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Review article

Fear conditioning and extinction in obsessive-compulsive disorder: A systematic review

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ABSTRACT

Laboratory experiments using fear conditioning and extinction protocols help lay the groundwork for designing, testing, and optimizing innovative treatments for anxiety-related disorders. Yet, there is limited basic research on fear conditioning and extinction in obsessive-compulsive disorder (OCD). This is surprising because exposure-based treatments based on associative learning principles are among the most popular and effective treatment options for OCD. Here, we systematically review and critically assess existing aversive conditioning and extinction studies of OCD. Across 12 studies, there was moderate evidence that OCD is associated with abnormal acquisition of conditioned responses that differ from comparison groups. There was relatively stronger evidence of OCD's association with impaired extinction processes. This included multiple studies finding elevated conditioned responses during extinction learning and poorer threat/safety discrimination during recall, although a minority of studies yielded results inconsistent with this conclusion. Overall, the conditioning model holds value for OCD research, but more work is necessary to clarify emerging patterns of results and increase clinical translational utility to the level seen in other anxiety-related disorders. We detail limitations in the literature and suggest next steps, including modeling OCD with more complex conditioning methodology (e.g., semantic/conceptual generalization, avoidance) and improving individual-differences assessment with dimensional techniques.

1. Introduction

Translating conditioning and extinction principles and paradigms to effective behavioral treatments has led to the development of effective first-line treatments for anxiety-related disorders, most notably exposure therapies (Foa and McLean, 2016; Rachman, 2015). One of the disorders that benefits from exposure intervention is obsessive-compulsive disorder (OCD; American Psychiatric Association, 2013). OCD is an anxiety-related disorder associated with considerable personal and occupational burden (Huppert et al., 2009; Markarian et al., 2010) and characterized by entrenched and intrusive obsessional cognitive content (including thoughts, images, and impulses) and interfering compulsive behaviors. The gold-standard exposure intervention for OCD is exposure and response prevention (EX/RP; Foa et al., 2012; Meyer, 1966; Rachman et al., 1971), which primarily involves techniques that teach the patient to resist enacting a compulsion while enduring obsession-related distress. Although EX/RP is the most effective available behavioral treatment for OCD (Olatunji et al., 2013), a significant minority of patients either do not respond to the treatment, drop-out, or show symptom remission and do not maintain treatment gain (Abramowitz, 1996; Fisher and Wells, 2005; Foa and McLean, 2016; Jacoby and Abramowitz, 2016; Johnco et al., 2020; Simpson et al., 2006). A noteworthy statistic regarding EX/RP is that up to 60% of patients with OCD who complete the treatment go on to experience partial relapse of symptoms (Eisen et al., 2013). Unfavorable exposure treatment outcomes are attributed to multiple factors. This includes factors common to many treatments, such as poor adherence to between-session work (Ojalehto et al., 2020), and those more specific to EX/RP's underlying classical conditioning framework, such as within-session learning failing to generalize to outside of the therapy context and insufficient habituation to a feared stimulus (Jacoby and Abramowitz, 2016). Due to these known difficulties related to EX/RP, as well as the associative learning underpinnings of exposure interventions in general, both basic and clinical scientists have proposed increased investigation into perturbed classical conditioning and extinction processes in OCD as a potential route forward for further innovation and improvement in EX/RP and related therapies (e.g., Foa and McLean, 2016; Jacoby and Abramowitz, 2016).

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1.1. OCD and Classical Conditioning and Extinction Principles

Classical fear conditioning (Pavlov, 1927) is the process through which an inherently neutral unconditioned stimulus becomes a conditioned stimulus (CS) through repeated pairings with an inherently aversive unconditioned stimulus (US). Through acquisition of the aversive CS-US association, the CS is capable of eliciting a conditioned response (CR), such as defensive reactions, increased physiological responses, and subjective reports of fear in humans. Following acquisition of the CR, the CR can be diminished through repeated presentations of the CS in the absence of the US (i.e., extinction). Both conditioning and extinction learning are increasingly well-understood across animal species at both the behavioral and neural levels (Fullana et al., 2016, 2018; Maren, 2001; Vervliet and Boddez, 2020). Conditioning and extinction offer a compelling and testable framework for understanding anxiety-related disorders, as they describe fundamental mechanisms through which people acquire severe anxiety that does not abate over time or through new experiences (Mineka and Zinbarg, 2006; Vervliet et al., 2013b).

The components of classical conditioning are evident in established behavioral models of OCD (Rachman and Hodgson, 1980; Teasdale, 1974) (see Fig. 1). For example, the CR can take the form of distressing obsessions that arise from observing, experiencing, or imagining a negative consequence (US) related to an object or situation (CS). Examples include a patient seeing a family member cut themselves on a knife the patient owns or imagining stabbing the family member, or the patient becoming sick after touching an unclean surface. Further, the obsessions are not limited to the period around the initial experience of the CS and US together and often continue unabated even when the US is not present, such as when the patient's family member uses a knife but does not sustain an injury. This is analogous to impaired extinction learning, such that the CR does not diminish in the absence of the US. In some circumstances, the obsessions can serve as the CS itself, as the obsessional content leads to subsequent thoughts that are also distressing. For example, some patients think about a family member being hurt and then think, "I am evil for wanting that to happen." Obsessions might inevitably gain additional distressing properties through this type of process (Salkovskis, 1985). Obsessional content and distress can also generalize to neutral stimuli that incidentally resemble the initial CS. In the case of a knife that caused a family member harm, generalization might lead to other bladed objects or household tools becoming CSs. Compulsions, such as constantly checking if dangerous objects are locked away, can temporarily reduce obsessions but circumvent the opportunity for exposure and lead to the return of maladaptive and unwanted thoughts and behavior (Meyer, 1966). In other words, extinction of the CR does not occur and there is only a temporary reduction. Further, compulsions are more likely to be enacted in the future due to strengthened associations with temporary relief from distress (i.e., negative reinforcement; Mowrer, 1947). Although the described conditioning model does not fully explain the phenomenology of OCD (see work on cognitive models, e.g., Abramowitz et al., 2007; Salkovskis, 1999; Taylor et al., 2007), it provides a key foundation for systematic empirical investigation into the pathological substrates of the disorder and offers considerable promise for productive clinical translational efforts.

1.2. The Current Review

To date, there has not been a systematic review of conditioning work in OCD, and thus there is not a current synthesis of the literature to serve as a foundation for future research. In particular, it is not clear if impaired acquisition and extinction of conditioned fear are characteristic of OCD and, if so, what form or pattern these deficits take. Synthesizing this literature and drawing cross-study conclusions is needed before the important next steps of leveraging experimental conditioning work to improve treatment for OCD, especially as exciting new avenues for extinction-based treatments, such as behavioral and pharmaceutical extinction enhancers, emerge from pre-clinical research (for reviews, see Craske et al., 2014; Dunsmoor et al., 2015). In the current review, we address this need by systematically reviewing the OCD and conditioning literature to determine if aberrant acquisition and extinction processes are consistently related to OCD across studies. We also evaluate design differences and experimental and assessment limitations that potentially hinder strong conclusions, with a goal of providing recommendations for future work in this area. We limit the scope of our review to studies using associative conditioning paradigms employing aversive USs. Empirical interest in conditioning and anxiety-related disorders primarily focuses on aversive conditioning, and current OCD treatments emphasize the reduction of unpleasant emotional experiences and the behaviors such emotions can motivate. We also limit reviewed articles to studies of classical (i.e., Pavlovian) aversive conditioning and extinction in OCD. Currently, there are not a sufficient number of published studies to allow for a comprehensive review of other forms of conditioning (e.g., operant conditioning) as they relate to OCD.

We first provide an overview of the methodological characteristics of identified studies and then provide a detailed narrative review of key findings from each study. We next briefly summarize acquisition and extinction results across studies, discuss the findings from our review in

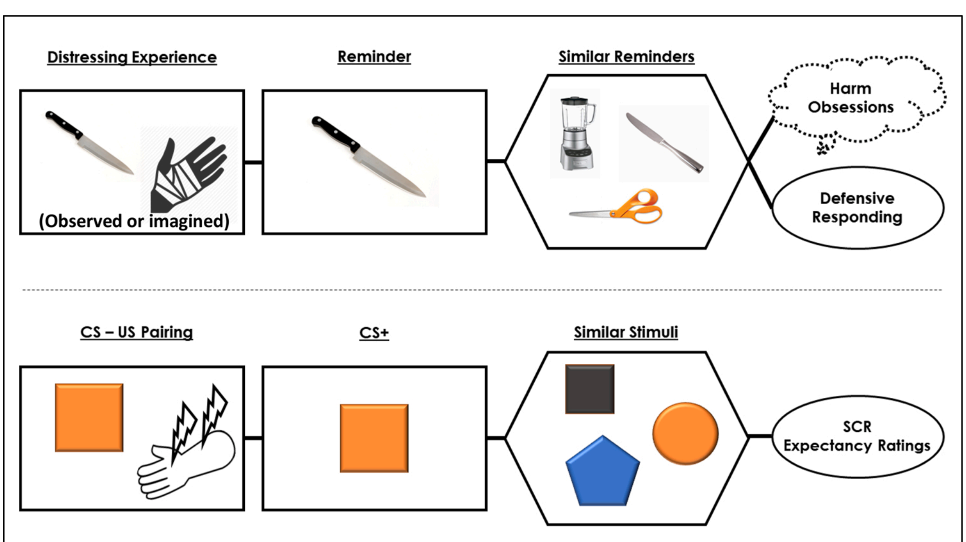

Fig. 1. Schematic of classical conditioning processes within the context of OCD and in the laboratory setting. Top half of figure models the development of obsessions and defensive responding. Note that in this example, the initial distressing experience could be observing actual harm or imagining harming others. Bottom half of figure shows the corresponding components of a classical conditioning protocol that uses electric shock as the US. CS = conditioned stimulus; CS+ = conditioned threat cue; SCR = skin conductance response; US = unconditioned stimulus.

the context of the larger conditioning and OCD literature, and conclude with a discussion of broad next steps and specific future recommendations in this area.

2. Method

Our systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher et al., 2009) statement. The documents used during literature search and screening for this review are available via this project's repository on the Open Source Framework (https://osf.io/a6wm4/).

2.1. Literature Search Strategy

Our strategy was designed to find published empirical work that 1) applied a classical conditioning protocol 2) using an aversive US 3) to test people with and without OCD or those with differing levels of OCD-related traits (e.g., personality traits that are empirically demonstrated to relate to OCD, but also are present to some degree in most people) and at least one group that included elevated trait levels consistent with OCD pathology, and 4) reported between-group differences or correlational analyses with an OCD scale on one or more conditioning index. We did not exclude eyeblink conditioning, which resembles basic classical conditioning except that the US is an air-puff to the eye and the CR is the eyeblink that is elicited by the anticipation of the air-puff. We included these studies because of the anticipated paucity of relevant OCD studies and because eyeblink conditioning is somewhat aversive (e.g., fear-relevant circuitry is involved in the acquisition of the eyeblink CR; Ng and Freeman, 2014). We limited the scope of this review to human research (for reviews of OCD-related research in non-human animals, see Abramowitz et al., 2011; Ahmari and Dougherty, 2015; Boulougouris et al., 2009; Szechtman et al., 2017).

