BRIEF REPORT

Symptom-Specific Threat Perception Mediates the Relationship Between Obsessive Beliefs and OCD Symptoms

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Abstract

Cognitive theories of obsessive compulsive disorder (OCD) propose that obsessive beliefs bias individuals' perception of OC-relevant threats, which in turn maintain OCD symptoms. However, no prior research has directly tested this mediational model in a clinical sample. The current study bridges this gap in the literature. Sixty adults with OCD completed a diagnostic interview, self-report questionnaires and a threat perception task. More specifically, participants rated the perceived threat associated with (a) OC-specific stimuli (e.g., toilet) that matched their most interfering symptom dimension (e.g., contamination) and (b) generally negative terms (e.g., pain). Results supported hypotheses, in that the threat associated with OC-specific—but not generally negative—terms significantly mediated the relationship between obsessive beliefs and the severity of participants' most interfering OCD symptom dimension. Findings underscore the importance of targeting inflated perceptions of OC-specific threats in the treatment of OCD. Limitations and future directions are discussed.

Keywords Cognitive model · OCD · Threat perception · Obsessive beliefs

Obsessive compulsive disorder (OCD) is a highly debilitating psychiatric illness that occurs in approximately 2–3.8% of the population (Angst et al. 2004; Ruscio et al. 2010). OCD is defined by the presence of obsessions—intrusive mental events—and compulsions—repetitive acts performed to control obsessions or distress (American Psychiatric Association [APA] 2013). Obsessions and compulsions result in substantial functional impairment (e.g., APA 2013; Eisen et al. 2006) and are highly heterogeneous (Mataix-Cols et al. 2005). In fact, research suggests that four thematically unique symptom dimensions exist within the OCD diagnostic category: contamination, responsibility for harm, unacceptable thoughts, and symmetry/need to feel "just right" (Abramowitz et al. 2010).

While obsessions are characteristic of OCD, Salkovskis (1985) and Rachman's (1997) cognitive theory posits that intrusive thoughts are not unique to those who suffer from this condition. Rather, it is distorted beliefs about the meaning of intrusive thoughts that distinguish individuals with OCD from the general population (e.g., Abramowitz et al. 2014; Rachman and de Silva 1978). Distorted obsessive beliefs most commonly involve: inflated estimates of risk/personal responsibility, the importance of one's thoughts and the need to control them, and the need for perfection/certainty (Obsessive Compulsive Cognitions Working Group [OCCWG] 2005). Per cognitive theory, when such a belief system is activated, information is filtered through that lens (Beck and Haigh 2014) and consequently, individuals perceive greater threat when confronting OC-relevant triggers. Taken together, cognitive theory proposes that obsessive beliefs bias the perception of OC-relevant threat, which in turn maintain or exacerbate OCD symptoms.

Prior research has tested components of this mediational maintenance model (e.g., see Calkins et al. 2013) by demonstrating a significant relationship between obsessive beliefs and OCD symptoms in large community samples (*N*'s = 562, 5015; Taylor et al. 2010; Tolin et al. 2003). Results have been replicated within clinical samples, while controlling for general negative affect (e.g., Sica et al. 2004; Wheaton et al. 2010). Using experimental methods, researchers refined our understanding of how obsessive beliefs relate to OCD symptoms by manipulating

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cognitive factors and recording subsequent changes in relevant symptoms (e.g., frequency of checking behaviors; Alcolado and Radomsky 2011; Berman et al. 2011, 2012). Building on the manipulation of cognitive factors, experimental studies have also documented that elevated threat estimation is specific to OC-relevant stimuli, as opposed to stimuli that are more generally threatening (e.g., Lavy et al. 1994; Tata et al. 1996).

