A Systematic Review of Fear Learning, Extinction Learning, and Reversal Learning in Obsessive-Compulsive Disorder: Implications for Treatment

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ABSTRACT

Objective: Given the implications in the etiology and treatment of obsessive-compulsive disorder (OCD), this systematic review examined fear acquisition, extinction learning, and reversal learning processes in individuals with OCD.

Data Sources: In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, PubMed (1946–October 26, 2021), PsycInfo, and Embase were searched for empirical studies utilizing classical or reversal learning paradigms to compare learning and extinction processes in individuals with and without OCD.

Study Selection: A total of 15,603 articles (7,761 from PubMed, 1,128 from PsycInfo, 6,711 from Embase, 3 from citation review) were identified. Articles were screened for duplicates and inclusion/exclusion criteria. Eleven studies met all inclusion/exclusion criteria.

Results: Across studies, minimal evidence of abnormal fear learning was found. However, developmental differences emerged for extinction learning. Youth with OCD displayed impaired extinction learning and safety signal discrimination. Meanwhile, adults largely showed deficits in extinction recall. Conflicting findings emerged regarding impairments in reversal learning. Across learning processes, neuroimaging data implicated the importance of the ventromedial prefrontal cortex (vmPFC).

Conclusions: The physiological and neuroimaging data suggest that extinction learning impairment varies across development. Notably, key associative learning processes remain largely unexamined. Findings underlying abnormalities in extinction learning suggest the potential of novel therapeutic approaches, such as neuromodulation and psychotherapy augmentation strategies (ie, attention bias modification training), to precisely target and resolve identified deficits.

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Obsessive-compulsive disorder (OCD) affects approximately 1%–2% of the general population.[1] It is a condition characterized by distressing thoughts and repetitive behaviors that are interfering, time-consuming, and difficult to control.[2] It is one of the most impairing psychiatric disorders, leading to substantial morbidity[1] and cost to society—including deleterious effects on academic, workplace, and interpersonal functioning.[3] The mainstay treatments for OCD include pharmacologic interventions, such as selective serotonin reuptake inhibitors (SSRIs), and cognitive behavioral therapy (CBT) with exposure and response prevention (ERP).[4] Both intervention approaches have demonstrated considerable efficacy across randomized controlled trials of pediatric and adult OCD.[4,5] However, despite their therapeutic benefit, these interventions are not universally effective for all patients with OCD.[5–7] Thus, it is critical to understand the learning processes and mechanisms underlying CBT to target them with precision. Such an understanding and its resultant targeted treatment modalities would ultimately optimize treatment outcomes, expedite therapeutic improvements, and personalize treatments for patients with OCD.

Given its role in the development, maintenance, and treatment of OCD, associative learning processes (ie, Pavlovian fear acquisition, extinction learning/recall, reversal learning) represent key underlying factors for consideration. In Pavlovian fear conditioning, a neutral stimulus is paired with an aversive unconditioned stimulus (US) that leads to an automatic untrained unconditioned response. This leads to the once-neutral stimulus becoming a conditioned stimulus (CS). Repeated pairing of the US and CS leads to the formation and strengthening of an associative fear memory (ie, a CS-US association) that leads the CS to produce a conditioned response that includes defensive behaviors (eg, avoidance, neutralizing rituals) and/or physiological responses (eg, changes in skin conductance or heart rate). In the case of OCD, the US is often a distressing intrusive thought that is paired with a stimulus and/or situation and produces a defensive response (eg, obsession that the bathroom door handle [CS] is "contaminated" and that contact will cause illness [US], which leads to avoidance or neutralizing behaviors [CR]). Over time and across situations, this acquired CS-US association (ie, door handle is contaminated) may generalize to other associated stimuli (ie, the hands of individuals who touch the bathroom door handle, other door handles that people touch afterward), leading to greater impairment in daily functioning.

Clinical Points

- Translational studies of fear learning, extinction learning, and reversal learning can provide novel insights that can lead to the development of targeted therapeutic interventions.
- While CBT with or without serotonin reuptake inhibitors represents first-line treatment for OCD, the utilization of novel therapeutic strategies (eg, optimizing inhibitory learning during exposures) can prove useful to enhance underlying therapeutic processes. For patients who do not respond to first-line treatments, novel therapeutics (eg, attention bias modification training, neuromodulation techniques) that target impaired learning mechanisms may prove useful.