All searches were performed using Google Scholar and Pubmed. We searched article titles, abstracts, and full text for the following keywords: (*OCD* OR *obsessive-compulsive* OR *obsessive* OR *compulsive)* AND *(conditioning OR conditioned AND fear* OR *disgust OR aversive* OR *classical* OR *Pavlovian* OR *extinction* OR *acquisition* OR *differential* OR *evaluative)* OR (*associative learning*) AND *human* AND NOT *review*. We also screened the references of articles from these searches, from recent reviews of exposure therapy in OCD that consider associative learning principles (Arch and Abramowitz, 2015; Jacoby and Abramowitz, 2016), and from two meta-analyses of classical conditioning in anxiety-related disorders (Duits et al., 2015; Lissek et al., 2005) for additional articles that met criteria for our review. Identified domain experts were also queried for potentially eligible articles. The final search for this review was conducted on December 02, 2020.

2.2. Screening

We screened identified articles using the following *a priori* inclusion criteria: 1) original data from an aversive conditioning paradigm was reported for a group with OCD or elevated traits closely associated with OCD; 2) a validated diagnostic measure of OCD, psychometric measure of OCD symptoms, or a measure of OCD-related traits was administered; 3) English language. After initial searches, tightened search criteria were re-applied to titles and abstracts only to ensure non-relevant incidental matches (e.g., match only found in reference section) were excluded. Screening was done by the first author (SC) and confirmed with the senior author (JD).

3. Results

3.1. Characteristics of Identified Studies

After full-text review, screening resulted in a total of twelve studies that met eligibility out of 6,190 from the initial search (see Fig. 2 for PRSIMA flow diagram). Of these studies, two used a single-cue design (Table 1; No. 11, 12; Nanbu et al., 2010; Tracy et al., 1999), which only involve one CS (termed a CS+) that is paired with the US during the acquisition phase. The remaining ten studies used a differential conditioning design, which includes CS+ trials as well as a CS that is never paired with the US (CS-). Six of these studies used a differential cue design (Table 1; No. 1, 2, 4, 5, 7, 8, ; Apergis-Schoute et al., 2017; Armstrong and Olatunji, 2017; Geller et al., 2017, 2019; Kaczkurkin and Lissek, 2013; McGuire et al., 2016). The remaining four differential studies used a differential cue-in-context design, in which the CSs were superimposed over a background context picture that varied between different phases of the experiment (Table 1; No. 3, 6, 9, 10; Fyer et al., 2020; Giménez et al., 2020; McLaughlin et al., 2015; Milad et al., 2013). Nine studies included at least one phase in which the CS+ was no longer reinforced, as most commonly done in extinction learning phases (Table 1; No. 1-6, 8-12; Apergis-Schoute et al., 2017; Armstrong and Olatunji, 2017; Fyer et al., 2020; Geller et al., 2017, 2019; Giménez et al., 2020; McGuire et al., 2016; McLaughlin et al., 2015; Milad et al., 2013; Nanbu et al., 2010; Tracy et al., 1999). Three studies tested children (as opposed to adults) (Table 1; No. 4, 5, 8; Geller et al., 2017, 2019; McGuire et al., 2016). Eleven studies used a tactile or auditory aversive US, and one study used disgust-inducing images as the US (Table 1; 2; Armstrong and Olatunji, 2017). Seven studies tested a group of participants with a current diagnosis of OCD (Table 1; No. 1, 3-6, 8, 10, 11; Apergis-Schoute et al., 2017; Fyer et al., 2020; Geller et al., 2017, 2019; Giménez et al., 2020; McGuire et al., 2016; Milad et al., 2013; Nanbu et al., 2010), one tested those with a lifetime, but not necessarily current, diagnosis of OCD (Table 1; No. 9; McLaughlin et al., 2015)[1], and the remaining three created OCD analogue groups (for review on this practice, see Abramowitz et al., 2014) for between-group comparisons (Table 1; 2, 7, 12; Armstrong and Olatunji, 2017; Kaczkurkin and Lissek, 2013; Tracy et al., 1999). Sample sizes ranged from N = 30 to N = 105. Most studies reported a sample of N = 64 or fewer; only three studies analyzed larger samples (Table 1; No. 1, 3, 4; Apergis-Schoute et al., 2017; Fyer et al., 2020; Geller et al., 2017). In studies comparing OCD groups to control groups, the ratio of OCD to control participants ranged from 0.64 to 1.87.

3.2. Detailed Narrative Review of Identified Studies

Given a limited number of studies that met criteria for inclusion in this review, we can provide a detailed narrative review of each study. Our detailed review is comprised of two subsections: acquisition of behavioral CRs (e.g., physiological arousal, self-report ratings) and extinction of behavioral CRs. We distinguish between extinction learning (i.e., extinction training or within-session extinction) and tests of extinction retention, such as extinction recall or contextual renewal. Common methodological variations or extensions of acquisition (e.g., generalization) or extinction processes (e.g., reversal) are included in the relevant subsection. Note that most studies are reviewed in both the acquisition and extinction sections, as all studies with an extinction component contained a preceding acquisition procedure. Additionally, three studies included in this review (Apergis-Schoute et al., 2017; Milad et al., 2013; Nanbu et al., 2010) reported both behavioral results and functional neuroimaging (electroencephalography [EEG] or functional

[1] The reported mean symptom severity for the OCD group from McLaughlin et al. (2015) is roughly comparable with reviewed studies testing those with current OCD diagnoses only, although it should be noted that the standard deviation is larger and likely reflects less-symptomatic individuals who might not meet full OCD criteria. That said, given that most participants in the OCD group are likely reporting significant symptoms, McLaughlin et al. (2015) appears to be more accurately described as testing a clinical, rather than an analogue, OCD group.

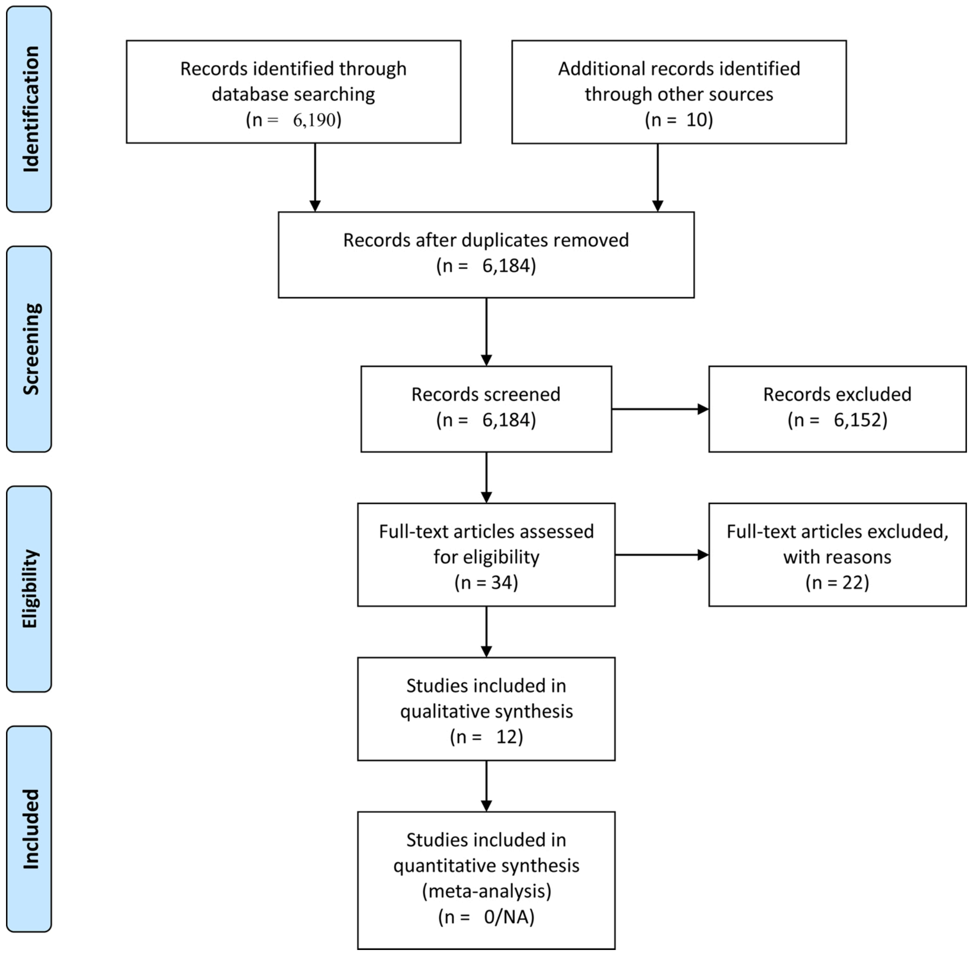

Fig. 2. PRISMA flow diagram.

magnetic resonance imaging [fMRI]) results. These studies' neuroimaging results are separately discussed in a subsequent section (see 3.2.3 Functional Neuroimaging Studies).

3.2.1. *Acquisition of Behavioral CRs*

Of the twelve identified studies, seven report at least one significant acquisition deficit or impairment related to OCD (see Table 1). One of these studies, conducted by Nanbu et al. (2010), was a single-cue study that used a shock US and measured SCR as one conditioning index. There were no between-group differences in SCR indices for the CS+ during the acquisition phase. The other single-cue study (Tracy et al., 1999) used eyeblink conditioning (air-puff US and eyeblink CR). There was a significant between-group difference at acquisition, with those higher on a composite of OCD-related traits more rapidly acquiring CRs to the CS+ (i.e., response potentiates within first few trials) compared with participants lower on these traits. However, more rapid acquisition might not correspond to a maladaptive or abnormal response (e.g., Cook et al., 1985; Rescorla, 1988). Thus, it is not clear if this finding can be considered an OCD-associated acquisition deficit. Tracy et al. (1999) also did not find between-group differences in the strength of the CRs. Considering both single-cue studies together, they do not appear to provide strong evidence for enhanced acquisition related to OCD. For a detailed description of the drawbacks of single-cue designs, see Lissek et al., 2005.

