Dr. José M Menchón c, MD, PhD, Dr Eva Real, MD, PhD c, Amparo Del Pino-Gutierrez, PhD d, Janet Sobell, PhD e, James Knowles, MD, PhD f, Michele Pato, MD f, Carlos Pato, MD, PhD f, Barbara Van Noppen, PhD f, Margaret Salisu, LMSW, M.Phil f, Helena Medeiros, MSW, LICSW f
a University of California Los Angeles, Los Angeles, CA 90095
b Grupo Médico Carracci, Mexico, City, Mexico
c Bellvitge University Hospital-IDIBELL, University of Barcelona, Cibersam, Barcelona
d University of Barcelona, Barcelona
e University of Southern California, Los Angeles, CA 90007
f SUNY Downstate Medical Center, Brooklyn, NY 11203

https://doi.org/10.1016/j.psychres.2020.112962
Received 4 November 2019; Received in revised form 17 March 2020; Accepted 27 March 2020
Available online 06 May 2020
0165-1781/

compulsive behaviors. With respect to BDD, symptomatology involves distressing or impairing intrusive/obsessive thoughts related to a perceived defect (one or more) in one's personal appearance and compulsive behaviors in response to appearance related concerns (e.g., mirror checking, excessive grooming, and comparing one's appearance to others). BDD's shared clinical features and comorbidity with OCD (between 3% and 37% of individuals with OCD also have BDD; Phillips, 2009), in addition to other similarities with OCD, prompted BDD's reclassification from a somatoform disorder to an obsessive compulsive and related disorder in the latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013; Phillips et al., 2010). Research has indicated similar functional impairment, similarly poor quality of life, and similar course of illness in both BDD and OCD (Phillips, 2015).

However, those with BDD (either with or without comorbid OCD) seem to differ from those with OCD without BDD in some important ways. Individuals with BDD are at greater risk for lifetime major depressive disorder (MDD), suicidal ideation and behavior, and substance use disorders than individuals with OCD without BDD (Phillips et al., 2009, 2007; Stewart et al., 2008; Costa et al., 2012; Phillips et al., 2015; Angelakis et al., 2016). Moreover, poorer insight is found in individuals with BDD with or without comorbid OCD (Phillips et al., 2007; Nakata et al., 2007, 2012; Costa et al., 2012 Phillips et al., 2015). Such impairments may make it more difficult to treat them. For instance, therapies such as exposure and response prevention (ERP) therapy may be less likely to be successful in individuals with BDD than in OCD alone unless additional components (e.g., motivational interviewing, behavioral experiments, cognitive therapy, lengthier treatments) are added (Phillips et al., 2015). Further, individuals with OCD and comorbid BDD have reported significantly earlier age of OCD onset than individuals with OCD alone (Stewart et al., 2008; Costa et al., 2012). However, there have been conflicting reports on whether or not there is a difference in OCD severity between these two groups (Phillips et al., 2007; Stewart et al., 2008; Costa et al., 2012).

Importantly, history of trauma has been associated with OCD. Cromer et al. (2007) found that 54% of 265 individuals with a DSM-IV OCD diagnosis had experienced at least one traumatic life event in their lives. Consistent with this finding, high rates of PTSD (19% to 39%) have been found in individuals with OCD (Welkowitz et al., 2000; Gershuny et al., 2008; Fontenelle et al., 2012).

The association between trauma, PTSD, and OCD with comorbid BDD is less well studied. One previous study found that individuals with OCD with comorbid BDD (n = 109) had significantly higher rates of PTSD than individuals with OCD without comorbid BDD (n = 792) (27% versus 18%) (Costa et al., 2012). In a study that combined a sample ascertained for OCD (n = 355) with a similarly ascertained sample with BDD (n = 200), the lifetime rate of PTSD in the comorbid OCD-BDD group (15%) was higher – but not significantly higher – than in the OCD (6.7%) and BDD (4.4%) groups; however, statistical power to examine group differences was limited (Phillips et al., 2007). One other study found similar PTSD severity scores among individuals with OCD with (n = 42) and without (n = 233) comorbid BDD (Stewart et al., 2008). However, data on this topic are to our knowledge limited to these studies, and none of these studies examined rates of exposure to a lifetime traumatic event in their samples.

The present study assessed rates of exposure to at least one lifetime traumatic event, presumed PTSD, and clinical characteristics (specifically, MDD and presumed Panic Disorder [PD]) in such a sample. We hypothesized that individuals in the OCD + BDD group would be significantly more likely to have experienced at least one lifetime traumatic event and have a higher rate of presumed PTSD than individuals in the OCD-Non-BDD group. Importantly, the present study is cross sectional, thus we cannot indicate the directionality of the onset of OCD, BDD, MDD, and PD symptoms and whether or not trauma preceded any of these symptom constellations. However, previous research indicates that trauma might contribute to the onset of these disorders via a variety of mechanisms (Bandelow et al., 2002; Horesh et al., 2008; Buhlmann et al., 2012; Adams et al., 2018). With respect to BDD, traumatic events related to physical or sexual abuse may cause negative core beliefs that lower self-esteem and disrupt emotional regulation (Buhlmann et al., 2012). Such characteristics might lead to appearance-related concerns that evolve over time from being benign to pathological. Further, individuals with BDD have high rates of perceived childhood abuse and neglect (Didie et al., 2006), and they have reported instances of teasing and bullying in adolescence as extremely stressful events that triggered the onset of their BDD symptoms (Weingarden et al. (2017). Thus, events that are likely to make an individual feel inferior, shamed, and flawed might be expected to precede the onset of BDD. Consistent with these previous findings, we predicted that presumed PTSD would significantly contribute to predicting the presence of presumed BDD in our subsample of trauma-exposed individuals. We also predicted that the OCD + BDD group would have significantly higher rates of MDD, consistent with prior studies.