Fortunately, presentations of the CS in the absence of the US create a new learned association (ie, CS-no US) that competes with the original CS-US association. Over repeated pairings, the new association (CS-no US) is strengthened and inhibits the original association (CS-US)—a process called extinction learning.[8,9] In the above example, during CBT with ERP, patients with OCD touch the "contaminated" door handle (the CS) to learn that the distressing outcome (the US; eg, the illness) does not occur. While extinction learning focuses on the creation and strengthening of the inhibitory CS-no US association, extinction recall refers to the process of recalling the inhibitory CS-no US association over time and across settings.

While extinction learning/recall aims to inhibit the learned association, reversal learning is a related process that measures the degree to which learned associations are updated and "reversed" based on new information. Specifically, reversal learning involves a contingency shift in which the previously safe stimulus (CS–) becomes associated with a threat during the reversal phase; meanwhile, the previously threatening stimulus (CS+) is no longer paired with a negative outcome. While a complete contingency shift may not entirely parallel treatment and/or real-world settings (ie, all "contaminated door handles" become safe, while other stimuli become "contaminated"), reversal learning provides a metric of how flexible and/or adaptable learned associations are for patients with OCD based on new information acquired in CBT with ERP (ie, cognitive flexibility, discriminating safety signals).

Alterations in associative learning (ie, fear learning, extinction learning, extinction recall, and reversal learning) have been observed in a range of psychiatric disorders including anxiety disorders, trauma-related disorders, and OCD.[10–13] Understanding altered patterns of associative learning and the markers that correlate with abnormal learning processes may lead to an improved understanding of why altered patterns occur in these conditions. This information would eventually lead to more targeted treatments to improve outcomes and personalize treatments for patients with OCD based on identified impairments and/or aberrations in associative learning processes. To the authors' knowledge, only 1 prior review has exclusively examined fear conditioning and extinction learning in OCD.[12] The authors found mixed evidence for impairments in fear learning, with more consistent evidence for impairments in extinction learning. While informative, the findings and clinical interpretations of the review are complicated by the inclusion of disgust conditioning, a mixture of clinical and nonclinical samples, and limited attention to developmental considerations affecting the findings. Lastly, several recent studies in clinical populations were not included in the prior review and warrant consideration. Building on this initial work, we conducted a systematic review of the existing literature examining fear acquisition, extinction learning/recall, and reversal learning processes in individuals with OCD compared to healthy controls. Here, we examine the evidence for impairments in these key processes across studies, apply these findings to optimize current treatments, and recommend future directions for treatment research to advance the field of OCD.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[14]