Three studies (Geller et al., 2017, 2019; McGuire et al., 2016) tested children with OCD (ages 7-18). These studies used a differential (CS+ and CS-) conditioning design with neutral female faces as CSs and an auditory scream as the US. Geller et al. (2017) reported significantly greater SCRs to the CS+ in those with OCD compared with control participants. Using the same design, McGuire et al. (2016) reported a positive correlation between a dimensional scale of OCD symptoms and SCR to the CS+. However, Geller et al. (2019) did not find a significant correlation between a dimensional OCD symptom measure and acquisition indices, which is inconsistent with the McGuire et al. (2016) correlational findings. A possible explanation is related to McGuire et al. (2016) including both those with and without an OCD diagnosis in their correlational analyses. In contrast, the sample in Geller et al. (2019) was only comprised of children who met criteria for OCD during testing. Reported OCD symptom scores had relatively moderate variance and therefore possibly limited range. Thus, attenuated range of and decreased variance in OCD symptom scores in Geller et al. (2019) might have impacted the strength of the association.

In a study of adults with OCD, Apergis-Schoute et al. (2017) used mildly angry male faces as CSs, a shock as the US, and SCR as one index of differential conditioning. In this study, early trials and late trials of the acquisition phase were analyzed separately. Those in the OCD group showed poorer discrimination (i.e., smaller differential SCRs between CS+ and CS-) compared with the control group during later, but not earlier, acquisition trials. Poor discrimination is sometimes taken to reflect a failure to learn safety signals relative to threat and is more characteristic of anxiety-related disorders than single-cue reactivity (Duits et al., 2015; Lissek et al., 2005). Their follow-up analyses showed that this effect was driven by greater responding to the CS+ in the OCD group relative to controls, indicating that safety learning was not necessarily aberrant in the OCD group.

Two studies conducted by Milad and colleagues (McLaughlin et al., 2015; Milad et al., 2013), as well as studies by Fyer et al. (2020) and Giménez et al. (2020), also tested adults with OCD using a shock US.

Table 1
Characteristics and primary results of N = 12 studies included in systematic review.

		Participants and Clinical Characteristics						Paradigm									Primary Significant Results (by Phase)	
No.	Study Name	N (OCD/ Control)[a]	Age Range	Clinical Status	Primary Diagnostic, Symptom, and Trait Assessments	Diagnostic Comorbidities Allowed?	Medications	Design	ACQ (Day 1)	EXT (Day 1)	REC (Day 2)	REN (Day 2)	CSs / CTXs	US	CS - US contingency	CR Measure	Behavioral	Functional Neuroimaging
1	Apergis-Schoute et al., 2017	43 / 35	Adult	Clinical	**Diagnostic:** MINI **Symptom:** YBOCS	No	Majority SSRI, also benzodiazepines, atypical antidepressants, antipsychotics	Differential cue	✓	✓[b]			2 mildly angry male faces	shock	33%	SCR, fMRI	**ACQ:** elevated SCR to CS+ in OCD during later trials. **Reversal:** elevated SCR to CS+ in OCD continues after reversal (when former CS+ is extinguished).	<u>CS+>CS- contrasts</u> **ACQ:** OCD > Control in vmPFC during first half. Increased functional connectivity between vmPFC and salience network in OCD. **Reversal:** OCD > Control in left caudate and left insula during second half.
2	Armstrong and Olatunji, 2017	32 / 30	Adult	Non-clinical	**Trait:** PI (contamination subscale)	Not assessed	Not assessed	Differential cue	✓	✓			2 neutral male faces	disgust images	100%	Retrospective disgust and US expectancy ratings	**ACQ:** elevated disgust ratings to CS+ in higher OCD trait group. **EXT:** elevated disgust ratings to CS+ in higher OCD trait group continues after extinction training. US expectancy ratings do not change from acquisition ratings in high OCD trait group.	
3	Fyer et al., 2020	41/64	Adult	Clinical	**Diagnostic:** DSM[c] **Symptom:** YBOCS	Yes	Unmedicated	Differential cue-in-context	✓	✓	✓	✓	2 lamp color pictures / 2 rooms	shock	67%	SCR	**ACQ:** elevated SCR to CS- in OCD across the entire phase. Elevated SCR to CS+ in OCD for specific trials. **EXT:** none **REC:** none. **REN:** poorer (larger) SCR discrimination in the OCD group.	
4	Geller et al., 2017	39 / 41	Youth (8-18)	Clinical	**Diagnostic:** KSADS-PL **Symptoms:** CY-BOCS	Yes	SSRIs only	Differential cue	✓	✓			2 neutral female faces	scream + fearful face	80%	SCR	**ACQ:** elevated SCR to CS+ in OCD. **EXT:** continued elevated SCR to CS+ in OCD.	

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Table 1 (*continued*)

		Participants and Clinical Characteristics						Paradigm									Primary Significant Results (by Phase)	
No.	Study Name	N (OCD/ Control)[a]	Age Range	Clinical Status	Primary Diagnostic, Symptom, and Trait Assessments	Diagnostic Comorbidities Allowed?	Medications	Design	ACQ (Day 1)	EXT (Day 1)	REC (Day 2)	REN (Day 2)	CSs / CTXs	US	CS - US contingency	CR Measure	Behavioral	Functional Neuroimaging
5	Geller et al., 2019	64 / 0	Youth (7-17)	Clinical	**Diagnostic:** KSADS-PL **Symptoms:** CY-BOCS	Yes	Majority SSRI, also stimulants and antipsychotics	Differential cue	✓	✓			2 neutral female faces	scream + fearful face	80%	SCR	**ACQ:** none. **EXT:** none.	
6	Giménez et al., 2020	17/13	Adult	Clinical	**Diagnostic:** SCID **Symptom:** YBOCS	Yes	SSRIs only	Differential cue-in-context	✓	✓	✓		3 lamp color pictures / 2 rooms	shock	60%	SCR	**ACQ:** none. **EXT:** none.	
7	Kaczkurkin and Lissek, 2013	28 / 31	Adult	Non-clinical	**Symptom:** OCI-R **Trait:** OBQ	Not assessed	Not assessed	Differential cue	✓[d]				large/small rings + intermediary rings	shock	75%	FPS, online risk ratings	**ACQ:** none. **Generalization:** elevated generalization of FPS in higher OCD trait group.	
8	McGuire et al., 2016	19 / 22	Youth (7-17)	Clinical	**Diagnostic:** KSADS-PL **Symptoms:** CY-BOCS	Yes	Majority SSRI, also benzodiazepines, stimulants, antipsychotics	Differential cue	✓	✓			2 neutral female faces	scream + fear face	80%	SCR	**ACQ:** OCD symptoms positively correlated with SCR to CS+ **EXT:** elevated SCR to CS+ in OCD group.	
9	McLaughlin et al., 2015	31 / 18	Adult	Clinical[e]	**Diagnostic:** SCID **Symptom:** YBOCS	Yes	SSRIs only	Differential cue-in-context	✓	✓	✓	✓	2 lamp color pictures / 2 rooms	shock	100%	SCR	**ACQ:** none. **EXT:** none. **REC:** poorer (larger) SCR discrimination in the OCD group. Poorer (smaller) % of extinction training retained in OCD group. **REN:** none.	
10	Milad et al., 2013	21 / 21	Adult	Clinical	**Diagnostic:** SCID **Symptom:** YBOCS	Yes	Majority SSRI, also benzodiazepines, atypical antidepressants, antipsychotics	Differential cue-in-context	✓	✓	✓		3 lamp color pictures / 2 rooms	shock	60%	SCR, fMRI	**ACQ:** none. **EXT:** none. **REC:** poorer (larger) SCR discrimination in the OCD group. Poorer (smaller) % of extinction training retained in OCD group.	<u>CS+ > CS- contrasts</u> **ACQ:** OCD < Control in caudate, hippocampus, vmPFC. **EXT:** OCD < Control in vmPFC. **REC:** OCD < Control in cerebellum, PCC, putamen, vmPFC.
11	Nanbu et al., 2010	39 / 21	Adult	Clinical	**Diagnostic:** SCID **Symptom:** YBOCS	No	SSRIs only	Single-cue cue	✓	✓			lightbulb on/ off	shock	100%	SCR, EEG (P50 ERP)	**ACQ:** none. **EXT:** none.	**ACQ:** none. **EXT:** elevated P50 ratio in OCD group.

(*continued on next page*)

Table 1 (*continued*)

No.	Study Name	Participants and Clinical Characteristics						Paradigm									Primary Significant Results (by Phase)	
		N (OCD/ Control)[a]	Age Range	Clinical Status	Primary Diagnostic, Symptom, and Trait Assessments	Diagnostic Comorbidities Allowed?	Medications	Design	ACQ (Day 1)	EXT (Day 1)	REC (Day 2)	REN (Day 2)	CSs / CTXs	US	CS - US contingency	CR Measure	Behavioral	Functional Neuroimaging
12	Tracy et al., 1999	20 / 22	Adult	Non-clinical	**Symptom:** MOCI	Not assessed	Not assessed	Single-cue	✓	✓			lightbulb on/ off	air-puff	90%	eyeblink	**ACQ:** quicker acquisition of CR to CS+ in higher OCD trait group. **EXT:** none.	

Abbreviations: ACQ = acquisition; CS = conditioned stimulus; CS+ = conditioned threat cue; CS- = conditioned safety cue; CR = conditioned response; CTX = context; CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale; DSM = Diagnostic and Statistical Manual; EEG = electroencephalography; ERP = event related potential; EXT = extinction training; fMRI = functional magnetic resonance imaging; FPS = fear potentiated startle; KSADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime; MINI = Mini International Neuropsychiatric Inventory; MOCI = Maudsley Obsessional Compulsive Inventory; OBQ = Obsessive Beliefs Questionnaire; OC = obsessive-compulsive; OCD = obsessive-compulsive disorder; OCI-R = Obsessive-Compulsive Disorder - Revised; PCC = posterior cingulate cortex; PI = Padua Inventory; REC = extinction recall; REN = extinction renewal; SCR = skin conductance response; SSRI = selective serotonin reuptake inhibitor; US = unconditioned stimulus; vmPFC = ventromedial prefrontal cortex.

[a] Here, OCD refers to both diagnosed OCD and groups designated as OCD-analogues (e.g., high OCD traits or symptoms).
[b] Extinction training in the context of a Reversal phase (i.e., in addition to omission of US with CS+ presentations, previous CS- is now paired with the US).
[c] OCD diagnosis established using DSM criteria by a clinician as part of the study assessment or by medical record.
[d] A generalization phase followed the acquisition phase for this study.
[e] Includes participants with either lifetime or current OCD diagnoses.

These four studies employed cue-in-context designs, with lamp colors as the cue CSs and pictures of different rooms used as contexts. Three of these studies did not find differences in conditioned SCRs between OCD and control groups during the acquisition phase. The exception was Fyer et al. (2020), which found significantly greater SCR to the CS- in the OCD group compared with control participants across the whole acquisition phase. When breaking this down at the trial level, however, CS+ responses to all but the initial trial are *greater* in the OCD group compared with the control group. The mixed nature of the findings from this set of studies, with the majority failing to find significant between-group acquisition differences, accords with earlier studies using this cue-in-context task in post-traumatic stress disorder (PTSD) or other anxiety-related disorders that did not find any differences in acquisition-related SCRs between disorder and comparison groups (e.g., Milad et al., 2009; Shvil et al., 2014).