Although research demonstrates that obsessive beliefs, OC-specific threat perception and OCD symptoms are inter-related, no prior studies have tested a full mediational model in which inflated perception of OC-relevant threat explains the relationship between obsessive beliefs and OCD symptoms. Support for this model can elucidate a mechanism by which OCD symptoms are maintained and highlight cognitive treatment targets for therapists. Moreover, including individuals whose OCD symptoms are not limited to a single dimension (e.g., Alcolado and Radomsky 2011; Lavy et al. 1994; Tata et al. 1996), and tailoring the threat perception stimuli to their most salient obsessional content, would extend the literature and bolster external validity.

To this end, the present study is the first to test the mediational role of symptom-specific threat perception in the relationship between obsessive beliefs and OCD symptoms. In a large and well-characterized sample of adults with OCD, we measured obsessive beliefs and OCD symptoms, and asked participants to complete a threat perception task that involved rating the degree of threat associated with (a) terms tailored to their primary OCD dimension and (b) general threat terms. Drawing from cognitive theory, our hypotheses are twofold. First, we expect that elevated threat perception of stimuli specific to a participant's primary OCD symptom dimension (e.g., responsibility for harm) will explain the relationship between obsessive beliefs and the severity of participants' OCD symptoms on that dimension. Paralleling past research (e.g., Wheaton et al. 2010), we predict that this relationship will remain after controlling for depression symptom severity. Second, we hypothesize that this mediated relationship will be specific to the perception of OC-stimuli and will not be replicated with general threat stimuli.

Materials and Methods

Participants

Sixty eligible participants were recruited at an OCD and Related Disorders program in the Northeast United States through advertisements. To be included, participants must have: (1) been at least 18-years-old, (2) met diagnostic criteria for OCD, and (3) sufficient fluency in English. Participants were excluded if they were actively suicidal or met criteria for autism, an intellectual disability or a bipolar- or psychotic-spectrum disorder.

The majority of participants were female, Caucasian, unmarried, employed, possessed at least a college degree and had previously participated in CBT (see Table 1). In addition to OCD, many participants met diagnostic criteria for other psychological conditions (see Table 2).

On average, participants met criteria for 1.62 ($SD = 1.56$) comorbid disorders.

Measures

Mini International Neuropsychiatric Interview Version 5.0 (MINI)

The MINI 5.0 is a clinician-administered interview that assesses DSM-IV mood, anxiety, attentional, and behavioral disorders (Lecrubier et al. 1997; Sheehan et al. 1998).

Table 1 Demographic characteristics of study sample (N = 60)

Age	$M = 34.10; SD = 13.15$
Gender	
Female	35 (58.3%)
Male	25 (41.7%)
Race	
Caucasian	54 (90%)
African–American	1 (1.7%)
Asian	3 (5%)
American Indian/Alaska Native	1 (1.7%)
Other	1 (1.7%)
Ethnicity	
Hispanic or Latino	5 (8.3%)
Not Hispanic or Latino	55 (91.7%)
Highest education attained	
High School/GED	6 (10%)
Associates or 2-year college	2 (3.3%)
Partial college (courses towards degree)	13 (21.7%)
College degree (4-year college)	21 (35%)
Masters degree	13 (21.7%)
Professional degree (MD, PhD, JD)	5 (8.3%)
Marital status	
Single	33 (55%)
Married	15 (25%)
Living with partner (not married)	8 (13.3%)
Separated or divorced	4 (6.7%)
Employment status	
Full-time (35 h or more/week)	24 (40%)
Part-time (less than 35 h/week)	11 (18.3%)
Full-time Student (3 or more classes)	16 (26.7%)
Unemployed	9 (15%)
Previous engagement in CBT	
Yes	33 (55%)
No	27 (45%)

Table 2 Participants' psychiatric diagnoses using MINI 5.0

	N (%)
Obsessive compulsive disorder	60 (100%)
Social phobia	19 (31.7%)
Major depressive disorder	12 (20%)
Generalized anxiety disorder	12 (20%)
Panic disorder	11 (18.3%)
Agoraphobia	9 (15%)
Post-traumatic stress disorder	4 (6.7%)
Alcohol dependence disorder	4 (6.7%)
Alcohol abuse disorder	1 (1.7%)
Substance dependence disorder	1 (1.7%)