Search Strategy

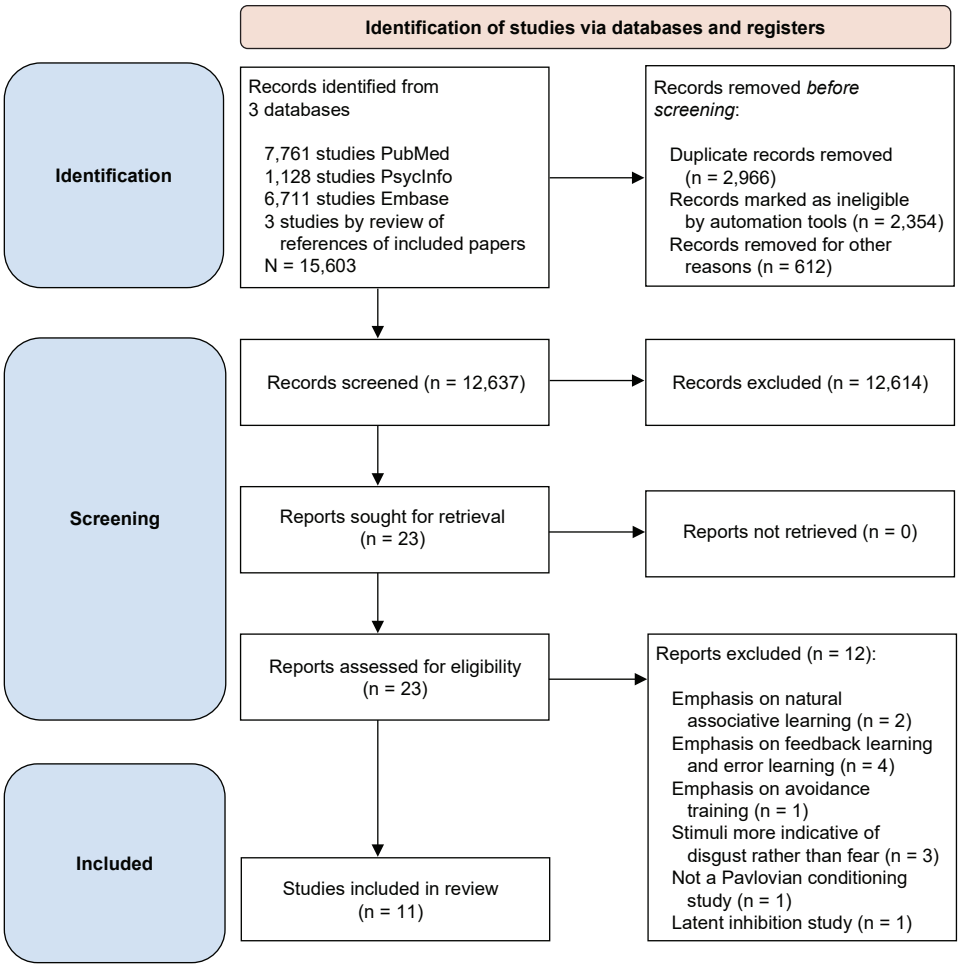
PubMed (1946–October 2021), PsycInfo, and Embase were searched using the search terms (OCD OR obsessive-compulsive OR obsessive OR compulsive) AND (conditioning OR conditioned AND fear OR disgust OR aversive OR classical OR Pavlovian OR extinction OR acquisition OR differential OR evaluative) OR (associative learning) AND human NOT review and NOT meta-analysis. Additionally, citations from searched articles were reviewed for possible missed studies from the above search. Abstracts were reviewed independently by 2 raters (E.S. and J.M.) for appropriateness of inclusion. Inclusion criteria for review included (1) empirical studies that utilized classical or reversal fear learning paradigms; (2) human participants who met diagnostic criteria for OCD by standardized diagnostic interview or clinician-rated scale; (3) reported results examining between-group differences of OCD and control groups on at least 1 physiologic marker of conditioning, such as skin conductance, fear-potentiated startle, and/or neuroimaging; and (4) reports available in English.

RESULTS

Characteristics of Identified Studies

The above search strategy identified 7,761 articles in PubMed, 1,128 articles in PsycInfo, and 6,711 articles in Embase. Three additional studies were found when references of articles were reviewed. Thus, a total of 15,603 potential reports were identified using these search criteria. All studies were imported into EndNote[15] and deduplicated using EndNote's software, which removed 2,354 studies. A manual review of abstract titles removed another 612

Figure 1. PRISMA Flow Diagram



duplicate articles. Thus, the final sample size of abstracts reviewed for screening purposes was 12,637 articles (Figure 1).

The titles and abstracts of all articles were manually screened for inclusion. As shown in Figure 1, 11 articles were identified as meeting all inclusion criteria. Table 1 provides the detailed characteristics of the 11 studies. To facilitate presentation and interpretation of findings, results were organized into 3 primary categories: Pavlovian fear acquisition, extinction learning/recall, and reversal learning. Given the role of potential differences across the developmental spectrum and neuroimaging findings, subcategories were provided for children, adults, and neuroimaging outcomes.

Pavlovian Fear Acquisition

Adults. Six studies using a classical conditioning paradigm met inclusion criteria for adults with OCD. First, Nanbu and colleagues[16] examined alterations in fear learning between adults with and without OCD utilizing a single-cue paradigm. Second, Milad and colleagues[17] examined fear conditioning in adults with OCD but employed a differential-cued paradigm (see Table 1). In addition to skin conductance response (SCR) to measure fear learning, functional magnetic resonance imaging (fMRI) data were also collected during conditioning procedures[17] (see below). Third, McLaughlin et al[18] examined fear conditioning with SCR data using a similar differential-cued paradigm to Milad et al.[17] This examination focused on the broader group of individuals with a lifetime OCD diagnosis instead of a current diagnosis—although 24 of the 31 OCD patients (77%) met current diagnostic criteria.[18] Fourth, Giménez et al[19] examined SCR and glutamate levels in the ventromedial prefrontal cortex (vmPFC; see below) in patients with OCD and healthy controls, with follow-up analyses exploring CBT response among OCD patients. No significant differences in sympathetic nervous system functioning, as measured by SCR, were observed in individuals with OCD and healthy volunteers across these 4 studies. Fifth, Fyer et al[20] compared healthy controls to patients with OCD, social anxiety disorder, and anorexia nervosa. While individuals with OCD had an enhanced absolute response to the CS– during acquisition compared to controls, no significant difference in the total magnitude of response (CS+ minus CS–) was seen.[20] Most recently, Pöhlchen et al[21] compared multiple markers of psychophysiological reactivity—including SCR, fear-potentiated startle (FPS), and pupillometry—between