No differences during acquisition were observed in fear-potentiated startle (FPS; a measure of central nervous system-mediated defensive responding; Davis, 1992) or subjective ratings of risk of shock between individuals characterized as high or low on OCD symptoms and related traits (Kaczkurkin and Lissek, 2013). This study followed the acquisition phase with a second phase that introduced generalization stimuli (GSs; in this study represented by rings of intermediary sizes between the CS+ and CS- sizes), along with continued presentation of CS+ (intermittingly reinforced to prevent extinction) and CS- trials. Those with high levels of OCD-related threat overestimation demonstrated higher FPS, but not risk ratings, to the GSs most resembling the CS+ (i.e., fear generalized from the CS+ to the most visually similar stimuli) compared with those low on this OCD-related trait. The process of acquiring fear to GSs overlaps with the process of CS+/CS- discrimination and is mediated by shared neurocircuitry (Hermans et al., 2013; Lissek, 2012). Accordingly, these generalization results can be interpreted as poorer discrimination learning in those with elevated levels of an OCD-related threat overestimation. They are also roughly comparable to other results in the current review that found poorer discrimination learning associated with OCD.

Armstrong and Olatunji (2017) employed a differential cue design using neutral male faces as CSs and disgust-related images as US.[2] Although disgust is a core emotion involved in OCD pathology (e.g., Cisler et al., 2009; Olatunji et al., 2007a,b), there are only two studies examining disgust conditioning within the broad context of OCD-related constructs (Armstrong and Olatunji, 2017; Olatunji et al., 2017), with only one meeting our inclusion criteria. In Armstrong and Olatunji (2017), groups were constructed based on a dimensional measure of contamination concerns (a preoccupation with becoming infected or dirtied by outside contaminants that has been strongly linked to OCD pathology; Brady et al., 2010), with a higher scoring group framed as an analogue-OCD group. The CRs were ratings of subjective level of disgust for the CS as well as expectancy for receiving the US. Ratings were collected after each phase instead of concurrently collected during conditioning. Participants with higher contamination concerns rated the CS+ as significantly more disgust-provoking than those in the lower group. Although this result superficially aligns with other findings of enhanced CRs to the CS+ in OCD, caution should be taken in considering this an equivalent finding due to the nature of the CR measurement in this study (a retrospective, single-trial report of perceived disgust). There were no group differences in US expectancy, which was

[2] The use of disgust-conditioning differentiates Armstrong and Olatunji (2017) from the other reviewed studies, which primarily test fear-conditioning. Conditioning differences between the two emotions have been directly compared and were found to share many of the same neural circuitry (Klucken et al., 2012), and affective responses to fear vs. disgust stimuli were mostly similar in an OCD sample (Schienle et al., 2005). Thus, we contend that disgust- and fear-conditioning sufficiently overlap for the purposes of the current review.

interpreted as indicating that cognitively-mediated processes (compared with the purportedly affective process that the disgust rating represents) are not aberrant in those with higher contamination concerns. As only one of the other reviewed studies included a comparable dependent variable (online US risk ratings in Kaczkurkin and Lissek, 2013), it is difficult to ascertain if this reflects a difference between disgust and fear conditioning.

Altogether, there is mixed evidence in the literature that OCD is associated with abnormal acquisition of conditioned fear. In the acquisition phase in single-cue and differential conditioning designs, the relationship between the CS+ and US is mostly unambiguous and a CR represents a normative response to a threat cue. Therefore, it is possible that mixed findings emerge due to a greater chance of uniform responding across all participants irrespective of diagnostic status or symptoms (i.e., a strong situation, see Lissek et al., 2006). In extinction procedures, the CS+-US contingency becomes more ambiguous due to the omission of the US, and therefore performance on extinction measures are perhaps better suited to detect meaningful differences between OCD and control groups.

3.2.2. *Extinction of Behavioral CRs*

Eleven of twelve studies included an extinction learning phase immediately after acquisition on the same day (see Table 1). On the day after initial testing, four studies included an extinction recall test, and two of these also included an extinction renewal test. We first review single-day studies that only tested extinction learning and then review the subset of two-day studies that tested extinction learning and then extinction recall (and renewal, for some) the next day.

3.2.2.1. Single-Day Studies of Extinction Learning. Neither single-cue conditioning study found behavioral differences during extinction learning between OCD and control groups (Nanbu et al., 2010; Tracy et al., 1999). Prior research that directly compared single-cue to differential extinction learning observed relatively quick and robust behavioral CR decreases in the single-cue condition (Norrholm et al., 2008) compared with the differential condition. The single-cue design might therefore not provide enough variance in extinction learning CRs to detect OCD-control group effects.

In studies of children with OCD, two studies identified extinction learning abnormalities related to OCD pathology. In McGuire et al. (2016), the OCD group maintained higher SCRs to the CS+ (similar in magnitude to the level of SCRs to the CS+ during the acquisition phase) throughout the extinction learning phase compared with control participants, which suggested a failure to extinguish. Additionally, both groups showed relatively poor discrimination between CS+ and CS-, but control participants showed slightly less discrimination than those with OCD and also demonstrated lower CRs to both stimuli. Unlike in acquisition, stronger discrimination is indicative of impaired learning during extinction learning, as the CR is expected to diminish over the course of the extinction learning phase. The authors suggested that maintaining a CR to both the CS+ and CS- is related to participants' belief that the US contingency will switch from one CS to the other, which has been observed in past conditioning studies in children (e.g., Jovanovic et al., 2014). Geller et al. (2017), which used the same task, also concluded that extinction learning is impaired in OCD. One subtle distinction between Geller et al. (2017) and McGuire et al. (2016) is that the former found a Group x Stimulus effect for the entire extinction phase, whereas the latter only found a group difference in later trials. Finally, Geller et al. (2019) did not find any evidence of impaired extinction learning in children with OCD.

Apergis-Schoute et al. (2017) used a reversal learning design following the acquisition phase, and therefore this study is comparable to other studies using standard extinction learning designs. In reversal learning, the acquisition CS+ is no longer paired with the US (i.e., it is extinguished), while at the same time, the previously unpaired CS- is now paired with the US. As measured by SCR, participants with OCD were impaired at learning the new associations for the CS+ and CS- relative to control participants, with the OCD group showing decreased discrimination between the CS+ and CS- across the entire reversal phase. These reversal learning results align with the other reviewed results that implicate impaired extinction learning is associated with OCD. Additionally, reversal learning involves both extinction learning and acquiring fear to a previously safe stimulus and is conceptualized as a probe of flexible learning (Schiller et al., 2008). Accordingly, a deficit in reversal learning in OCD potentially indicates that the ability to adjust responding to new fear and safety information in a flexible manner is impaired in the disorder, as shown previously in PTSD (e.g., Homan et al., 2019).

The single available study of disgust conditioning (Armstrong and Olatunji, 2017) reported impaired extinction learning in a sample with elevated OCD-related traits. Specifically, a group with elevated contamination concerns demonstrated impaired extinction relative to a group with lower contamination concerns on measures of disgust and US expectancy. US-expectancy ratings were overall elevated for the higher group, whereas disgust ratings were specifically elevated for the CS+ relative to the CS-. Further, the change in US-expectancy for the CS+ from acquisition to extinction was significantly smaller for the higher group; this effect was not observed for disgust ratings. Notably, ratings were collected retroactively after the extinction phase. These results align with extinction results from the reviewed studies using non-disgust USs, albeit with dependent measures collected retrospectively following extinction. An additional consideration for interpretation of disgust learning data is the possibility that non-classical conditioning processes contributed to extinction results. Evaluative conditioning (learning to like or dislike a stimulus; De Houwer et al., 2001) is implicated in disgust learning (e.g., Olatunji et al., 2009) and is more resistant to extinction procedures than classically conditioned fear (e.g., Blechert et al., 2008; Olatunji et al., 2007a,b; Vansteenwegen et al., 2006). If interpreting through the lens of evaluative conditioning, difficulty extinguishing in the higher contamination group might reflect an initially acquired dislike of the CS+, as opposed to any specific difficulty with classical extinction that is explicitly linked with individual differences in contamination concerns. Although we cannot confirm this explanation or not, given that Armstrong and Olatunji (2017) did not collect evaluative ratings, it remains a viable alternative explanation and caution is recommended when synthesizing these results with fear conditioning studies of OCD.

3.2.2.2. Two-Day Studies of Extinction Learning and Recall. All the reviewed two-day studies (Fyer et al., 2020; Giménez et al., 2020; McLaughlin et al., 2015; Milad et al., 2013) applied a cue-in-context paradigm to adults with OCD. These studies included a second day of testing to test for recall of the extinction memory. Compared with immediate testing of extinction learning, extinction recall tests provide insight into the *retention* of extinction learning, which is often impaired in anxiety-related disorders (Milad and Quirk, 2012). In these cue-in-context designs, the context for both extinction learning and extinction recall incorporated the same background picture (referred to as an ABB design).

None of these four studies found evidence for extinction learning deficits in OCD, and all reported significant extinction results were found during day-two testing. In Milad et al. (2013), impaired extinction recall was operationalized with two metrics: differential SCRs between the CS+ and CS- across the first two recall trials, and an "extinction retention index" that quantified extinction recall as the magnitude of SCR during recall relative to initial extinction. Higher values on this index indicated increased maintenance of extinction learning. In this study, differential SCR analyses yielded limited evidence for impaired extinction recall in the OCD group, which showed overall greater SCR during this phase, but without a significant difference in CS+ vs. CSmagnitudes. In a group comparison, the extinction retention index showed that the OCD group failed to maintain initial extinction levels relative to the control group. Conversely and surprisingly, improved extinction retention was positively correlated with the degree of OCD symptom severity, which was at odds with the hypothesis that extinction learning would not persist in those with OCD. The study by McLaughlin et al. (2015), which also assessed extinction recall, replicated the primary group difference findings from Milad et al. (2013). However, in this study, extinction retention index scores were not significantly correlated with OCD symptom scores, which is different from Milad and colleagues' (2013) findings. Extinction recall differences in Fyer et al. (2020) were limited to significant differential SCR responding, with elevated CS+ responses, for a subset of trials within the OCD group. This pattern was not seen within the control group, but the direct statistical comparison between the two groups was not significant. Similarly, the extinction retention index was not significantly different between groups. The remaining study, Giménez et al. (2020), did not find any significant between-group differences during the extinction recall phase. The mixed nature of extinction recall and retention results here is reminiscent of a broader pattern in the literature, particularly as recall and retention processes relate to individual differences (Lonsdorf et al., 2017; Lonsdorf and Merz, 2017). Also notable is that operationalization of recall and retention varies across studies, most notably in regards to the number of trials that are analyzed. Inconsistent operationalization of recall and retention are identified as contributing to ambiguity and failure to replicate across studies (Lonsdorf et al., 2019).