(1) Table 2 lists all diagnoses, not only the primary diagnosis, for which participants met criteria; (2) If a diagnosis is not listed, then no participants met current diagnostic criteria for that condition

When data collection began, the MINI had not been updated for DSM-5 and we therefore were not able to assess OC spectrum conditions (e.g., hair-pulling disorder) included in the most recent iteration. The MINI is reliable and valid, including: strong inter-rater reliability (kappas > 0.75), concordance with the Structured Clinical Interview for DSM (SCID-P; kappas = 0.43–0.90), sensitivity (0.45–0.96) and specificity (0.86 − 1.0; Sheehan et al. 1998).

Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al. 1989a, b)

The Y-BOCS is a clinician-administered interview that includes a comprehensive checklist of the most common obsessions and compulsions and 10 questions that assess the severity (and impairment) of OCD symptoms over the past week. Each item is rated on a scale from 0 to 4, wherein higher scores reflect greater symptom severity. The Y-BOCS has strong inter-rater reliability ($r = .98$), internal consistency (Cronbach's alpha = 0.89) and construct validity (Goodman et al. 1989a, b).

Dimensional Obsessive Compulsive Scale (DOCS; Abramowitz et al. 2010)

The DOCS complements the Y-BOCS with a dimensional perspective of OCD. This 20-item self-report measure separately assesses the severity of four OC symptom dimensions: contamination, responsibility for harm, unacceptable thoughts, and symmetry. Following a description of each dimension, participants rate the following on a scale from 0 to 4: (a) time occupied by obsessions and rituals, (b) avoidance behavior, (c) distress, (d) interference, and (e) difficulty disregarding obsessions and resisting the rituals. The DOCS has strong psychometric properties,

including: factorial validity established via exploratory and confirmatory factor analysis, internal consistency, and construct validity (Abramowitz et al. 2010). In the current sample, internal consistency estimates for the four subscales and total score were excellent ($\alpha = 0.95$ [contamination], 0.92 [responsibility for harm], 0.92 [unacceptable thoughts], 0.93 [symmetry] and 0.90 [total]).

Obsessional Beliefs Questionnaire-44 (OBQ-44; OCCWG 2005)

This 44-item self-report questionnaire assesses three types of obsessive beliefs: exaggerated responsibility and threat estimation (RT; "When I see any opportunity to do so, I must act to prevent bad things from happening"), perfectionism and certainty (PC; "I should be upset if I make a mistake"), and the importance and control of thoughts (ICT; "I should be able to rid my mind of unwanted thoughts"). Each item is rated from 1 ("disagree very much") to 7 ("agree very much"). The OBQ-44 possesses excellent psychometric properties, including factorial validity based on factor analysis, internal consistency and construct validity (OCCWG 2005). In the current sample, internal consistency estimates for the three subscales and total score were excellent ($\alpha = 0.94$ [RT], 0.94 [PC], 0.90 [ICT], and 0.96 [total]).

Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR; Rush et al. 2003)

The 16-item self-report instrument assesses the severity of major depressive disorder criteria over the past week (Trivedi et al. 2004). Participants rate each item (e.g., "decreased appetite") on a 4-point scale that aligns with the specific criterion (0 = "There is no change in my usual appetite" to 3 = "I rarely eat within a 24-h period, and only with extreme personal effort or where others persuade me to eat"). The QIDS-SR has strong psychometric properties, including internal consistency, sensitivity to change, and construct validity (Rush et al. 2003). In the current sample, the internal consistency for the total QIDS-SR score was adequate ($\alpha = 0.84$) and comparable to previously published estimates of reliability ($\alpha = 0.86$; Rush et al. 2003).