Table 1. Study Characteristics and Results of Included Studies (N = 11)

Study	N (OCD/ control)	Age group	Diagnostic and symptom assessments	Comorbidities	Medications	Design	Phases studied	CS	US	Contingency pairing	Physio/ neural marker	Significant results
Nanbu et al, 2010[16]	60 (39/21)	Adult	*DSM-IV* criteria by SCID, Y-BOCS	None	SSRI (72%), trazodone (5%), TCA (3%)	Single cue	Acquisition, extinction	CS+: green light	Shock	100%	SCR, EEG	SCR: ACQ: no group differences EXT: OCD: increased SCR (trend) EEG: ACQ: no group differences EXT: OCD: higher S2/S1 ratio than HVs
Milad et al, 2013[17]	42 (21/21)	Adult	*DSM-IV* criteria by SCID, Y-BOCS	Dysthymia, PD, SoPh, SpPh, PTSD, GAD	Antidepressant (43%), anticonvulsant (5%), NMDA receptor antagonist (5%)	Differential cue	Acquisition, extinction, retention, renewal	CS: 3 colored lamps (2 separate CS+, 1 extinguished)	Shock	60%	SCR, fMRI	SCR: ACQ: no group differences EXT: no group differences EXT REC: OCD: greater SCR to CS+ fMRI: ACQ: OCD: fail to recruit right caudate, subgenual cortex, and hippocampus EXT: OCD: reduced vmPFC activation EXT REC: OCD: reduced vmPFC, PCC, cerebellum, putamen, hippocampus activation
McLaughlin et al, 2015[18]	55 (37/18)	Adult	Lifetime (but not necessarily current OCD) by *DSM-IV* criteria by SCID, Y-BOCS	MDD, BPAD, dysthymia, SUD, PD, SoPh, tics, impulse-control disorder, PTSD, agoraphobia Controls: past MDD and SUD	SSRI (94%), BZD (55%)	Differential cue in context	Acquisition, extinction, retention, renewal	CX: 2 rooms CS: 2 lamp colors	Shock	100%	SCR	ACQ: no group differences EXT: no group differences EXT REC: OCD: impaired recall; first trial had higher SCR to CS+ and CS, only CS+ remained high EXT REN: no group differences
McGuire et al, 2016[22]	41 (19/22)	Pediatric (7–17 y)	*DSM-IV* criteria by K-SADS-PL, CY-BOCS, OCI-CV	SpPh, anxiety, ADHD, depressive disorder, tic, disruptive behavior disorder	SSRI (42%) neuroleptic (11%), stimulant (11%), BZD (5%)	Differential cue	Acquisition, extinction	CS: facial expressions	Scream	80%	SCR	ACQ: no group differences EXT: OCD: greater SCR to CS– initially, SCR to CS+ increased over trials
Apergis-Schoute et al, 2017[25]	85 (43/35)	Adult	MINI, Y-BOCS	None	SSRI (42%), TCA (12%), neuroleptic (7%), BZD (2%)	Reversal	Acquisition, reversal	CS: faces	Shock	33%	SCR, fMRI	SCR: ACQ: OCD: stronger differentiation deficit in late acq REV: OCD: impaired differential learning fMRI: ACQ: OCD: increased vmPFC activation to CS+, absent vmPFC CS– activation; increased salience network connectivity to CS+ REV: OCD: increased vmPFC activation to the CS+; absent vmPFC CS– activation

(continued)

Table 1 (Continued).