McLaughlin et al. (2015) and Fyer et al. (2020) included an additional phase after extinction recall that tested contextual fear renewal (i.e., return of CR related to an incidental change in context without reintroducing the US; Bouton, 2004). During renewal, the background context was the same as the one used during the acquisition phase (referred to as an ABA renewal design). Fyer et al. (2020) found the OCD group demonstrated significantly greater CS+/CS- differential SCRs compared with the control group, with CS+ SCRs in the OCD group consistently elevated across the entire renewal phase. Conversely, there were no group differences in renewal in McLaughlin et al. (2015), as both groups demonstrated similarly elevated SCRs to both CS+ and CS- during early trials that gradually decreased. A possible explanation for the inconsistent group differences in renewal is that context at test was the same background used when the CS was paired with shock, which might generate a heightened expectation of threat in both groups that weakens the potential between-group difference. For this reason, additional research on fear renewal in OCD is warranted that perhaps compares contextual renewal in a novel environment (referred to as an ABC renewal design) rather than in the acquisition or extinction context (for reviews, see Bouton, 2002; Vervliet et al., 2013a). It is also important to note that the OCD group in McLaughlin et al. (2015) was less symptomatic than in Fyer et al. (2020) and that participants all had a lifetime, but not necessarily current, OCD diagnosis. Accordingly, it is possible that significant renewal differences are contingent on higher severity of current OCD symptoms.

3.2.3. Functional Neuroimaging Studies

To date, only three studies have used functional neuroimaging to examine associative fear learning processes in OCD. Neuroimaging of OCD, at a broader level, has tended to focus on a set of orbitofrontal-striatal interactions (or "fronto-striatal loops") that operate in parallel function and appear dysregulated in OCD (Breiter and Rauch, 1996; Graybiel and Rauch, 2000; Menzies et al., 2008; Saxena and Rauch, 2000). These circuits contribute to a broad suite of behavioral control functions and consist of projections from orbitofrontal regions associated with a range of higher-order operations, such as affect regulation (e.g., ventromedial prefrontal cortex [vmPFC]) and executive functioning (dorsolateral prefrontal cortex [dlPFC]), to striatal reward and action regions (e.g., nucleus accumbens, caudate, putamen), which then project back to the frontal regions via the thalamus (Alexander et al., 1986). These regions have also been meta-analytically implicated as underlying emotional processing aberrations in other anxiety-related disorders (Etkin and Wager, 2007). Milad and Rauch (2012) linked the fronto-striatal model of OCD to a fear-conditioning neural model that centers on the amygdala, hippocampus, and dorsal anterior cingulate cortex (dACC) (Fullana et al., 2018; Milad et al., 2007). This aligns with meta-analytic findings that regions implicated in fear extinction, namely the amygdala and ACC (data was insufficient to implicate the dACC subdivision), are impaired in OCD (Thorsen et al., 2018).

Milad et al. (2013) found that during acquisition, participants with OCD demonstrated decreased fMRI activity (relative to control participants) to the CS+ (relative to the CS-) in the hippocampus, caudate, and vmPFC. All these regions are involved in fear conditioning, with the vmPFC receiving particular attention due to its relation to safety learning (Milad and Quirk, 2012). During extinction, vmPFC activity to the CS+ (relative to CS) remained lower for the OCD group relative to control participants. The extinction recall stage yielded the strongest collection of findings in favor of deficits related to OCD: the vmPFC was hypoactive in OCD relative to control participants, as were the cerebellum (implicated in behavioral response related to conditioning processes, e.g., Thompson and Steinmetz, 2009), the putamen region within the striatum, and the posterior cingulate cortex (a region implicated in mediating internally-focused cognition and found to be related to impaired inhibition in OCD, e.g., Del Casale et al., 2011; Leech and Sharp, 2014).

Apergis-Schoute et al. (2017) also employed fMRI and found vmPFC hyperactivity in the OCD group in response to the CS+ (relative to CS-) in the first, but not the second, half of the acquisition phase. This finding is striking because one of the most consistent findings from univariate contrasts of differential fear conditioning in fMRI is greater activity to the unpaired (i.e., safe) CS- versus the CS+ (i.e., CS- > CS+) in healthy adults (Fullana et al., 2016). That the OCD group exhibited the opposite result (i.e., CS+ > CS-) indicates an absence of safety signaling in the vmPFC, at least during early learning as participants attempted to learn which CS predicted danger and which CS predicted the absence of danger. Task-related functional connectivity analysis during early acquisition, using the vmPFC as the seed region, revealed multiple areas within the functionally-defined salience network (Uddin, 2015) were more strongly co-activated in the OCD group on CS+ trials. These areas included dACC, bilateral insula, and right thalamus. Stronger task-related connectivity between vmPFC and these salience network nodes in participants with OCD was interpreted as biased processing towards threat at the expense of safety processing. During late reversal, the left caudate and left insula tracked the new CS+ better in the control group than in the OCD group. These results highlight that OCD is characterized by impaired fear and safety updating in brain regions putatively involved in tracking the threat and safety value of conditioned stimuli.

Nanbu et al. (2010) used EEG in conjunction with auditory probes to measure P50 event-related potentials as a CR. The P50 response is indexed during CS+ presentations by calculating the response ratio between an initial and subsequent auditory probe. The P50 is interpreted as a deficit in sensory-gating processes and proposed to index enhanced cue conditioning. There were no between-group differences in the P50 ratio during acquisition. However, during extinction, participants with OCD had significantly higher P50 ratios on CS+ trials compared with control participants. This difference was interpreted as increased difficulty inhibiting sensory processing during extinction for those with OCD, which the authors link to poor inhibition of intrusive thoughts and obsessions.

4. Discussion

Based on this review of the literature of fear conditioning and extinction in OCD, results implicate mixed evidence for impaired fear acquisition but compelling evidence for impaired extinction in OCD.

Acquisition and extinction deficits were apparent across different types of self-report, behavioral, and neurobiological indicators. Amassed results also suggest that these deficits are detectable in both children and adults with OCD, in sub-clinical OCD and analogue groups, and are associated with symptom-level features of the disorder. Limited evidence also supports the assertion that conditioning deficits are not limited to fear-related processing (as a single study tested disgust conditioning). However, this is a tentative conclusion, and more research is warranted, as we discuss below.

4.1. Tentative Evidence for Increased Acquisition of CS+ Response in OCD

Overall, evidence for acquisition deficits in OCD is mixed. Six out of twelve studies reported behavioral evidence and two studies reporting neuroimaging evidence in support of an OCD-associated deficit. Additionally, the specific form of acquisition deficit was not consistent across studies. This heterogeneity in results suggests that impaired acquisition is only weakly associated with OCD, at least in the context of relatively simple conditioning tasks. A defensive CR is also a normative response to impending threat during acquisition, and thus only a notably and consistently elevated response would likely differentiate an anxiety-related disorder sample from the rest of the population.

The most consistent OCD-associated pattern to emerge from these results was increased CR magnitude to the CS+ without a corresponding increase in CS- response. This specific pattern has been related to the concept of enhanced conditionability (most often discussed in conjunction with PTSD, see Lissek and van Meurs, 2014; Orr et al., 2000). Enhanced conditionability, which broadly refers to a between-subjects difference in speed and magnitude of CS+ acquisition, is not an ideal description for the reviewed results because only one set of results provide evidence of more rapid CS+ acquisition in OCD (Tracy et al., 1999). Speed of acquisition was either not tested in the other studies or did not differ by group. That said, abnormally elevated CS+ responding (irrespective of speed of acquisition) could be consistent with the clinical phenomenology of obsessions in OCD. There is strong evidence that pervasive and repetitive thoughts are common for everyone, not just those who have or go on to develop OCD (García-Soriano et al., 2011; Fullana et al., 2009), which suggests that the mere presence of these types of thoughts are not sufficient for the development of the severe obsessions that are characteristic of OCD. Therefore, an increased tendency to form stronger aversive associations might promote the conversion from normal to maladaptive intrusion/obsession and thus act as both predisposing risk factor and key pathogenic mechanism of OCD. Put another way, two people might have the same intrusive thought over a period of days, but the one who responds with greater distress is more likely to have the intrusion develop into a full obsession and thus develop OCD.

Also consistent with a pattern of increased CS+ responding in OCD are results from a quasi-experimental self-report study that found a general cognitive tendency (indexed by measures of different dysfunctional beliefs) towards overestimating threat in the disorder (for review, see Hezel and McNally, 2016). That said, none of the currently reviewed studies found evidence for increased CS+ responding on more cognitively mediated measures, such as US expectancy or risk ratings, although these measures weren't assessed in each study. In general, based on the empirical research, it is premature to integrate evidence of broad belief patterns with the physiological and neuroimaging evidence reviewed here. Further, a pattern of increased CS+ responding in differential conditioning paradigms also diverges from some non-conditioning experimental work in OCD. This body of work consistently finds that inhibitory or regulatory, but not excitatory, processes differentiate those with OCD from those without (for reviews, see Cavedini et al., 2006; Milad and Rauch, 2012) and would suggest that CS- responding would also differentiate OCD from control groups. The only reviewed study that aligned with this pattern was Fyer et al. (2020).

In terms of neuroimaging results, the only notable acquisition finding was poorer discrimination between CS+ and CS- in those with OCD within the hippocampus, caudate, and vmPFC in the study by Milad et al. (2013). Although these results do not necessarily contradict the findings of increased CS+ responding as seen in the behavioral data, they also do not explicitly support those findings. That is, poorer discrimination between the CS+ and CS- in OCD does not imply increased activity to the CS+ in these regions relative to control groups. Additionally, the vmPFC is more often associated with safety/inhibitory learning, rather than threat acquisition, in the context of fear conditioning protocols (Fullana et al., 2016).

4.2. Stronger Evidence for Extinction Deficits in OCD

OCD was associated with some form of extinction deficit, either during extinction learning, recall, or contextual renewal, in nine of the eleven studies we reviewed that tested extinction processes. The most prominent findings were that those with OCD showed elevated CRs during extinction and poor discrimination during extinction recall. Of note is that the two of the three studies that did not report significant group differences or symptom associations during extinction learning (Geller et al., 2019; Tracy et al., 1999) also employed relatively atypical designs compared with the other reviewed articles. Geller et al. (2019) tested dimensional relations within a group of children with OCD and did not include a group of children without OCD symptoms. Tracy et al. (1999) used eyeblink conditioning, which is different in many ways from standard delay conditioning designs. The third study which did not find any form of extinction deficit, Giménez et al., 2020, was published as a pilot study and had the smallest N of all the reviewed studies (17 OCD, 13 control). Thus, the amassed evidence for extinction deficits in OCD is relatively consistent when considering the limited number of available studies and the limitations of the studies that did not find significant extinction differences.