Threat Terms

Past experimental research (e.g., Emotional Stroop) suggests that OC-specific and general threat terms can be used as threat stimuli for patients with OCD (Lavy et al. 1994). To generate OC-specific threat terms, we used the Y-BOCS checklist and DOCS. Given the heterogeneity of

OCD symptoms, one set of terms would not be applicable to all participants. We therefore generated four sets, each mapping onto a unique dimension of OCD: contamination (e.g., "unclean"), responsibility (e.g., "irresponsible"), unacceptable thoughts ("immoral"), and symmetry (e.g., "uneven"). The initial list for each dimension included over 30 terms. To establish content validity, three doctoral-level OCD specialists reviewed the lists. Any term that was not unanimously considered to reflect the symptom dimension was dropped. Next, the specialists, along with the principal investigator (NCB), rank-ordered the terms' subjective degree of threat (from 0 to 100) within each dimension. The 26 terms with the highest subjective degree of threat were then used for each symptom dimension. Importantly, participants only rated the threat terms for their primary OCD dimension (e.g., contamination) and did not rate those that corresponded to the other three symptom dimensions. Terms were presented one at a time and participants rated "how threatening or scary this word is to you right now" on a scale from 0 ("not at all threatening") to 100 ("extremely threatening"). In the current sample, internal consistency for each dimension's threat terms was excellent ($\alpha = 0.95$ [contamination], 0.97 [responsibility for harm], 0.96 [unacceptable thoughts], and 0.97 [symmetry]).

We also created a list of general negative terms (e.g., "pain") that assessed non-specific threat perception, which were reviewed by the OCD specialists to ensure they did not tap into OC phenomena. To reduce participant burden, we only used seven general negative terms and they were each rated on the same 0–100 scale. Internal consistency ($\alpha = 0.86$) across the general negative terms was adequate.

Procedure

Interested participants first completed a phone screen with a clinical research assistant. Eligible participants were then mailed an informed consent form. Verbal consent was obtained to conduct the diagnostic assessments and complete study measures. Next, participants were administered the MINI and Y-BOCS by a licensed clinical psychologist (NCB) or advanced graduate student in clinical psychology who underwent reliability training. Specifically, following didactic and observational training, student interviews were audio-taped, reviewed in supervision, and final diagnostic decisions were made by consensus. At the end of the study, 20% of the interviews were randomly chosen and rated by a clinician who achieved reliability on both measures and was uninvolved in the study. High inter-rater reliability was obtained on both the MINI (kappa = 0.97) and Y-BOCS (Cronbach's alpha = 0.99).

Following the interview, participants were emailed a unique hyperlink using Research Electronic Data Capture (REDCap)—a free and HIPAA compliant web-based application (Harris et al. 2009). Participants first completed self-report questionnaires (OBQ-44, DOCS, QIDS-SR) and then the threat rating task. The OC-specific and general negative terms were presented to participants in a random order. Participants were required to complete the survey within 1 week. Lastly, at a visit to our clinic, participants provided written consent and engaged in behavioral paradigms that are beyond the scope of the current paper. At study completion, participants were given a debriefing form and compensated at a rate of $25 per hour. Our hospital IRB reviewed and approved all measures and procedures.

Analytic Approach

Analyses were conducted using SPSS Version 24 (IBM Corp. 2016). First, we conducted descriptive statistics to examine sample characteristics. Next, zero-order correlations were used to evaluate relationships among the OCD measures and threat perception ratings. Lastly, we conducted three mediation analyses using the Sobel z-test (see Preacher and Hayes 2008). Model 1 examined whether threat ratings for OC-specific words (i.e., terms that map onto participants' primary OCD symptom dimension) mediated the relationship between obsessive beliefs (OBQ-44 total) and the severity of participants' primary OCD symptom dimension on the DOCS, while controlling for depression symptom severity (QIDS-SR). Model 2 tested the directionality of Model 1, by examining whether participants' obsessive beliefs mediated the relationship between OC-specific threat perception and the severity of their primary OCD symptom dimension. Lastly, Model 3 tested the specificity of Model 1, by examining whether the relationship between obsessive beliefs and the severity of participants' primary OCD symptom dimension could be explained by the perception of threat more broadly (e.g., general negative terms), while again controlling for depression symptom severity.