2. Methods

2.1. Subjects

The participants in the study were recruited as part of the larger Genomic Psychiatry Cohort OCD research study (GPC—OCD). The ongoing GPC—OCD research study seeks to enroll 3500 participants that include individuals with OCD as well as unaffected and affected relatives. Trained diagnosticians determine a range of psychiatric diagnoses via a semi-structured interview (participants complete self-report surveys and are also asked follow up questions when psychiatric symptoms are endorsed). For the present report, 605 consecutive individuals (377 females), ages 9–80 (M = 35.29, SD = 16.61) all diagnosed with OCD via the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; details below), were recruited between January of 2015 and May of 2018. The OCD-Non-BDD group included 436 individuals, and the OCD + BDD group included 169 individuals (see Table 1). These groups were further stratified based on history of trauma (whether or not an individual experienced at least one lifetime traumatic event; see assessment section below) in order to assess clinical characteristics between the following groups: OCD-Non-BDD & no presumed PTSD (n = 77), OCD-Non-BDD & presumed PTSD (n = 60), OCD + BDD & no presumed PTSD (n = 31), OCD + BDD & presumed PTSD (n = 48) (see Table 2). The racial/ethnic composition of the entire sample was 73.9% White, 6.3% Asian, 2.5% Black, and 17.3% other race/ethnicities.

Exclusion criteria for the present study from the larger GPC—OCD research study were: individuals without an OCD diagnosis (unaffected relatives, n = 203) and individuals with a DSM-IV co-morbid diagnosis of Bipolar Disorder I or II, Schizophrenia, or Schizoaffective Disorder (n = 58). While comorbidities of schizophrenia or mania did not preclude individuals from participating in the GPC—OCD study, these samples were excluded from the present report since the symptomatology of these disorders could confound our assessments of PTSD, PD, and MDD in the present study. We also excluded individuals with only a BDD diagnosis (not comorbid with OCD). Although individuals with BDD without comorbid OCD can participate in the GPC—OCD study, at the time of this analysis only one such subject had been enrolled. Informed consent was obtained from all participants, and an Institutional Review Board approved all procedures.

2.2. Measures

2.2.1. GPC screening questionnaire

The GPC screening questionnaire (Pato et al., 2013; available upon request) collects demographic information, history of a lifetime traumatic event, history of PTSD symptoms, and any history of symptoms related to anxiety disorders, affective disorders, psychotic disorders, substance abuse history, and medical history. History of a lifetime

Table 1
Demographic and psychiatric characteristics of the participants.

Variable[1]	OCD-Non-BDD (n = 436)	OCD + BDD (n = 169)	Test statistic	p[2]	ES[6]
Gender (female)	61.50%	64.50%	$\chi2$ = 0.48	0.276	.028
Age	36.14 ± 17.30	33.11 ± 14.51	t = 2.02	0.044	.189
Age of OCD onset	17.38 ± 10.69	15.62 ± 8.83	t = 1.95	0.052	.179
Y-BOCS Score	25.58 ± 8.73	24.15 ± 8.36	t = 1.83	0.068	.136
Traumatic Event[3]	32.40%	47.30%	$\chi2$ = 11.48	0.001	.139
Presumed PTSD[4]	43.80%	60.80%	$\chi2$ = 5.77	0.012	.171
Lifetime MDD	56.80%	88.20%	$\chi2$ = 53.23	< 0.001	.296
Suicidality[5]	36.70%	38.20%	$\chi2$ = 0.085	.428	.014
Presumed P.D.	34.20%	52.10%	$\chi2$ = 16.10	< 0.001	.165

[1] Results are presented as n (%) or mean ± standard deviation.
[2] Difference and significance determined by chi square analyses for percentages or independent samples T-tests for mean values.
[3] At least one lifetime traumatic event.
[4] Among individuals that experienced at least one lifetime traumatic event (n = 216) that met criteria for presumed PTSD.
[5] Individuals that met criteria for lifetime MDD (n = 397) that also had a history of suicidal ideation for at least one week or a previous suicide attempt.
[6] Effect sizes (ES) are presented as Φ for $\chi2$ and Cohen's d for T-tests.

traumatic event was determined by the question:

- "Have you ever experienced a traumatic event in which you felt that your life might be in danger? (Examples: serious car or other accident, natural disaster [like earthquakes or hurricanes], being physically attacked or threatened with a knife or gun, being sexually assaulted or raped, experienced combat or been in a war zone, or observed sudden violent death [homicide or suicide].)"

When a subject endorsed a traumatic event, presumed PTSD was determined by answering yes to each of the following additional questions (while each of these questions represent a criterion for PTSD as per DSM-5 [Criterion B, C, E], we are designating an endorsement of **all 3** as presumed PTSD since we do not have further information regarding negative thoughts or feelings caused by symptoms, length of time impacted by symptoms, and whether or not the symptoms caused functional impairment [Criterion D, F, G] [American Psychiatric Association, 2013]):

- Sometimes images or strong memories of traumatic events keep coming back in flashbacks, thoughts that you can't get rid of, or repeated nightmares. Has that ever happened to you?
- Did you make a special effort to avoid thinking or talking about what happened or deliberately stayed away from things or people that reminded you of the terrible experience?
- After this experience did you have trouble sleeping, have difficulty concentrating, were unusually irritable, have outbursts of anger, felt overly watchful or on guard, or been very jumpy or easily startled?

Presumed Panic Disorder (PD) was determined by answering yes to both of the screening questions below. Again we are designating an endorsement of these two questions as presumed PD since we do not have further information regarding whether or not panic attacks were caused by a substance or whether or not symptoms are better explained by another mental disorder – two additional criteria required for a DSM 5 diagnosis (American Psychiatric Association, 2013):

- "Did you ever have an experience of suddenly feeling very anxious or fearful and having panic-like physical symptoms that developed and got intense within 10 min? (Examples: racing heart, chest pain, choking feelings, nausea, sweating, faint, thinking you were going crazy, or dying.)"
- "Have you had more than one attack like this…and had a period lasting at least 1 month of intense worries about having another attack or changed your behaviors for at least 1 month because of the attacks?"