Although significant extinction abnormalities related to OCD were found in most of the reviewed studies, the particular form of the extinction deficit and if the deficit was during initial extinction learning or during extinction recall was not entirely consistent. Specifically, there is a discrepancy between the studies using cue-only conditioning and those using a cue-in-context conditioning design. In terms of the cue-only studies, most analyzed extinction as a function of time (e.g., trial-by-trial or first half vs. second half) and found that those with OCD demonstrated larger CRs to the CS+, compared with control participants, during the later trials of extinction. The normative response reflective of full extinction is for CRs to reach floor for both the CS+ and CS- by the later trials of extinction (e.g., Bouton et al., 2006; Fullana et al., 2018). That several studies showed maintained CRs within the extinction learning session suggests the ability to adaptively regulate behavioral response is impaired in OCD despite repeated presentations of the CS+ in the absence of the US. However, the four reviewed studies using a cue-in-context design (Fyer et al., 2020; Giménez et al., 2020; McLaughlin et al., 2015; Milad et al., 2013) did not find within-session differences in extinction learning performance between OCD and control groups. Rather, the majority of these studies report group differences in SCRs between-sessions (i.e., during day-two testing). These results support the argument that a strong return of fear after initial extinction (commonly referred to as spontaneous recovery; Pavlov, 1927) is more characteristic of anxiety pathology than initial difficulty extinguishing fear (Bouton et al., 2001; Craske et al., 2011), and align with clinical observation (e.g., Furst and Cooper, 1970; Marks et al., 1969; Pitman, 1993; Rachman et al., 1970) and empirical theory and data (Craske et al., 2008; Kozak et al., 1988) indicating that successful within-session fear reduction does not necessarily correspond to sustained improvement in those with anxiety-related disorders. However, caution is recommended in interpreting extinction recall results given documented methodological inconsistencies across studies, both in this review and in the literature more broadly (Lonsdorf et al., 2019).

A possible explanation for the discrepancy between the cue-only and cue-in-context studies is that the CS-US association is partially dependent on the context in which it is learned, such that stronger CRs to the CS+ emerge in the original conditioning context. The context switch in the cue-in-context design, in which acquisition is conducted in one novel context and extinction in another, potentially weakened the CS-US association (as is seen in occasion setting studies, e.g., Bouton and Swartzentruber, 1986; Myers and Gluck, 1994) to the point that those with OCD could sufficiently extinguish their CR and resemble the control group during this phase.

Neuroimaging results from the two studies using fMRI (Apergis--Schoute et al., 2017; Milad et al., 2013) also potentially provide evidence of an extinction learning deficit in OCD. Both studies found differences in vmPFC activity during extinction between OCD and control groups, although the multiple differences in study and analytic design preclude direct comparisons. Human work based on animal models has proposed the vmPFC as a central region for extinction learning (e.g., Diekhof et al., 2011; Dunsmoor et al., 2019; Phelps et al., 2004). However, the relation between vmPFC and extinction learning is not robust, and a recent meta-analysis of 31 studies did not find the vmPFC to be related to extinction learning. Additionally, the vmPFC has also been implicated as a key point of dysfunction in non-aversive learning processes (Nielen et al., 2009) and as a central contributor to impaired decision making and error-detection in OCD (Nielen et al., 2002; Stern et al., 2011), suggesting that disrupted vmPFC engagement during extinction might reflect a global deficit in the disorder, as opposed to a fear extinction-specific abnormality. Further work is needed to more conclusively determine how vmPFC differences in OCD relate to impaired extinction processes.

An important qualifier on the reviewed extinction results is that all the studies that tested extinction learning did so immediately after the acquisition phase, as opposed to testing after a controlled delay. This design is not unique to OCD research. Most human extinction studies, both in clinical and non-clinical samples, use this design (see Duits et al., 2015; Fullana et al., 2018). However, the neural mechanisms underlying immediate extinction learning differ from those underlying delayed extinction learning (Maren, 2014). The clinical implications are different as well, as delayed extinction learning is a more accurate analogue of clinical intervention, which almost always targets a well-established fear memory given that intervention typically takes place months or years after initial fear acquisition (e.g., Hollandt et al., 2020).

4.3. Comparing Conditioning Process in OCD to Other Anxiety-Related Disorders

Over decades of conditioning studies of anxiety-related disorders, multiple studies have identified patterns of aversive conditioning deficits that appear to operate trans-diagnostically and represent core pathogenic mechanisms of these disorders. The current review affords the opportunity to compare how conditioning in OCD compares to other anxiety-related disorders. Two comprehensive meta-analyses of behavioral studies in anxiety-related disorders identified increased CS- responding during acquisition and increased CS+ responding during extinction as differentiating anxiety-related disorder groups from control groups (Duits et al., 2015; Lissek et al., 2005). In terms of acquisition, a pattern of elevated CRs to CS+, but no significant differences in CRs to CS- in all but one study (Fyer et al., 2020), distinguishes OCD from the other anxiety-related disorders. It is difficult to explain this discrepancy when considering how OCD differs from other anxiety-related disorders: OCD is perhaps the anxiety-related disorder most easily defined by difficulties with inhibition of unwanted thoughts and behaviors. Therefore, it seems likely CS- deficits would be evident. However, a crucial detail is that data showing poor inhibition in OCD is typically in terms of poor inhibition of *compulsions* (e.g., Chamberlain et al., 2005; Morein-Zamir et al., 2010). Classical aversive conditioning is assumed to map onto obsession symptoms in OCD more cleanly than compulsions. Therefore, the observed pattern of CS+ responding might not necessarily disagree with prior non-conditioning work. However, this does not explain why OCD would not show CS- acquisition deficits that are apparent in other anxiety-related disorders, and additional work to clarify this discrepancy is needed.

In contrast to acquisition deficits, the CS+ related extinction deficits that differentiated OCD from control groups are consistent with the meta-analyses that also find this pattern in other anxiety-related disorders during initial extinction training, indicating difficulty learning that the CS+ is no longer a signal for the US. Further, the finding in a subset of studies that people with OCD had particular difficulty reducing their CR to the CS+ during the final parts of extinction aligns with several studies of PTSD that obtained a similar pattern of results (for reviews, see Lissek and van Meurs, 2014; Zuj et al., 2016). In terms of extinction recall, the finding that OCD is associated with elevated return of fear compared with control participants resembles a subset of prior behavioral results, particularly those from studies of PTSD (e.g., Garfinkel et al., 2014; Milad et al., 2008; Rabinak et al., 2017). However, it should be noted that some studies fail to find recall group differences on behavioral measures in PTSD (Milad et al., 2009) or in a trans-diagnostic anxiety-related disorders sample (Marin et al., 2017). Additionally, the noted discrepancy between extinction results from the cue-only and cue-in-context studies align with other studies failing to find initial extinction learning deficits in PTSD (Garfinkel et al., 2014; Marin et al., 2017; Milad et al., 2008, 2009; Shvil et al., 2014). Prior reviews have suggested that these discrepancies in the PTSD data emerge from cross-study methodological difference and overall weak or inconsistent underlying effects (Lissek and van Meurs, 2014; McGuire et al., 2016; Zuj et al., 2016), an explanation that could also be applied to the discrepancy observed in the currently reviewed OCD studies.

In terms of functional neuroimaging work involving aversive conditioning and extinction in clinical populations, much of this work has focused on PTSD, likely because conditioning theory remains important in contemporary models of PTSD (e.g., Bowers and Ressler, 2015; Pitman et al., 2012). A recent meta-analysis of seven studies found that PTSD was associated with a robust amygdala response across acquisition and extinction, with aberrant insula and ACC activity related to PTSD during acquisition and vmPFC during extinction (Suarez-Jimenez et al., 2019). Similar results have been found in studies of panic disorder (e.g., Kircher et al., 2013; Schwarzmeier et al., 2019) and generalized anxiety disorder (e.g., Greenberg et al., 2013), although not all anxiety-related disorders are associated with this pattern of neural results, including specific phobia (e.g., Lange et al., 2019) and social anxiety disorder (e.g., Savage et al., 2020). Relatively consistent vmPFC and ACC results from the two neuroimaging studies of conditioning in OCD suggest that, at the neural level, OCD might have more in common with PTSD and the other anxiety-related disorders characterized by vmPFC and ACC dysfunction.

4.4. Design Complexity and Improving Parallels Between Conditioning Techniques and Clinical Reality of OCD

At present, the OCD and conditioning literature is primarily comprised of studies using basic differential acquisition and extinction paradigms that use relatively unambiguous and straightforward perceptual cues and contexts. These designs have the advantage of offering more parsimonious interpretation but likely limit the ability to discern more complex and clinically relevant processes as they relate to OCD. Researchers have consistently advocated for the use of more complex conditioning designs to disentangle nuanced or difficult-to-measure emotional learning phenomena (e.g., Beckers et al., 2013; Dunsmoor et al., 2015; Gewirtz and Davis, 2000; Rescorla, 1988), enhanced detection of pathogenic markers (Lissek et al., 2006), and provide further avenues for novel treatment advances (e.g., Craske et al., 2014). In this case, increased complexity refers to experimental manipulations that potentially increase ecological validity through increasing the number and/or abstractness of stimuli, associations between stimuli, or task demands and rules. In the following sections, we consider iterations or elaborations on the basic differential design that were absent from the reviewed literature and how improving design complexity could substantially contribute to conditioning models of OCD, potentially clarify emerging patterns of results, and enhance clinical translation.

4.4.1. Conditioning Through Conceptual and Semantic Routes

Many obsessions are verbal-linguistic in nature (Knapton, 2016), and the complex and frequently abstract or bizarre contents of obsessional thought in OCD are important aspects of the pathology that can differentiate clinical obsessions from non-clinical cognitive intrusions and uncomfortable thoughts (García-Soriano et al., 2011; Rassin et al., 2007). Further, these OCD-related obsessions are distinct from the typically simpler associations that frequently occur in other anxiety-related disorders due to their elaborative and abstracted quality and the level of inductive reasoning involved in their generation. For example, consider a contamination obsession in someone with OCD. The obsession might have started with an initial observation in a bathroom that there were many sensory cues indicating the bathroom is dirty and has germs, such as unwashed floors and aversive smells. However, there is also the known function of a bathroom and the commonly expressed societal view of bathrooms as “dirty places” that contribute to this obsession, which is an abstract concept without a direct sensory correlate. Further, the person has been told that “germs can cause disease” and, even though it is statistically unlikely to contract a disease in a bathroom, catching a disease is the assumed outcome of entering a bathroom and thus a focus of the obsession. The only way for this type of cognition to develop is through abstraction and inductive reasoning, and these processes are indeed identified as related to OCD and linked to a model of obsession development (Liew et al., 2018; O’Connor, 2002; Pélissier and O’Connor, 2002). Accordingly, understanding this aspect of obsessions is crucial to furthering OCD research and increasing the ecological validity of said research. However, the reviewed studies all use conditioning paradigms that employ perceptual stimuli and test for CRs that are therefore related to more automatic, sensory-level associations and responses. The predominance of perceptual stimuli is not unexpected, as more abstract or conceptual forms of conditioning have received less empirical attention overall (for review, see Dunsmoor and Murphy, 2015), largely owing to the predominance of animal-to-human translations driving conditioning efforts in humans. This represents a notable gap in the literature and an important area for future conditioning work in OCD.