Study	N (OCD/ control)	Age group	Diagnostic and symptom assessments	Comorbidities	Medications	Design	Phases studied	CS	US	Contingency pairing	Physio/ neural marker	Significant results
Geller et al, 2017[23,a]	80 (39/41)	Pediatric (7–17 y)	*DSM-IV* criteria by K-SADS-PL, CY-BOCS	MDD, anxiety, tic	SRI (41%)	Differential cue	Acquisition, extinction	CS: facial expressions	Scream	80%	SCR	ORIENT: OCD: greater response ACQ: OCD: increased to CS+ EXT: OCD: increased to CS+
Geller 2019[24,a]	64 (64/0)	Pediatric (7–17 y)	*DSM-IV* criteria by K-SADS-PL, CY-BOCS	MDD, anxiety, tic	SSRI (22%), antipsychotic (3%), ADHD/tic (6%)	Differential cue	Acquisition, extinction	CS: facial expressions	Scream	80%	SCR	ACQ: severity and treatment response unrelated EXT: severity unrelated. Treatment responders had improved discrimination
Fyer et al, 2020[20]	166[b] (41/64)	Adult	*DSM-IV* criteria by SCID, Y-BOCS	SpPh, tic	None	Differential cue	Acquisition, extinction, retention, renewal	CX: 2 rooms CS: 2 lamp colors	Shock	67%	SCR	ACQ: OCD: stronger response to CS–, but overall no group differences EXT: no group differences EXT REC: OCD: impaired (trend) EXT REN: OCD: increased
Giménez et al, 2020[19]	30 (17/13)	Adult	*DSM-IV* criteria by SCID; Y-BOCS	Affective disorder, anxiety disorder	SSRI (82%), SNRI (6%)	Differential cue	Acquisition, extinction, retention	CS: 3 colored lamps (2 separate CS+, 1 extinguished)	Shock	60%	SCR, vmPFC glutamate	SCR ACQ: No group differences EXT: No group differences EXT REC: No group differences vmPFC glutamate levels No group differences EXT REC: OCD: higher levels correlated with decreased EXT REC
Elsner et al, 2021[26]	73 (41/32)	Adult	Y-BOCS, OCI-R	Anxiety, somatoform, MDD	SSRI (29%), *Hypericum* (2%)	Reversal	Acquisition, reversal	CS: faces	Shock	33%	SCR	ACQ: OCD: impaired differential learning REV: no group differences
Pöhlchen et al, 2021[21]	93 (37/53)	Adult	Y-BOCS, OCI-R, MCID	SpPh, phobia, PD, PTSD, MDD, dysthymia, BPAD	SSRI (8%), amphetamine (3%), SSRI + neuroleptic (3%)	Differential cue	Acquisition, extinction, retention	CS: 3 colored shapes (1 CS–, 1 CS+ [shock], 1 CS+ [air puff])	Shock, air puff	75%	FPS, SCR, pupillometry	SCR: ACQ: no group differences EXT: no group differences EXT REC: no group differences FPS: ACQ: no group differences EXT: OCD: increased FPS (trend) EXT REC: no group differences Pupillometry: ACQ: no group differences EXT: no group differences EXT REC: no group differences

[a]Geller et al (2017)[23] and Geller et al (2019)[24] are from the same sample.
[b]Study included social anxiety disorder and anorexia nervosa as other comparison groups.
Abbreviations: ACQ = acquisition, ADHD = attention-deficit/hyperactivity disorder, BPAD = bipolar affective disorder, BZD = benzodiazepine, CS = conditioned stimulus, CX = context, CY-BOCS = child Yale-Brown Obsessive Compulsive Scale, EEG = electroencephalography, EXT = extinction, EXT REC = extinction recall, EXT REN = extinction renewal, fMRI = functional magnetic resonance imaging, FPS = fear-potentiated startle, GAD = generalized anxiety disorder, HV = healthy volunteer, K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime, M-CID = Munich-Composite International Diagnostic Interview, MDD = major depressive disorder, MINI = Mini-International Neuropsychiatric Inventory, NMDA = *N*-methyl-D-aspartate, OCD = obsessive-compulsive disorder, OCI-CV = Obsessive Compulsive Inventory-Child Version, OCI-R = Obsessive Compulsive Inventory-Revised, PCC = posterior cingulate cortex, PD = panic disorder, PTSD = posttraumatic stress disorder, SCID = Structured Clinical Interview for *DSM-IV* Disorders, SCR = skin conductance response, SoPh = social phobia/social anxiety disorder, SpPh = specific phobia, SRI = serotonin reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, SUD = substance use disorder, TCA = tricyclic antidepressant, US = unconditioned stimulus, vmPFC = ventromedial prefrontal cortex, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

individuals with OCD and unaffected controls.[21] No group differences were found across all metrics during fear learning.