2.2.2. Diagnostic interview for OCD (DI-OCD)

The DI-OCD (available upon request) includes the FOCI and Y-BOCS as well as additional questions to collect demographic information, medical history, and medication use. Age of onset of OCD was defined by the self-reported age in which OCD symptoms "first started to interfere with or disrupt daily life." This delineation is consistent with previous research assessing age of onset of OCD (Taylor, 2011).

2.2.3. Florida obsessive compulsive inventory (FOCI)

The FOCI (Storch et al., 2007) is a self-report questionnaire that assesses OCD symptom types and severity as well as symptoms related to BDD. In the present study, the presence of presumed BDD was determined by the question, "Are you or have you been excessively concerned with a part of your body or aspect of your appearance (worries that your face, ears, nose, eyes or another part of your body) is hideously ugly, despite reassurance to the contrary)?" The FOCI questionnaire was developed as a shortened version of Yale-Brown

Table 2
Clinical Characteristics in trauma-exposed participants.

Variable[1]	OCD-Non-BDD & No PTSD (n = 77)	OCD-Non-BDD & PTSD (n = 60)	OCD + BDD & No PTSD (n = 31)	OCD + BDD& PTSD (n = 48)	Test statistic	p[2]	ES[4]
Lifetime MDD	51.90%	83.30%	80.60%	97.90%	$\chi2$ = 38.02	< 0.001	.422
Presumed P.D.	34.70%	51.70%	50.00%	72.90%	$\chi2$ = 17.20	< 0.01	.284
Y-BOCS Score	24.78 ± 8.62	26.17 ± 9.31	23.45 ± 8.81	23.31 ± 7.97	F = 1.19	0.316	.016
Age of OCD onset	18.02 ± 12.86	19.68 ± 10.84	16.64 ± 12.78	15.75 ± 7.31	F = 1..08	0.361	.018
Suicidality[3]	64.00%	72.30%	64.10%	71.40%	$\chi2$ = 1.10	0.777	.083

[1] Results are presented as n (%) or mean ± standard deviation.
[2] Difference and significance determined by chi square analyses for percentages or analysis of variance for mean values.
[3] Individuals that met criteria for lifetime MDD (n = 162) that also had a history of suicidal ideation for at least one week or a previous suicide attempt.
[4] Effect sizes (ES) are presented as Φ for $\chi2$ and η^2 for analysis of variance.

Table 3
Logistic Regression Predicting OCD + BDD among trauma-exposed participants.[1]

Predictor	*O.R.*	95% CI	*B*	*p*
Presumed PTSD	2.02	1.12 – 3.63	.701	<0.05
MDD	5.42	2.29 – 12.84	1.69	<0.001
Presumed PD	2.36	1.32 – 4.23	.675	<0.01

[1] Adjusted for gender and age, variables entered separately to assess independent regression effects.

Obsessive- Compulsive checklist in order to rapidly assess number of OCD symptoms and severity and has similar reliability and validity to the lengthier rater-administered version of the "Checklist" and Y-BOCS (details below) (Storch et al., 2007).

2.2.4. Yale brown obsessive compulsive scale (Y-BOCS)

The Y-BOCS (Goodman et al., 1989) is a semi-structured interview that is designed to assess OCD symptom severity. Scores range from 0 to 40 (present sample; $M = 25.18$, SD = 8.65). Clinical severity of OCD as assessed by the Y-BOCS scores has been previously described as the following: moderate symptoms range from 14 to 25, moderate-severe symptoms range from 26 to 34, and severe symptoms range from 35 to 40 (Storch et al., 2015).

2.2.5. Diagnostic interview for psychosis and affective disorders (DI-PAD)

The DI-PAD (Pato et al., 2013) is a semi-structured clinical interview that assesses symptoms related to MDD, bipolar disorder, and schizophrenia. Any participant that endorsed affective or psychotic symptoms on the GPC Screening Questionnaire were administered the corresponding portions of the DI-PAD. MDD diagnosis in the present sample was determined by DSM-IV diagnostic criteria for MDD. Suicidiality was assessed in MDD by a question on the DI-PAD that collected history of suicidal ideation or suicide attempt.

2.3. Procedures and statistical analyses

Participants completed the GPC Screening Questionnaire and semi-structured interviews (DI-PAD and DI-OCD) that collected demographic details and information related to OCD and OCD related disorders symptoms, history of a lifetime traumatic event, PTSD symptoms, PD symptoms, and MDD symptoms.

Chi-square analyses were used to test whether differences existed between categorical variables while t-tests and a univariate analysis of variance were used to compare means between continuous variables.

In addition, we conducted separate binomial logistic regressions to investigate whether presumed PTSD, MDD, and presumed PD (controlling for age and gender) predicted the presence of presumed BDD in individuals that experienced a traumatic event in our sample. Analyses employed a two-sided alpha = 0.05 type I error rate.

3. Results

3.1. Sample characteristics

A high proportion (27.9%) of individuals with OCD had comorbid presumed BDD. As hypothesized, the OCD + BDD group had significantly higher rates than the OCD-Non-BDD group of experiencing at least one lifetime traumatic event (47.3% vs 32.40%, $p = .001$) (see Table 1). Among the trauma-exposed group, the OCD + BDD group was significantly more likely to meet our criteria for presumed PTSD (60.80 vs 43.80, $p = .012$). The OCD + BDD group also had significantly higher lifetime rates of MDD (88.20% vs 56.80%, $p < .001$) and presumed PD (52.10% vs 34.20%, $p < .001$). The OCD + BDD group was significantly younger, but there were no significant differences for other demographic and clinical variables, including rates of suicidality.