One intuitive explanation for how obsessions spread and become unbearable for people with OCD is through semantic generalization. Exposure hierarchies for OCD typically resemble a personalized list of generalized stimuli (Himle and Franklin, 2009). Given the abstract nature of many obsessions, it follows that many of the associations between these generalized stimuli are conceptual in nature. For example, a person with OCD might report that their primary obsession is about “catching germs” from dirty surfaces in bathrooms and kitchens. They then might generalize this obsession to people who work in what are considered dirty places (e.g., janitorial staff, mechanics), places that have lots of people touching multiple surfaces with different body parts (e.g., gyms), and clothing or tools that are used to negate or clean environmental hazards (e.g., face masks, mops) Although there is no perceptual overlap to account for the association between these stimuli, the conceptual association is clear: they are all indirectly related to dirt and germs, some of them quite distally.

Generalization across conceptual pathways is as yet untested in OCD, although it has been successfully implemented in non-clinical samples (e.g., Dunsmoor et al., 2012; Dunsmoor and Murphy, 2014; Vervoort et al., 2014). A recent study by Morey et al. (2020) identified PTSD-specific neural responses to novel stimuli that were part of a conditioned conceptual category (e.g., a participant has not seen a cat yet in a task, but responds fearfully because they were conditioned to fear the mammal category, of which the cat is a member) within fronto-limbic regions commonly associated with perceptual fear generalization (see Webler et al., 2021). This type of design applied to people with OCD holds promise for more precisely modeling how obsessional content and associations spread on the neural level. Further, the success of the task used by Morey et al. (2020), which uses disorder-aspecific stimuli (e.g., generic animals and tools) applied to PTSD, suggests that similar results might emerge for those with OCD even without disorder-specific conceptual categories. The use of neutral, disorder-aspecific stimuli in this type of task might help identify if overgeneralization of conceptual associations is a basic mechanism underlying OCD broadly or if it is more circumscribed to the specific type of obsession. Based on the currently reviewed studies, particularly those with neuroimaging findings, we would predict that those with OCD would also overgeneralize fronto-limbic responses across a fear conditioned conceptual category.

4.4.2. Instrumental Conditioning and Approach-Avoidance Conflicts

A fundamental understanding regarding OCD pathology is that compulsions serve to relieve distress related to obsessions, but only temporarily. In turn, this temporary relief reinforces the belief that obsessions are unbearable and that compulsions must be enacted (Meyer, 1966). The obsession-compulsion dynamic fundamentally “holds the disorder together,” and this link is the primary target of EX/RP: if you can disrupt the compulsions, then patients will learn that associated obsessions are tolerable and be less likely to enact compulsions (Foa et al., 2012; Wheaton et al., 2018). Functionally, compulsions serve as a form of avoidance (McGuire et al., 2012), which fits with research that finds avoidance of emotionally salient material is a primary maintenance factor that prolongs many forms of psychopathology (e.g., Borkovec et al., 2004; Hayes et al., 1996; Pittig et al., 2018; Salters-Pedneault et al., 2004). Putting obsessions and compulsions together, we see that they cleanly fit into Mowrer’s influential two-factor theory of anxiety (Mowrer, 1939, 1947, 1951), in which avoidance of a threat cue results in relief that serves as a motivator for future avoidance and prevents opportunities to learn that a feared stimulus is not dangerous. Importantly, this theory links the underlying classical and instrumental (i.e., operant) conditioning processes in a functional framework that explains how the passive-emotional process of classical conditioning exerts its pathogenic influence through the behavior it motivates. Although Mowrer’s model has received criticism and its limitations have been expanded on through empirical testing (Rachman, 1976), the proposed functional relationship between the two conditioning processes remains a compelling foundation for explanatory models of anxiety-related pathology. Further emphasizing the need for instrumental conditioning studies in OCD are neural models of avoidance that implicate frontal and temporal structures implicated in OCD pathology (e.g., Bravo-Rivera et al., 2015; Rosas-Vidal et al., 2018).

Notably, none of the reviewed conditioning studies included an instrumental conditioning test (or tested compulsions with any other experimental model of avoidance) despite the applicability of Mowrer’s two-factor model and its presence in treatment-focused writings related to OCD (e.g., Franklin and Foa, 2011; Storch et al., 2007). Outside of the aversive conditioning literature, there are a handful of relevant studies of those with OCD or OCD symptoms. These include tests of habitual avoidance (Gillan et al., 2014a, 2014b), probabilistic reinforcement learning (Endrass et al., 2011; Nielen et al., 2009; Remijnse et al., 2006; Voon et al., 2015), simple operant conditioning in a non-emotional context (Hassoulas et al., 2014), and self-report studies of subjective, broadly defined avoidance tendencies (e.g., Abramowitz et al., 2009; Ettelt et al., 2008; Summerfeldt et al., 2014). Generally, the patterns of results from these studies indicate that people with OCD or higher levels of OCD-related traits describe themselves as more risk-averse and avoidant, more readily associate avoidance with negative outcomes and increased threat sensitivity, and are more likely to enact avoidance responses than comparison participants in a laboratory setting. However, none of these studies involve truly aversive USs. Therefore, we still know very little about how aversive conditioning contributes to avoidance (and vice versa) and are likely missing key information on how obsessions are associated with compulsions.[3]

An important next step is formally testing those with OCD on a task that combines classical aversive conditioning and instrumental avoidance. There is a rich history of animal studies that test these processes (e.g., Kirlic et al., 2017; Mackintosh, 1974). Human studies of instrumental avoidance have been less common compared with classical conditioning studies and, until relatively recently, had fallen out of favor in the conditioning field (LeDoux et al., 2017; Pittig et al., 2018). A recent resurgence in this area has resulted in efforts to revitalize the study of avoidance in the context of anxiety-related pathology. These efforts have also resulted in new experimental paradigms, or modifications of past paradigms, that hold great promise for the study of OCD. Perhaps the most relevant are avoidance tasks that require an active response to remove or escape the aversive outcome (analogous to enacting a compulsion) and tasks in which avoidance has an associated cost (e.g., Hunt et al., 2019; Pittig and Scherbaum, 2019; Rattel et al., 2017). Cost is a particularly important parameter to model in experimental studies of OCD, as part of the clinical definition of compulsions is that these behaviors are repeated excessively or otherwise interfere with a person's life, thus denying more valued activity. For example, some people with OCD have very strong checking obsessions and compulsions report social and romantic discord due to others accommodating the time-intensive and frequently inconvenient checking behavior of the person with OCD (e.g., Boeding et al., 2013). In other words, the "cost" of avoidant behavior is the valued outcome of relational stability. Conditioning tasks that test these situations, termed approach-avoidance conflicts or mixed outcome designs, typically involve an inherently salient reward that, when removed or lost, serves as the cost of an avoidance response and can potentially buffer against avoidance of a feared stimulus (Pittig et al., 2014, 2018). Examples of rewards used in these tasks are monetary compensation or winning a specific task and receiving points (for review, see Pittig et al., 2018).

4.4.3. *Inhibitory Learning During Acquisition and Extinction*

Although aversive conditioning is commonly used as an explanatory model for excitatory responding that results in excessive negative emotionality (e.g., a strong fear response in anxiety-related disorders), understanding how people learn to inhibit their conditioned responses has clear scientific and clinical relevance. Inhibitory learning is of particular interest to the study of OCD because of clinical conceptualizations of the disorder centrally involving failures to inhibit obsessions and compulsions, as well as consistent experimental evidence for neural abnormalities in inhibitory regions (e.g., Thorsen et al., 2018). As with excitatory learning, inhibitory learning plays a central role in both acquisition and extinction of conditioned associations. Below we discuss each separately in the context of future studies of OCD.

During the initial acquisition of an aversive association, excitatory and inhibitory information and processes simultaneously contribute to the expressed CR (e.g., Fullana et al., 2016; Krabbe et al., 2018). Thus, the CR can be seen as the result of competition between excitatory and inhibitory influences, with the stronger of the two dictating the behavioral expression for a particular CS. Although the reviewed studies suggest that CS+, but not CS-, responding during acquisition differentiated OCD groups from the control group, this does not necessarily correspond to impaired inhibitory learning in OCD. The observed CR to a CS+ or CS- is comprised of some combination of excitatory and inhibitory activity, but the exact contributions of each are not identifiable using standard differential conditioning designs (Jovanovic et al., 2005; Myers and Davis, 2004). For example, a relatively decreased CR to the CS- could be equally related to a decrease in excitatory activation or an increase in inhibitory activation. Similarly, a strong CR to a CS+ could equally be the result of a complete lack of inhibitory activation or a maximal excitatory response that has been tampered down by a moderate inhibitory response.

An elegant solution to the issue of entangled excitatory and inhibitory processes is the conditioned inhibition paradigm (Rescorla, 1969; Rescorla and Holland, 1977). This paradigm is a modification of the differential conditioning design in which some trials present the previously conditioned CS+ simultaneously alongside a novel stimulus and without US reinforcement. This novel stimulus is then combined with the CS- and other novel stimuli to measure inhibitory learning, which is operationalized as a lack of CR on these later trials. Researchers have used conditioned inhibition paradigms to measure PTSD-control differences in inhibitory responding (e.g., Jovanovic et al., 2010; Jovanovic and Norrholm, 2011; Sijbrandij et al., 2013), and this paradigm would also be a logical next step for OCD conditioning work. Despite acquisition in OCD being somewhat biased towards CS+ reactivity, we would expect that conditioned inhibition during acquisition would also be impaired in OCD relative to comparison participants and reflect the broader inhibition learning deficits – both emotional and non-emotional – that are commonly seen in the disorder (e.g., Berlin et al., 2015; Enright and Beech, 1993; Kampman et al., 2002; van Velzen et al., 2014).