Children. Two studies have examined Pavlovian fear conditioning in children with OCD. McGuire et al[22] found no SCR differences between children with OCD and age- and gender-matched unaffected youth during fear acquisition. Interestingly, they identified a moderate positive association ($r = 0.31–0.34$) between SCR to the CS+ and self-reported OCD and anxiety severity. Similarly, Geller et al[23] examined fear conditioning in children with OCD relative to healthy control youth. In contrast to prior studies, children with OCD exhibited a more robust SCR to the CS+ during acquisition compared to the children without OCD.

Neuroimaging. To date, only 3 studies included neural correlates in their design.[16,17,19] First, Nanbu et al[16] collected electroencephalogram (EEG) responses during fear acquisition. An increased S2/S1 (second stimulus sound/first stimulus sound) ratio was observed in the single-cue paradigm for the individuals with OCD compared to controls.[16] Second, Milad et al[17] collected fMRI data during fear acquisition, which identified that individuals with OCD failed to recruit the right caudate, subgenual cortex, vmPFC, and hippocampus during fear learning—despite not exhibiting alterations in physiological metrics of SCR. Finally, Giménez et al[19] examined glutamate levels in the vmPFC during fear learning and found no group differences between patients with OCD and healthy controls. Glutamate levels were not linked to pre-treatment OCD severity, nor were associations between glutamate and fear learning identified.[19]

Pavlovian Extinction Learning and Extinction Recall

Adults. Six studies have evaluated Pavlovian extinction learning/recall in adults with OCD. None of the studies included found significant differences during extinction learning between individuals with and without OCD.[17–20] However, Nanbu et al[16] observed a nonsignificant trend toward increased SCR in the OCD group, while Pöhlchen et al[21] identified a trend toward increased FPS during extinction learning in OCD.

Conversely, differences between OCD and unaffected samples were identified during extinction recall. Specifically, Milad et al[17] and McLaughlin et al[18] identified impairments in extinction recall among individuals affected by OCD. Here, the CS+ remained elevated for OCD-affected individuals compared to the control groups throughout the extinction recall phase. While Milad et al[17] noted increased symptom severity correlated with improved extinction recall, McLaughlin et al[18] found no correlation. During the extinction renewal phase, no between group differences were detected by McLaughlin et al.[18] Additionally, Fyer et al[20] found a trend toward decreased extinction recall and significantly increased fear renewal was observed among patients with OCD. In contrast, Giménez et al[19] and Pöhlchen et al[21] found no group differences in extinction recall between individuals with OCD and unaffected controls.

Children. Two studies have evaluated Pavlovian extinction learning/recall in children with OCD, with findings suggesting notable differences in extinction learning relative to adults with OCD. McGuire et al[22] identified a differential pattern of SCRs between groups during extinction learning with 2 notable findings. First, youth with OCD exhibited a greater differential response to CSs compared to the matched control sample, suggestive of impairments in extinction learning. Second, youth with OCD showed an initial reversal of SCR to the CS+ and CS– during extinction trials, which was later followed by increased reactivity to the CS+ and decreased reactivity to the CS– in later extinction trials. Geller et al[23] also found evidence of impaired extinction learning in youth with OCD compared to the control groups. The OCD group continued to exhibit a greater SCR to the CS+, whereas the control participants displayed a diminished SCR to both CSs.[23] Following up on these initial findings, Geller et al[24] showed that CBT treatment responders had significantly better discrimination between the CS+ and CS– during extinction in comparison to CBT treatment nonresponders. This suggests that CBT nonresponders had difficulty recognizing the CS– as a "safety signal" and highlights that extinction learning may be a likely marker of treatment response in CBT. To date, no published studies have examined extinction recall in youth with OCD.

Neuroimaging. Only 3 studies included neuroimaging in their investigations.[16,17,19] Similar to the findings for fear learning, Nanbu et al[16] found an increased S2/S1 ratio in the individuals with OCD compared to the control group during extinction in a single-cue paradigm. Additionally, Milad et al[17] identified reduced vmPFC activation compared to the unaffected control group—which is similar to the study's findings for fear acquisition. Similarly, for extinction recall, reduced vmPFC activation was seen among individuals with OCD relative to controls, as well as reduced activation in the posterior cingulate cortex, putamen, and hippocampus. Curiously, OCD severity was found to positively correlate with both the magnitude of extinction recall and vmPFC functional response. Finally, Giménez et al[19] revealed that higher vmPFC glutamate levels were associated with worse extinction recall but improved CBT outcomes among OCD patients.