Results

Sample Characteristics

Table 3 presents the descriptive statistics of study variables. Participants' OCD (Y-BOCS and DOCS total score) and depression (QIDS-SR) severity fell within the moderately severe range. Moreover, participants' scores on the OBQ-44 and each of the four DOCS dimensions reflected clinically significant OCD severity (Abramowitz et al. 2010; OCCWG, 2005).

Table 3 Descriptive statistics of study measures (N = 60)

	M (SD)
OCS severity scales	
YBOCS-O	10.81 (3.20)
YBOCS-C	11.47 (3.45)
YBOCS-total	22.28 (5.91)
DOCS-total	25.10 (13.38)
OCS dimensions	
DOCS-C	6.03 (5.73)
DOCS-R	5.43 (4.44)
DOCS-U	8.28 (5.08)
DOCS-S	5.50 (4.90)
Obsessional beliefs	
OBQ-RT	67.02 (22.36)
OBQ-PC	72.63 (24.11)
OBQ-ICT	39.45 (17.87)
OBQ-total	179.12 (54.82)
Depression symptom severity	
QIDS-SR total	8.43 (4.38)
Average threat ratings	
OC-specific terms	47.24 (25.27)
Contamination	52.63 (25.09)
Responsibility	50.61 (23.21)
Unacceptable thoughts	32.89 (23.70)
Symmetry average	45.65 (27.39)
Negative terms	46.76 (24.61)

YBOCS Yale-Brown Obsessive Compulsive Scale, *YBOCS-O* obsession total score, *YBOCS-C* compulsion total score, *DOCS* Dimensional Obsessive Compulsive Scale, *DOCS-C* contamination, *DOCS-R* responsibility for harm, *DOCS-U* unacceptable thoughts, *DOCS-S* symmetry, *OBQ* Obsessional Beliefs Questionnaire, *OBQ-RT* responsibility and threat exaggeration, *OBQ-PC* perfectionism and certainty, *OBQ-ICT* importance and control of thoughts, *QIDS-SR* quick inventory of depressive symptomology-self report

Threat Perception Scores

We calculated each participant's OC-specific threat perception score by averaging their ratings. Descriptive statistics indicated that contamination terms were rated as the most threatening, followed by responsibility for harm, symmetry, and unacceptable thoughts (see Table 3). A one-way ANOVA demonstrated that participants' threat perception ratings did not significantly differ by dimension, $F(3,55) = 1.27$, $p > .05$. Therefore, we created an overarching variable that included each participant's average OC-specific threat ratings, regardless of their dimension. We similarly averaged participants' ratings for the negative terms. As demonstrated in Table 3, participants rated the OC-specific and negative terms as similarly threatening.

Zero-Order Correlations Among Study Variables

Measures of OCD beliefs and dimension-specific severity (OBQ-44 and DOCS subscales) possessed moderately strong, significant, and positive associations with one another; however, the relationship between the OBQ-44 total score and the contamination subscale of the DOCS only trended towards significance ($p < .10$; see Table 4). Threat ratings of OC-specific terms were positively and significantly associated with the OBQ-44 total and dimension-specific OCD symptom severity scores at similarly strong magnitudes. The relationship between OC-specific threat perception and the OBQ-44 total score and contamination subscale of the DOCS emerged as the strongest in magnitude, whereas the relationship between OC-specific threat perception and the unacceptable subscale of the DOCS was the weakest. In regards to the threat ratings for general negative terms, the relationship with OBQ-44 total score and the unacceptable thoughts subscale of the DOCS emerged as the strongest, whereas correlations with the contamination subscale were the weakest and non-significant. Lastly, there was a positive, strong and significant association between the threat perception of OC-specific and general negative terms.