Inhibitory learning during extinction is crucial to understanding the mechanisms and conditions through which a CR can decrease and eventually abate. Modern understanding of the extinction process is that through repeated presentation of the CS+ in the absence of the US, two competing memory traces are formed: the original CS+-US association and a new inhibitory memory of the CS+ without the US (Bouton, 1993, 2004). A corollary to this extinction model is that CR reductions are not necessarily solely driven by repeated exposure (habituation) to the CS+ that results in a weakening of the CS+-US association and instead also involve promotion of the competing inhibitory memory. Consequently, exposure therapy's effectiveness is not exclusively dependent on successful habituation, as initially proposed (Foa and Kozak, 1986), but is also related to the strength of new inhibitory memories and experiences (Craske et al., 2008, 2014, 2018; Tolin, 2019). Modern research on extinction learning and exposure therapy has started to center on how to harness inhibitory learning models most effectively during treatment, with OCD discussed as one disorder that would benefit from this type of work (e.g., Arch and Abramowitz, 2015; Craske et al., 2008; Jacoby and Abramowitz, 2016; Krompinger et al., 2019). Findings of OCD-related extinction deficits in the reviewed studies, as well as the need to improve upon the limitations of EX/RP, suggest that this would be a fruitful avenue of future research and a natural next step for conditioning investigations of OCD.

A potential template for future empirical studies can be found in the clinical techniques developed in line with the inhibitory learning model and based on basic science work (such as that reviewed in Dunsmoor et al., 2015), but still need validation within OCD samples. Craske et al. (2014) detailed eight techniques with strong conditioning foundations, and a review by Jacoby and Abramowitz (2016) specified four techniques that hold great promise for treatment of OCD in particular:

[3] It should also be noted that differing views on compulsions in OCD exist, such as compulsions being conceptualized as the manifestation of broad and excessive habit formation as opposed to behaviors that are enacted with a goal of avoidance (Gillan and Robbins, 2014). We acknowledge that multiple processes are likely contributing to the behavioral output of compulsions, but that at the present we cannot directly compare habit models of avoidance to conditioning models of avoidance in OCD due to the lack of studies of the latter. A recent review on this subject provides a more detailed and neurobiologically informed discussion of this issue (Geramita et al., 2020), and other reviews delineate and compare the forms and stages of avoidance more broadly (e.g., LeDoux and Daw, 2018).

expectancy violation (maximizing the discrepancy between the expected and actual aversive outcome), combining multiple fear cues/deepened extinction (increasing inhibitory learning by extinguishing two or more CS+s during extinction), maximizing contextual variability (presenting extinction in multiple contexts to promote durable and generalized CR reductions), and expanding the inter-session interval (increasing the duration between extinction trials). All these techniques have corresponding laboratory-based conditioning protocols and are ideal next steps for OCD conditioning research that builds off the reviewed studies' findings.

4.4.4. Adjuncts to Exposure Therapy and Improved Conditioning Models of OCD

Exposure techniques for OCD can be enhanced with therapeutic adjuncts from outside of the conditioning toolbox to improve effectiveness. However, the interaction between these adjunct interventions and conditioning techniques and processes is not well-studied in OCD, and results in other anxiety-related disorders or pre-clinical results are ambiguous. Improved conditioning methodology that more precisely tests clinically relevant processes in OCD could be valuable for future research on these adjunct interventions.

For example, pharmacological enhancement of extinction has been a goal for clinical researchers for decades (Fitzgerald et al., 2014). D-cycloserine (DCS), a N-methyl-D-aspartate (NMDA) receptor partial agonist, has been put forward as a potential extinction enhancer and tested in multiple clinical trials for OCD and other anxiety-related disorders. Meta-analytic results indicate that DCS has a small-to-null faciliatory effect on exposure treatment in anxiety-related disorders, with some of the smallest observed effects seen in studies of OCD (Bürkner et al., 2017; Mataix-Cols et al., 2017; McGuire et al., 2017) Other meta-analyses suggest that DCS is a viable adjunct for exposure under certain timing and dose parameters (e.g., Rosenfield et al., 2019; Xia et al., 2015). However, these meta-analyses are somewhat at odds with meta-analytic findings that DCS improves fear extinction in experimental animal and human studies (Norberg et al., 2008), and with some moderators even showing opposite effects in the clinical vs. experimental literature (e.g., fewer DCS doses enhanced extinction in experimental studies, Norberg et al., 2008, but more DCS doses enhanced exposure in clinical studies, Rosenfield et al., 2019). The questions that arise from these conflicting meta-analytic findings suggest that increased insight into the mechanisms underlying DCS and its relation to the processes underlying exposure therapy is needed. In terms of behavioral adjuncts to exposure therapy, one intriguing option is improving deliberate emotion regulation, such as reappraising or suppressing an emotional response or impetus. Evidence for emotion regulation strategies enhancing extinction (Delgado et al., 2008; Hennings et al., 2021; Wang et al., 2021) or exposure therapy (Renna et al., 2017; Wisco et al., 2013) in non-clinical and clinical populations is mixed. Accordingly, conditioning tasks that more closely align with the clinical reality of OCD and might provide more precise and ecologically valid outcomes could be valuable for future studies of DCS, emotion regulation, and other candidate pharmacological and behavioral adjuncts to exposure.

4.5. Clinical Considerations in Conditioning Studies of OCD: Assessment, Classification, and Medication

4.5.1. Assessment and Classification

Most of the reviewed conditioning studies employed the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2013) to assign a categorical OCD diagnosis. Those studies that contained dimensional symptom measures either used those measures to form analogue groups that were analyzed categorically or did not assess all participants (e.g., those designated as psychiatric controls) with these measures. Categorical diagnostic systems, including the DSM, have increasingly received intense criticism (Kotov et al., 2017; Krueger et al., 2018; Watson, 2005). As it pertains to OCD, evidence broadly suggests that OCD does not conform to the categorical DSM structure (Kotov et al., 2011; Pinto et al., 2008; Raines et al., 2015), and the DSM category for OCD is viewed as inflexible for clinical and research use (Hollander et al., 2007). Further, heterogeneity within the disorder category is problematically high (Abramowitz and Jacoby, 2015; Lochner and Stein, 2003; McKay et al., 2004) and results in the grouping together of people who drastically differ from each other in terms of the themes of their obsessions and compulsions (Baer, 1994; Leckman et al., 1997; Summerfeldt et al., 1999, 2014). Conversely, dimensional trait systems are an appropriate fit for reported OCD symptoms and psychometrically outperform categorical diagnosis of OCD while better accounting for symptom heterogeneity (see Kotov et al., 2007, 2010, 2015; Watson, 2005).

Adapting a dimensional assessment and classification approach in future conditioning studies of OCD could yield numerous benefits. At a statistical level, dimensional indices of OCD naturally yield greater variance than categorical indices. Accordingly, testing dimensional indices of OCD as a primary predictor could result in increased precision to detect subtle conditioning abnormalities related to the pathology. The use of multivariate techniques to identify latent dimensions that cut across DSM-defined OCD criteria (such as empirically identified OCD symptom dimensions or higher-order internalizing traits, e.g., Faure and Forbes, 2021) might also improve detection of relevant conditioning abnormalities related to the pathology.

Dimensional approaches also help address psychiatric comorbidities that obscure a clearer picture of psychopathology and its relations (e.g., Kim and Eaton, 2015; Kotov et al., 2017). Comorbidity, a natural consequence of a categorical classification system, creates difficulties in reliably assigning etiological or pathophysiological processes to specific categories (e.g., Krueger and Markon, 2006). In the current review, almost all the tested clinical groups contained participants who were also diagnosed with other anxiety-related disorders or mood disorders. Thus, the possibility remains that the patterns of conditioning deficits are not necessarily related to "pure" OCD but rather reflect an amalgamation of pathogenic processes in both OCD and commonly comorbid disorders. Alternatively, it is possible that the comorbidities created additional noise in an OCD-specific signal and that a more consistent pattern of conditioning deficits in OCD would emerge if comorbid presentations were excluded from tested samples. Adapting a dimensional approach could help address both of these possibilities, as each potential source of conditioning-related individual variation (e.g., OCD symptoms and traits, mood disorder symptoms and traits, etc.) could be included and tested in a statistical model.

To facilitate a more dimensional approach to OCD assessment, future studies might consider use of the Dimensional Yale-Brown Obsessive Compulsive Scale (DY-BOCS; Rosario-Campos et al., 2006). The DY-BOCS provides fine-grained OCD symptom severity subscales that are not typically derived from the standard adult or child Y-BOCS (Goodman et al., 1989, 1991) that was used in many of the reviewed studies (see Table 1). In addition to a primary interview measure of OCD symptom severity, we recommend employing an additional self-report measure when possible (e.g., Abramowitz et al., 2010; Foa et al., 2002); primarily because of documented differences in reported symptoms based on the measurement technique (Federici et al., 2010). Additionally, some OCD self-report measures are able to cover a broader range of content than interviews.

4.5.2. Medications

In the current review, the majority of studies tested OCD groups that contained participants reporting current use of psychotropic medication (see Table 1). The most frequently reported medication was the selective serotonin reuptake inhibitor (SSRI) class of antidepressants that are frequently prescribed as a first-line pharmaceutical treatment for anxiety-related disorders and show acceptable efficacy (Soomro et al., 2008). Animal work finds that acute serotonergic challenge reliably attenuates conditioned fear acquisition and extinction (for review, see Inoue et al., 2011). Human studies are less conclusive: one study found SSRI treatment facilitates extinction (Bui et al., 2013), whereas another found that use of SSRIs, along with other medications, weakened but did not eliminate significant anxiety patient-control differences in fear acquisition (Otto et al., 2014). Other common psychotropic medications used by participants in the reviewed studies, such as sedatives and beta-blockers, have also been shown to affect human fear expression (e.g., Grillon et al., 2004, 2006). Specific to OCD, there is evidence that medication usage in studies of OCD patients confounds efforts to identify reliable biomarkers of the disorder (for review, see Fullana et al., 2020); and that machine learning algorithms applied to neural data reliably distinguished between medicated and unmedicated patients with OCD at a higher rate than OCD patient vs. control (see Heuvel et al., 2020). Taken together, there is a clear need to systematically investigate medication usage in OCD within the context of conditioning studies to determine the degree and form of confounding effect. That said, we contend that restricting study participation to those with OCD who are medication-free is not the answer. In the interest of generalizability and translation, future studies would benefit from studying conditioning processes within the clinical reality of OCD, and that clinical reality frequently involves psychotropic medication.

4.6. Conclusion

Our review of conditioning studies of OCD has revealed that a small but promising body of research supports a conditioning perspective of the disorder, especially regarding extinction deficits. Current priorities in the treatment research suggest that the next wave of conditioning work in OCD would benefit from building on basic acquisition and extinction paradigms to address more experimentally complex but clinically relevant questions. We hope that with future conditioning studies, translational scientists will have a robust and detailed foundation of data on which to build the next wave of exposure treatments, as has been done in the past in regard to other anxiety-related disorders. We also anticipate that the addition of new studies to the growing OCD conditioning literature will be conducive to an eventual quantitative synthesis (e.g., meta-analysis) in the future. Although the bulk of the scientific work has likely yet to be done, we view the field as well-positioned to make a scientifically impactful and clinically meaningful difference for those with OCD.

Declaration of Competing Interest

The authors report no declarations of interest.

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