3.2. Clinical characteristics by presumed PTSD group among trauma-exposed individuals

We further examined the study groups by analyzing trauma-exposed individuals and whether or not they met criteria for presumed PTSD (see Table 2). Individuals in the OCD + BDD group who also had presumed PTSD had significantly higher rates of MDD ($p < .001$) and presumed PD ($p < .01$) than the OCD + BDD group without presumed PTSD and both OCD-Non-BDD groups with or without Presumed PTSD. OCD severity, age of onset, and rates of suicidiality did not significantly differ between the four groups.

3.3. Predictors of presumed BDD

After controlling for the effects of age and gender, Presumed PTSD, MDD, and presumed PD were independently significantly associated with presumed BDD among trauma-exposed individuals. Individuals with presumed PTSD were twice as likely to experience BDD symptoms as individuals without presumed PTSD ($p < .05$; O.R. = 2.02) (see Table 3).

4. Discussion

The present study examined demographic and clinical characteristics in individuals diagnosed with OCD with or without presumed BDD. Consistent with our hypothesis, individuals in the OCD + BDD group were significantly more likely to have experienced at least one lifetime traumatic event and significantly more likely to have presumed PTSD than individuals in the OCD-Non-BDD group. Indeed, trauma-exposed individuals who met criteria for presumed PTSD were almost twice as likely to report BDD symptoms than trauma-exposed individuals without presumed PTSD. Further, individuals in the OCD + BDD group with presumed PTSD were particularly vulnerable to having comorbid MDD and presumed PD.

Our findings are in line with previous research indicating high rates of PTSD in OCD. In fact, our results are comparable to assessments of 1001 (Fontenelle et al., 2012) and 910 (Welkowitz et al., 2000) individuals with OCD that determined that 19% of their samples met criteria for PTSD via the use of the SCID and a screening measure with high reliability and validity, respectively (18% of our entire sample met criteria for presumed PTSD). Further, our results also replicate Costa et al's (2012) study indicating higher rates of PTSD in OCD with comorbid BDD than in OCD without BDD. They do not replicate Phillips et al. (2007) study, which found no significant differences between these groups, although their statistical power was limited, and PTSD occurred more than twice as frequently in the comorbid OCD-BDD group than in the OCD without BDD group. Importantly, to our knowledge, our study is the first to report differential rates of exposure to at least one lifetime traumatic event between individuals with OCD with and without BDD symptoms, finding significantly higher rates in the OCD group with comorbid presumed BDD.

Our findings also extend previous research indicating significantly higher rates of comorbid MDD in individuals with OCD and comorbid BDD than in those with OCD alone. In our sample, 88.2% of the OCD + BDD group and 56.8% of the OCD-Non-BDD group met criteria for lifetime MDD, similar to rates found in Costa et al.'s (2012) report (81% and 65%, respectively) and Phillips et al. (2007) report (80.0% vs. 65.2%). By contrast, rates of suicidality in the present sample did not replicate Costa's (2012) or Phillips' (2007) reports indicating significantly higher rates of suicidal ideation and suicide attempts in individuals with OCD and comorbid BDD. However, our assessment of suicidiality did not allow us to differentiate suicidal ideation from suicide attempts. We are now collecting specific information about ideation and attempt history in order to better understand suicidiality

in the GPC—OCD study.

The present study found significantly greater presumed PD rates in the OCD + BDD group than the OCD-Non-BDD group (52.1% versus 34.2%). Two other studies have shown the PD rate in the comorbid BDD group was higher, but not significantly so, than in the OCD alone group (Phillips et al., 2007; Costa et al., 2012). Of note, the presumed PD rates in the present OCD + BDD sample are much greater than PD rates in the OCD with comorbid BDD samples found in Phillips et al. (2007) and Costa et al.'s (2012) reports (32.5% and 17%, respectively). One caveat to our findings is that our screening for PD did not assess all PD diagnostic criteria or include questions that would rule out panic attacks caused by obsessions in OCD or BDD or by reminders of trauma related to PTSD – criteria required by the DSM-5. Thus, our presumed PD rates may be overestimated.

As we noted in the introduction the cross-sectional nature of this GPC—OCD study does not allow us to comment on the directionality of the onset of these comorbid conditions: OCD, BDD, MDD, and PD nor whether and which of the traumatic experiences preceded any of these disorders. However, other studies indicate that trauma might contribute to the onset of these disorders (Bandelow et al., 2002; Horesh et al., 2008; Buhlmann et al., 2012; Adams et al., 2018;; Dykshoorn, 2014). More specifically in BDD, stressful life events have included high rates of perceived childhood abuse and neglect (Didie et al., 2006) and reported instances of teasing and bullying in adolescence, have triggered the onset of BDD symptoms (Weingarden et al. (2017);Buhlmann et al., 2012). Future research is necessary in order to investigate how trauma might differentially be involved in the etiology of comorbid OCD and BDD.

There are several clinical implications from the present findings, both in the assessment and treatment of comorbid OCD, BDD, and PTSD. Clinicians should assess thoroughly for trauma histories and symptoms of PTSD in individuals presenting for treatment for OCD, and especially in those who experience BDD symptoms or have a comorbid BDD diagnosis. Individuals with comorbid presumed BDD were at greater risk for presumed PTSD, presumed PD, and MDD than individuals without BDD symptoms in the present sample. These symptoms should also be specifically assessed in comprehensive psychiatric evaluations and monitored in ongoing treatment.

In addition to the need for a thorough evaluation, there are several points to consider when planning and providing treatment. Research on comorbid PTSD and OCD shows that PTSD diagnoses often complicate treatment outcomes for individuals with OCD. For instance, individuals with comorbid OCD and PTSD tend to initially present with more severe symptoms. Ojserkis et al. (2017) examination of 266 individuals with OCD found that those with comorbid PTSD had significantly higher Y-BOCS scores than those without comorbid PTSD (27.48 ± 5.18 versus 23.23 ± 5.71, respectively). Furthermore, individuals with OCD that also have PTSD are also more likely to have treatment-resistant OCD than those without PTSD (Gershuny et al., 2002, 2008). This important issue has not been examined in BDD and requires investigation.