Mediation Analyses

The Sobel z-test indicated that the perceived threat of OC-specific stimuli significantly mediated the relationship

Table 4 Zero-order correlations among study measures

	2	3	4	5	6	7
1. OBQ-44 total	0.23	0.52[c]	0.39[b]	0.31[a]	0.61[c]	0.62[c]
2. DOCS-C total		0.21	−0.01	0.37[b]	0.43[c]	0.05
3. DOCS-R total			0.47[c]	0.34[b]	0.30[a]	0.34[b]
4. DOCS-U total				0.17	0.27[a]	0.43[c]
5. DOCS-S total					0.42[c]	0.35[b]
6. OC-specific threat ratings						0.73[c]
7. General threat ratings						

OBQ-44 Obsessional Beliefs Questionnaire, *DOCS* Dimensional Obsessive Compulsive Scale; *DOCS-C* contamination, *DOCS-R* responsibility for harm, *DOCS-U* unacceptable thoughts; *DOCS-S* symmetry

[a]$p<.05$; [b]$p<.01$; [c]$p<.001$

between the severity of participants' OBQ-44 total and primary symptom dimension score on the DOCS, while controlling for the QIDS-SR (Model 1; $z = 2.86$, $SE = 0.008$, $p < .01$; see Fig. 1). We evaluated the directionality of the effect by examining whether obsessive beliefs mediated the relationship between OC-specific threat perception and the severity of participants' primary OCD symptom dimension (Model 2). The Sobel z-test indicated that this mediation test was not statistically significant ($z = -0.17$, $SE = 0.012$, $p > .05$). Next, we evaluated whether the perceived threat of general negative terms mediated the relationship between the severity of participants' OBQ-44 score and their primary OCD symptom dimension on the DOCS, while controlling for the QIDS-SR (Model 3). Results demonstrated that general threat perception was not a statistically significant (or trending) mediator ($z = 1.24$, $SE = 0.006$, $p > .05$).

Discussion

The present study tested a key element of the cognitive model of OCD—whether obsessive beliefs enhance the perceived threat of OC-specific stimuli, and in turn, elevate OCD symptom severity. Results supported this personalized mediational model and extend prior research that tested the model's singular components; namely, that OC cognitions are significantly related to OCD symptoms (e.g., Wheaton et al. 2010; Sica et al. 2004), and that exaggerated perception of OC-specific, as opposed to general, threat is implicated in OCD (e.g., Tata et al. 1996). In addition to the well-characterized clinical sample, a clear strength of this study is that participants' self-reported threat perception was specific to their most interfering symptom subtype. Moreover, the severity of participants' most interfering symptom

dimension on the DOCS operated as the outcome in mediational models. This facilitated inclusion of participants with heterogeneous OCD symptoms and increased the generalizability of study findings.

Our pattern of results possesses potential treatment implications. Most notably, targeting patients' idiosyncratic perception of OC-specific threat may weaken the strong relationship between their obsessive beliefs and OCD symptoms. These findings align with recent research on mechanisms of change in cognitive therapy for OCD, in that a reduction in patients' threat perception, and other similarly distorted cognitions, occurred prior to improvement in patients' OCD symptoms (Wilhelm et al. 2015). Clinicians can target patients' inflated threat perceptions via behavioral experiments (see Berman et al. 2015) or with cognitive bias modification (CBM) exercises. In fact, targeting interpretation biases via CBM can effectively modify patients' obsessive beliefs (Clerkin and Teachman 2011; Williams and Grisham 2013).