Pavlovian Reversal Learning

Acquisition. Two studies have investigated Pavlovian fear reversal learning in adults with OCD without parallel examinations in youth with OCD. First, Apergis-Schoute et al[25] demonstrated that individuals with OCD can discriminate between the CS+ and CS– during acquisition but identified that this ability was reduced compared to healthy volunteers. Follow-up analyses revealed that a deficit in stimuli discrimination during later acquisition trials mostly accounted for this difference. Notably, concurrent fMRI data identified increased connectivity between the vmPFC and salience network among patients with OCD during acquisition.[25] Second, Elsner et al[26] also examined reversal learning and found a deficit in stimuli discrimination during

late acquisition that paralleled Apergis-Schoute et al.[25] While the healthy control group showed a differential SCR to the CS+ and CS–, individuals with OCD displayed similar SCR responses to the CS+ and CS– suggesting deficits in threat discrimination and/or safety signal learning.[26] Across these 2 studies, OCD severity did not correlate with the differential SCR between the CS+ and CS–, which suggests this is a state-independent trait.

Reversal. In the reversal learning stage, Apergis-Schoute et al[25] identified that individuals with OCD had decreased SCR differentiation between threatening and non-threatening stimuli after reversal.[25] Alongside these physiological markers, increased activation in the vmPFC to the CS+ in early acquisition predicted the magnitude of accurate stimulus discrimination in the reversal stage for individuals with OCD. Furthermore, decreased activity in the left globus pallidus and insula was observed in the latter half of the reversal phase, which may be related to aberrant signaling of the vmPFC earlier in the task. In contrast, Elsner et al[26] displayed different results during reversal learning. Individuals with OCD did not exhibit impairments during reversal learning, which is different from their findings during the acquisition phase. The authors attribute these findings to differences in study methodology and suggest that participants had greater contingency awareness of the CS+ and CS–, which was thought to decrease the difficulty of the task. Consequently, the reversal task had less inherent uncertainty that may have contributed to the differential outcomes between studies.

DISCUSSION

This review examined the extant literature related to essential associative learning processes implicated in the development, maintenance, and treatment of OCD (ie, Pavlovian fear conditioning, extinction learning/recall, reversal learning). Several important findings emerged related to the psychophysiological and neural correlates of fear conditioning, extinction, and reversal learning in children and adults with OCD.

Fear Learning

Across studies, there was minimal support for abnormal fear learning in both children and adults with OCD on physiological outcomes. However, there was some evidence of altered vmPFC activity during fear acquisition in adults with OCD.[17] This suggests that underlying abnormalities in threat processing and stimuli discrimination (ie, differentiating the CS+ and CS–) may be present in adults with OCD, which has potential implications for extinction learning.

Extinction Learning and Extinction Recall

Different patterns of extinction learning were observed across the spectrum of development in OCD. Although alterations in vmPFC activation were detected, minimal differences in SCR response were found during extinction learning between adults with OCD and healthy controls.[17,18] Meanwhile, children with OCD consistently exhibited impairments in extinction learning, characterized by difficulty inhibiting the prior threat association (CS-US) with newly learned non-threat associations (CS-no US). Additionally, youth with OCD displayed an initial reversal of learned association during early extinction in 1 report (ie, greater SCR to the CS– compared to the CS+), which suggests some difficulty accurately discriminating between the threat stimulus (CS+) and the safety signal (CS–) in the absence of a clear contingency.[22] This is highly relevant because children with OCD who were CBT treatment responders had better discrimination between the CS+ and CS– during extinction. Stated differently, CBT nonresponders had difficulty discriminating the CS– as a "safety signal" during extinction learning. Thus, extinction learning phenotypes may be a relevant marker in pediatric OCD.

While extinction recall has not yet been examined in pediatric OCD, the findings from Milad et al,[17] McLaughlin et al,[18] and Fyer et al[20] suggest impairments in extinction recall among individuals with OCD relative to controls. Alongside these differences in physiological response during extinction learning, individuals with OCD also demonstrated reduced vmPFC activation compared to unaffected controls. As no correlation between extinction recall and OCD severity emerged, this finding may be state-independent.