Given that these studies indicate the complex clinical presentation of comorbid conditions, treatments should not necessarily rely on only one modality. For example, cognitive-behavioral therapy (CBT) and psychopharmacology have been established as an evidence-based approach for treating OCD as well as BDD (Hong et al., 2018; Krebs et al., 2017; Phillips, 2004; Wilhelm et al., 2019). However, the current CBT approaches for OCD as well as BDD do not include trauma-focused interventions to address trauma or co-occurring PTSD symptoms in individuals with trauma histories. Traditionally, the gold standards for treatment of PTSD have included prolonged exposure, SRIs, and cognitive processing therapy (Cusack et al., 2016). There have still been very few studies that examine treatment considerations for treating comorbid OCD and PTSD. A review of studies examining individuals with trauma-related OCD suggested that the trauma must be addressed, or the patient may be resistant to the OCD treatment. The trauma can be treated simultaneously or separately, based on the clinician's judgment (Dykshoorn, 2014). A recent case study attempted to integrate OCD and PTSD treatments to address the way these two disorders may maintain each other if not treated simultaneously (Van Kirk et al., 2018). In BDD, imagery rescripting methods have been proposed for the treatment of distressing or traumatic memories related to appearance concerns, but this approach has not been rigorously studied (Veale et al., 2017; Willson et al., 2016). Future directions in research could explore the feasibility of integrating PTSD treatments with those for OCD with and without BDD.

The limitations of this report include the use of a FOCI checklist question as an indicator of BDD symptomology and lack of a more thorough assessment such as the BDDQ and BDD-YBOCS (Phillips, 1996; Phillips et al., 1997). The study's requirements to endorse being "hideously ugly" and to have not responded to reassurance about the perceived appearance flaws are a high threshold for diagnosing BDD, as "hideously" is a strong term, and not all people with BDD seek reassurance about their appearance; on the other hand, not requiring the appearance concerns to cause clinically significant distress or impairment in functioning, as required by DSM-5, likely lowered the diagnostic threshold. Further, we cannot rule out possible eating disorder diagnoses in our sample. Whereas the FOCI includes a checklist of symptoms associated with OCD and OCD-related disorders, the BDD-YBOCS assesses severity of BDD symptoms by assessing how disruptive the symptoms are (assesses time occupied by thoughts about perceived body defects, interference due to thoughts about body defects, distress associated with thoughts about body defects, etc.). Our findings that revealed similar severity of OCD symptoms between individuals with and without BDD symptoms (Y-BOCS scores; 24.15 ± 8.36 versus 25.58 ± 8.73, respectively) contributes to a conflicting literature. In some reports those with OCD and comorbid BDD had significantly lower Y-BOCS scores (Stewart et al., 2008; 25.7 ± 6.5 versus 28 ± 5.5) and in others significantly higher scores (Phillips et al., 2007: 25.1 ± 6.6 versus 23 ± 5.8; Costa et al., 2012: 27 ± 6.5 versus 25 ± 8.2). Future research should further examine the influence that comorbid BDD symptoms might have on OCD severity.

In the case of PTSD, while a specific PTSD diagnostic instrument such as the PCL-5 (Weathers et al., 2013) was not used, the four questions included in our GPC screener closely overlap with DSM-IV and DSM-5 criteria. However, our assessment of trauma history was limited as we did not assess for certain traumas that might lead to PTSD (e.g., parental abuse or neglect (Carr et al., 2013)). Further, as previously mentioned, our assessment of PD did not fully screen for PD as determined by the DSM-5. Of note, shortened instruments have been able to accurately determine clinical diagnoses in past studies of psychiatric disorders (Kroenke et al., 2001; Löwe et al., 2005; Bradley et al., 2007). Furthermore, brief screening instruments (such as the questions we used) are valuable in primary care settings where patients can be quickly referred for further evaluation and treatment specific to their symptoms. Finally, we did not have a group of participants that endorsed BDD symptoms without an OCD diagnosis. Future studies should include such a group in order to further examine the relationship between those disorders and PTSD. Despite some limitations, our study strengths include the use of a clinical interview to determine MDD and OCD diagnoses and our large sample size (when compared to other studies of examining OCD with comorbid BDD).

A funded goal of the GPC—OCD research study is to merge phenotypic data with genotypic analysis. This work is exciting because of what small preliminary studies of neural circuitry have revealed about trauma, OCD, and BDD and their potential relations to each other. Research has shown that trauma-induced stress can impair circuitry in brain regions known to exhibit abnormal functioning in OCD and in BDD (Feusner et al., 2007; McEwen, 2012; Shansky and Lipps, 2013; Wilker and Kolassa, 2013; Adams et al., 2018). Dysfunctions in the frontostriatal system, which include the medial frontal cortex (mFC) and the striatum, have been found in individuals with a history of

trauma as well as in individuals with OCD or BDD. Specifically, some studies have shown that the anterior cingulate cortex (ACC; a part of the mFC) is smaller in samples of OCD, BDD, and trauma-exposed individuals when compared to healthy controls (Cohen et al., 2006; Atmaca et al., 2010; Ansell et al., 2012; Adams et al., 2018). The ACC is important for processing emotional information, plays a role in the emergence of repetitive behaviors, and modulates activity in the amygdala – a brain area important for processing fear and anxiety (Etkin et al., 2006; Adams et al., 2018). Abnormal activity in the amygdala has been previously found in both OCD and BDD (Feusner et al., 2007; Adams et al., 2018).