The implications of the present study should be considered in the context of several limitations. First, while data are consistent with mechanistic inferences about the role of obsessive beliefs and threat perception in the maintenance of OCD symptoms, data are cross-sectional and therefore cannot be interpreted as causal. To further test the directionality of our cross-sectional mediation analysis, we conducted a "reverse mediation" analysis, which showed that beliefs do not significantly mediate the relationship between threat perception and OCD symptoms. Our non-significant effect lends evidence that our mediation model reflects mechanistic processes, but results must be replicated longitudinally as a next step to infer causality.

Fig. 1 Symptom-specific threat perception mediates relationship between obsessive beliefs and primary OCD symptom dimension severity, controlling for depression symptom severity
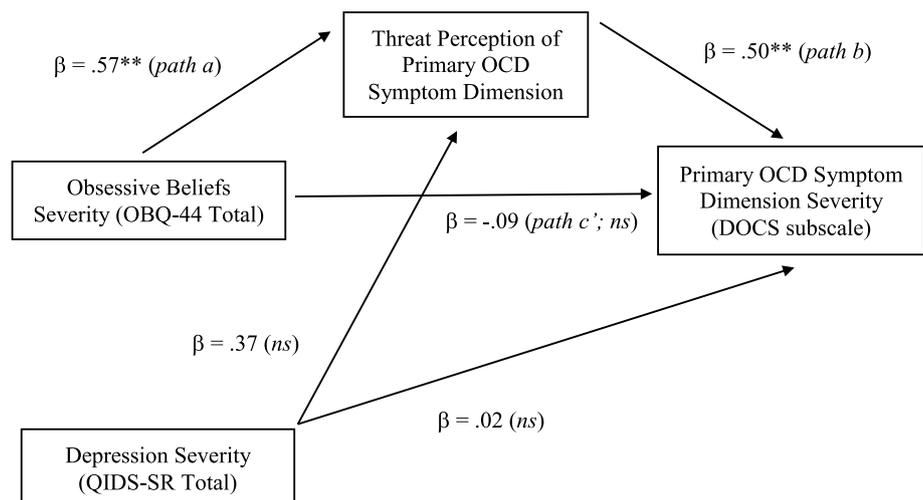
Note. ** $p < .001$; *ns* = not significant

Additionally, threat ratings for "unacceptable thoughts" words were lower than ratings for other symptom domains. Indeed, the unacceptable thoughts dimension may encompass the most diverse range of content. For example, unacceptable thoughts may include aggressive, blasphemous, or sexual intrusions. Therefore, it is possible that the average threat score for this domain was somewhat diluted if individual threat words were not relevant to participants' unacceptable thought content.

While this study examined participants' threat perception for OC-specific and general negative terms, we did not examine threat terms relevant to other fear-based disorders (e.g., social anxiety). Future research could evaluate the model's specificity by examining whether perceptions of other-disorder threat terms similarly mediate the relationship between obsessive beliefs and OCD symptoms. Relatedly, distress in some OCD presentations (e.g., "not-quite-right" symptoms) is generated more from intolerance of uncertainty or imperfection than from perceived threat. Future research could extend this study by examining whether estimates of distress related to uncertainty/imperfection mediates the link between beliefs about the need for perfection/certainty with "not-quite-right" symptoms. Finally, while the present study relied on self-reported threat perception, future research should incorporate objective indices of threat perception, such as galvanic skin response or pupil dilation.

In closing, the current study builds upon the cognitive model of OCD and is the first to suggest that symptom-specific threat perception mediates the relationship between obsessive beliefs and OCD symptom severity in a sample of participants with OCD. Results preliminarily suggest that modifying the exaggerated threat associated with patients' unique constellation of symptoms may, in turn, weaken the association between their distorted belief system and OCD symptoms. To strengthen causal inferences of this mediational model, future research must replicate this study design using a longitudinal approach.

Compliance with Ethical Standards

Conflict of interest Drs. Berman, Weingarden and Wilhelm declare that they have no conflict of interest.

Ethical Approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Animal Rights No animal studies were carried out by the authors for this article.

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