Additionally, research also indicates that individuals with BDD exhibit abnormal visual cortex activity when processing low spatial resolution of faces (Feusner et al., 2010). A recent review of studies examining brain structure and function in BDD indicates that abnormal activity in visual cortex areas when processing information about faces or objects indicates that there is a greater focus on fine-detail information versus holistic visual information (Grace et al., 2017). Such abnormalities might contribute to distorted perceptions (e.g., perceived defects in one's appearance) found in BDD. Similarly, abnormal activity has also been found in the visual cortex of individuals with OCD (Stern et al., 2017). This apparent dysfunction has been thought to contribute to difficulty in processing external information that might be helpful in decreasing fears and concerns during moments of internally generated obsessions and urges (Stern et al., 2017). While abnormal visual processing has been found in PTSD, its potential contribution to the development of OCD or BDD is not known (Hendler et al., 2003). Likewise, how the visual cortex, frontostriatal system, and amygdala function in individuals with OCD and comorbid BDD has not been examined. Future research should address these gaps to further understand the relationship between trauma, OCD, and BDD.

In conclusion, the present study included a large cohort of individuals diagnosed with OCD and is the first to report on differential rates of exposure to a lifetime traumatic event between individuals with OCD with and without BDD symptoms. Individuals with BDD symptoms were significantly more likely to have experienced a lifetime traumatic event and have presumed PTSD than individuals without BDD symptoms. In addition, individuals with BDD symptoms and presumed PTSD had the highest rates of presumed PD and MDD when compared to individuals with OCD without BDD symptoms and/or presumed PTSD. Our findings provide further evidence of the association between trauma, PTSD symptoms, and BDD in individuals with OCD. We have begun to collect information regarding age of traumatic event exposure, traumatic event type, and frequency of trauma experiences in new individuals who are enrolled in our GPC—OCD study. Such data will allow us to determine a clearer picture of the potential interplay between traumatic event exposure and OCD with or without comorbid BDD in future studies while also providing more in-depth phenotypic data to merge with our future genomic analyses.

Funding Acknowledgment

NIMH R01MH103657

References

Adams, T.G., Kelmendi, B., Brake, C.A., Gruner, P., Badour, C.L., Pittenger, C., 2018. The role of stress in the pathogenesis and maintenance of obsessive compulsive disorder. Chronic Stress. https://doi.org/10.1177/2470547018758043.

Ansell, E.B., Rando, K., Tuit, K., Guarnaccia, J., Sinha, R., 2012. Cumulative adversity and smaller gray matter volume in medial prefrontal, anterior cingulate, and insula regions. Biol. Psychiat. 72 (1), 57–64. https://doi.org/10.1016/j.biopsych.2011.11.022.

Atmaca, M., Bingol, I., Aydin, A., Yildirim, H., Okur, I., Yildirim, M.A., Gurok, M.G., 2010. Brain morphology of patients with body dysmorphic disorder. J. Affect. Disorders 123 (1–3), 258–263. https://doi.org/10.1016/j.jad.2009.08.012.

American Psychiatric Association. 2013. Diagnostic and statistical manual of mental disorders(5th ed.). Washington, DC.

Angelakis, I., Gooding, P.A., Panagioti, M., 2016. Suicidality in body dysmorphic disorder (BDD): a systematic review with meta-analysis. Clin. Psychol. Rev. 49, 55–66. https://doi.org/10.1016/j.cpr.2016.08.002.

Bandelow, B., Späth, C., Tichauer, G.Á., Broocks, A., Hajak, G., Rüther, E., 2002. Early traumatic life events, parental attitudes, family history, and birth risk factors in patients with panic disorder. Compr. Psychiat. 43 (4), 269–278. https://doi.org/10.1053/comp.2002.33492.

Bradley, K.A., DeBenedetti, A.F., Volk, R.J., Williams, E.C., Frank, D., Kivlahan, D.R., 2007. AUDIT-C as a brief screen for alcohol misuse in primary care. Alcohol Clin. Exp. Res. 31 (7), 1208–1217. https://doi.org/10.1111/j.1530-0277.2007.00403.x.

Buhlmann, U., Marques, L.M., Wilhelm, S., 2012. Traumatic experiences in individuals with body dysmorphic disorder. J. Nerv. Ment. Dis. 200 (1), 95–98. https://doi.org/10.1097/NMD.0b013e31823f6775.

Carr, C.P., Martins, C.M.S., Stingel, A.M., Lemgruber, V.B., Juruena, M.F., 2013. The role of early life stress in adult psychiatric disorders: a systematic review according to childhood trauma subtypes. J. Nerv. Ment. Dis. 201 (12), 1007–1020. https://doi.org/10.1097/NMD.0000000000000049.

Cohen, R.A., Grieve, S., Hoth, K.F., Paul, R.H., Sweet, L., Tate, D., Niaura, R., 2006. Early life stress and morphometry of the adult anterior cingulate cortex and caudate nuclei. Biol. Psychiat. 59 (10), 975–982. https://doi.org/10.1016/j.biopsych.2005.12.016.

Conceição Costa, D.L., Chagas Assunção, M., Arzeno Ferrão, Y., Archetti Conrado, L., Hajaj Gonzalez, C., Franklin Fontenelle, L., Gedanke Shavitt, R., 2012. Body dysmorphic disorder in patients with obsessive–compulsive disorder: prevalence and clinical correlates. Depress Anxiety 29 (11), 966–975. https://doi.org/10.1002/da.21980.

Cromer, K.R., Schmidt, N.B., Murphy, D.L., 2007. An investigation of traumatic life events and obsessive-compulsive disorder. Behav. Res. Ther. 45 (7), 1683–1691. https://doi.org/10.1016/j.brat.2006.08.018.

Cusack, K., Jonas, D.E., Forneris, C.A., Wines, C., Sonis, J., Middleton, J.C., Gaynes, B.N., 2016. Psychological treatments for adults with posttraumatic stress disorder: a systematic review and meta-analysis. Clin. Psychol. Rev. 43, 128–141. https://doi.org/10.1016/j.cpr.2015.10.003.

Didie, E.R., Tortolani, C.C., Pope, C.G., Menard, W., Fay, C., Phillips, K.A., 2006. Childhood abuse and neglect in body dysmorphic disorder. Child Abuse Neglect. 30, 1105–1115. https://doi.org/10.1016/j.chiabu.2006.03.007.

Dykshoorn, K.L., 2014. Trauma-related obsessive-compulsive disorder: a review. Health Psychol. Behav. Med. 2 (1), 517–528. https://doi.org/10.1080/21642850.2014.905207.

Etkin, A., Egner, T., Peraza, D.M., Kandel, E.R., Hirsch, J., 2006. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron 51 (6), 871–882. https://doi.org/10.1016/j.neuron.2006.07.029.

Feusner, J.D., Townsend, J., Bystritsky, A., Bookheimer, S., 2007. Visual information processing of faces in body dysmorphic disorder. Arch. Gen. Psychiat. 64 (12), 1417–1425. https://doi.org/10.1001/archpsyc.64.12.1417.

Feusner, J.D., Moody, T., Hembacher, E., Townsend, J., McKinley, M., Moller, H., Bookheimer, S., 2010. Abnormalities of visual processing and frontostriatal systems in body dysmorphic disorder. Arch. Gen. Psychiat. 67 (2), 197–205. https://doi.org/10.1001/archgenpsychiatry.2009.190.

Fontenelle, L.F., Cocchi, L., Harrison, B.J., Shavitt, R.G., do Rosário, M.C., Ferrão, Y.A., de Jesus Mari, J., 2012. Towards a post-traumatic subtype of obsessive compulsive disorder. J. Anxiety Disord. 26 (2), 377–383. https://doi.org/10.1016/j.janxdis.2011.12.001.

Gershuny, B.S., Baer, L., Jenike, M.A., Minichiello, W.E., Wilhelm, S., 2002. Comorbid posttraumatic stress disorder: impact on treatment outcomes for obsessive-compulsive disorder. Am. J. Psychiat. 159, 852–854. https://doi.org/10.1176/appi.ajp.159.5.852.

Gershuny, B.S., Baer, L., Parker, H., Gentes, E.L., Infield, A.L., Jenike, M.A., 2008. Trauma and posttraumatic stress disorder in treatment-resistant obsessive compulsive disorder. Depress Anxiety 25 (1), 69–71. https://doi.org/10.1002/da.20284.

Goodman, W.K., Price, L.H., Rasmussen, S.A., Mazure, C., Fleischmann, R.L., Hill, C.L., Charney, D.S., 1989. Yale-brown obsessive compulsive scale (Y-BOCS). Arch. Gen. Psychiatry 46, 1006–1011.

Grace, S.A., Labuschagne, I., Kaplan, R.A., Rossell, S.L., 2017. The neurobiology of body dysmorphic disorder: a systematic review and theoretical model. Neurosci. Biobehav. R. https://doi.org/10.1016/j.neubiorev.2017.10.003.

Hendler, T., Rotshtein, P., Yeshurun, Y., Weizmann, T., Kahn, I., Ben-Bashat, D., Bleich, A., 2003. Sensing the invisible: differential sensitivity of visual cortex and amygdala to traumatic context. Neuroimage 19 (3), 587–600. https://doi.org/10.1016/s1053-8119(03)00141-1.

Horesh, N., Klomek, A.B., Apter, A., 2008. Stressful life events and major depressive disorders. Psychiat. Res. 160 (2), 192–199. https://doi.org/10.1016/j.psychres.2007.06.008.

Krebs, G., Fernandez de la Cruz, L., Mataix-Cols, D., 2017. Recent advances in understanding and managing body dysmorphic disorder. Evid. Based Ment. Health 1–5. https://doi.org/10.1136/eb-2017-102702. 0(0).

Kroenke, K., Spitzer, R.L., Williams, J.B., 2001. The PHQ-9: validity of a brief depression severity measure. J. Gen. Med. 16 (9), 606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x.

Löwe, B., Kroenke, K., Gräfe, K., 2005. Detecting and monitoring depression with a two-item questionnaire (PHQ-2). J. Psychosom. Res. 58 (2), 163–171. https://doi.org/10.1016/j.jpsychores.2004.09.006.

McEwen, B.S., 2012. The ever-changing brain: cellular and molecular mechanisms for the effects of stressful experiences. Dev. Neurobiol. 72 (6), 878–890. https://doi.org/10.1002/dneu.20968.

Morgan, C., Gayer-Anderson, C., 2016. Childhood adversities and psychosis: evidence, challenges, implications. World Psychiatry 15 (2), 93–102. https://doi.org/10.1002/

wps.20330.
Nakata, A.C.G., Diniz, J.B., Torres, A.R., De Mathis, M.A., Fossaluza, V., Bragancas, C.A., Miguel, E.C., 2007. Level of insight and clinical features of obsessive-compulsive disorder with and without body dysmorphic disorder. CNS Spectr. 12 (4), 295–303. https://doi.org/10.1017/s1092852900021052.
Norman, R.E., Byambaa, M., De, R., Butchart, A., Scott, J., Vos, T., 2012. The long term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. PLOS Med. 9 (11), e1001349. https://doi.org/10.1371/journal.pmed.1001349.
Ojserkis, R., Boisseau, C.L., Reddy, M.K., Mancebo, M.C., Eisen, J.L., Rasmussen, S.A., 2017. The impact of lifetime PTSD on the seven-year course and clinical characteristics of OCD. Psychiat. Res. 258, 78–82. https://doi.org/10.1016/j.psychres.2017.09.042.
Pato, M.T., Sobell, J.L., Medeiros, H., Abbott, C., Sklar, B.M., Buckley, P.F., Macciardi, F., 2013. The genomic psychiatry cohort: partners in discovery. Am. J. Med. Genet. B 162 (4), 306–312. https://doi.org/10.1002/ajmg.b.32160.
Phillips, K.A, 1996. The Broken mirror: Understanding and Treating Body Dysmorphic Disorder. Oxford University Press, New York, NY US.
Phillips, K.A., Hollander, E., Rasmussen, S.A., Aronowitz, B.R., 1997. A severity rating scale for body dysmorphic disorder: development, reliability, and validity of a modified version of the Yale-Brown Obsessive Compulsive Scale. Psychopharmacol. Bull. 33 (1), 17.
Phillips, K.A., 2004. Body dysmorphic disorder: recognizing and treating imagined ugliness. World Psychiatry 3 (1), 12–17.
Phillips, K.A., Pinto, A., Menard, W., Eisen, J.L., Mancebo, M., Rasmussen, S.A., 2007. Obsessive–compulsive disorder versus body dysmorphic disorder: a comparison study of two possibly related disorders. Depress Anxiety 24 (6), 399–409.
Phillips, K.A., 2009. Understanding Body Dysmorphic Disorder. Oxford University Press, Chicago.
Phillips, K.A., Stein, D.J., Rauch, S.L., Hollander, E., Fallon, B.A., Barsky, A., Fineberg, N., Mataix-Cols, D., Ferrão, Y.A., Saxena, S., Wilhelm, S., Kelly, M.M., Clark, L.A., Pinto, A., Bienvenu, O.J., Farrow, J., Leckman, J., 2010. Should an obsessive-compulsive spectrum grouping of disorders be included in DSM-V? Depress Anxiety 27, 528–555. https://doi.org/10.1002/da.20705.
Phillips, K.A., Pinto, A., Hart, A.S., Coles, M.E., Eisen, J.L., Menard, W., Rasmussen, S.A., 2012. A comparison of insight in body dysmorphic disorder and obsessive-compulsive disorder. J. Psychiat. Res. 46, 1293–1299. https://doi.org/10.1016/j.jpsychires.2012.05.016.
Phillips, K.A., 2015. Body dysmorphic disorder: clinical aspects and relationship to obsessive-compulsive disorder. Focus 13 (2), 162–174. https://doi.org/10.1176/appi.focus.130205.
Shansky, R.M., Lipps, J., 2013. Stress-induced cognitive dysfunction: hormone neurotransmitter interactions in the prefrontal cortex. Front. Hum. Neurosci. 7. https://doi.org/10.3389/fnhum.2013.00123.
Stern, E.R., Muratore, A.F., Taylor, S.F., Abelson, J.L., Hof, P.R., Goodman, W.K., 2017. Switching between internally and externally focused attention in obsessive-compulsive disorder: abnormal visual cortex activation and connectivity. Psychiat Res–Neuroim 265, 87–97. https://doi.org/10.1016/j.pscychresns.2016.08.006.
Stewart, S.E., Egan Stack, D., Wilhelm, S., 2008. Severe obsessive-compulsive disorder with and without body dysmorphic disorder: clinical correlates and implications. Ann. Clin. Psychiat. 20 (1), 33–38. https://doi.org/10.1080/10401230701844463.
Storch, E.A., Bagner, D., Merlo, L.J., Shapira, N.A., Geffken, G.R., Murphy, T.K., Goodman, W.K., 2007. Florida obsessive-compulsive inventory: development, reliability, and validity. J. Clin. Psychol. 63 (9), 851–859.
Storch, E.A., De Nadai, A.S., do Rosário, M.C., Shavitt, R.G., Torres, A.R., Ferrão, Y.A., Fontenelle, L.F., 2015. Defining clinical severity in adults with obsessive–compulsive disorder. Compr. Psychiat. 63, 30–35. https://doi.org/10.1016/j.comppsych.2015.08.007.
Taylor, S., 2011. Early versus late onset obsessive–compulsive disorder: evidence for distinct subtypes. Clin. Psychol. Rev. 31 (7), 1083–1100. https://doi.org/10.1016/j.cpr.2011.06.007.
Van Kirk, N., Fletcher, T.L., Wanner, J.L., Hundt, N., Teng, E.J., 2018. Implications of comorbid OCD on PTSD treatment: a case study. B. Menninger. Clin. 82, 344–359. https://doi.org/10.1521/bumc.2018.82.4.344.
Veale, D., Phillips, K.A., Neziroglu, F., 2017. Challenges in assessing and treating patients with body dysmorphic disorder and recommended approaches. In: Phillips, KA (Ed.), Body Dysmorphic Disorder: Advances in Research and Clinical Practice. Oxford University Press, New York, NY editor.
Weathers, F.W., Litz, B.T., Keane, T.M., Palmieri, P.A., Marx, B.P., & Schnurr, P.P., 2013. The PTSD Checklist for DSM-5 (PCL-5). Scale available from the National Center for PTSD at www.ptsd.va.gov.
Weingarden, H., Curley, E.E., Renshaw, K.D., Wilhelm, S., 2017. Patient-identified events implicated in the development of body dysmorphic disorder. Body Image 21, 19–25. https://doi.org/10.1016/j.bodyim.2017.02.003.
Welkowitz, L.A., Struening, E.L., Pittman, J., Guardino, M., Welkowitz, J., 2000. Obsessive-compulsive disorder and comorbid anxiety problems in a national anxiety screening sample. J. Anxiety Disord. 14 (5), 471–482. https://doi.org/10.1016/s0887-6185(00)00034-7.
Wilhelm, S., Phillips, K.A., Greenberg, J.L., O'Keefe, S.M., Hoeppner, S.S., Keshaviah, A., Schoenfeld, D.A., 2019. Efficacy and posttreatment effects of therapist delivered cognitive behavioral therapy vs supportive psychotherapy for adults with body dysmorphic disorder: a randomized clinical trial. JAMA Psychiat. https://doi.org/10.1001/jamapsychiatry.2018.4156.
Wilker, S., Kolassa, I.T., 2013. The formation of a neural fear network in posttraumatic stress disorder: insights from molecular genetics. Clin. Psychol. Sci. 1 (4), 452–469. https://doi.org/10.1177/2167702613479583.
Willson, R., Veale, D., Freeston, M., 2016. Imagery rescripting for body dysmorphic disorder: a multiple- baseline single case experimental design. Behav. Ther. 47 (2), 248–261. https://doi.org/10.1016/j.beth.2015.08.006.