The discrepancy in findings between children and adults with OCD warrants consideration. Children with OCD appear to struggle with the formation of inhibitory associations and contingency recognition/stimulus discrimination during extinction learning. As these youth transition into adulthood, impairments in extinction learning are no longer observed—possibly due to brain maturation particularly in the prefrontal cortex and/or compensatory learning strategies acquired over time.[27] Prior research has highlighted that extinction recall develops later in life than the development of fear learning (see Shechner et al[28] for a review of developmental considerations in fear learning). However, for adults with OCD, impairments in the recall and/or retention of extinction learning over time and across settings are present, with the abnormal vmPFC functioning heavily implicated as a contributing factor.

Reversal Learning

Findings from the 2 reversal learning studies consistently indicated abnormal SCR responses during fear acquisition for individuals with OCD. Moreover, both studies demonstrated that adults with OCD had difficulty differentiating between the CS+ and CS– during acquisition, highlighting impairments in differential learning and safety signaling.[25,26] Compared to the traditional Pavlovian conditioning paradigms, reversal learning tasks have markedly lower contingency pairing rates (Table 1). The relatively low rate of paired association (33%–35%) may have influenced study findings. Specifically, a lower rate of association increases the degree of uncertainty individuals with OCD would have that a CS is associated with the US. Thus, the poor discrimination identified in the acquisition phase may have

been attributed to greater uncertainty between threat and non-threat cues. The first neuroimaging findings suggested deficits in sensory gating among individuals with OCD,[16] with later work implicating abnormal vmPFC function.[17,19,25] Adults with OCD displayed functional alterations in the vmPFC during fear learning and showed underactivation when the safety cue was presented.[25] This suggests the presence of impaired safety signaling learning. As such, the observed poor discrimination was likely due to increased generalized fear to both stimuli, rather than reduced fear to both stimuli, indicative of a negative cognitive bias in uncertain circumstances.

Implications of Findings for Future OCD Treatments

While the above literature laid the foundation describing the processes that work to develop and sustain OCD symptoms, only 2 studies examined the role of associative learning in relation to CBT treatment response.[19,24] Thus, there is a clear need for more fear conditioning/extinction research in both children and adults with OCD using multimodal assessments. Ideally, this research would occur in the context of treatment. Treatment-focused studies could replicate and extend the important work by Geller et al[24] and Giménez et al[19] that highlights the clinical implications of conditioning/extinction tasks to predict treatment outcomes and personalize treatment recommendations (ie, identifying individuals with OCD who may be likely to respond to CBT).

Findings show that impairments in extinction learning and extinction recall are present in children and adults with OCD. As CBT with ERP is the first-line treatment recommended for OCD,[29–31] it is critical that exposures in this treatment employ strategies that optimize the formation of inhibitory associations (ie, "inhibitory learning"). This would help youth and adults with OCD better develop, strengthen, and recall non-threat associations within and across therapy sessions. Several strategies have been suggested by experts to optimize extinction processes during exposures in CBT.[32–35] One strategy involves designing exposures to specifically challenge the patient's feared expectation rather than relying upon reductions in subjective distress to determine exposure completion. Once the feared expectation is identified in CBT, exposures can tailored to specifically challenge the feared expectation by modifying the duration, intensity, and number of exposure trials. For example, consider an adult with OCD who has an obsessive thought that they will harm a loved one if they hold a sharp object (a common harm-related obsession). Here, the therapist would clarify parameters regarding time/duration and proximity of the feared expectation to refine exposures. Subsequently, the time/duration, proximity to stimuli, and intensity of stimuli could be modified to challenge the feared expectation. While challenging feared expectations, the therapist would actively call attention to the expectation-reality mismatch to strengthen the inhibitory association. This approach also permits increasing the variability of stimuli and contexts in which exposures are conducted, which are also other strategies to enhance inhibitory learning.[32,33]

Beyond impairments in extinction learning, findings suggest that children and adults with OCD have impairments in threat discrimination. Specifically, these findings suggest that individuals with OCD can display greater reactivity to safety signals (CS–) in the context of an uncertain contingency.[20,22,25,26] When faced with uncertainty, it appears that individuals with OCD tend to react by predicting danger or a negative outcome, which may underlie the extinction learning and recall deficits observed. Indeed, prior studies have identified impairments in extinction processes in the context of uncertainty.[36–38] Interestingly, within the classical conditioning paradigms, authors pointed to the lack of ambiguity in the paradigm as a reason for null findings, pointing to the importance of uncertainty in fear processing in OCD.[21] Clinically, low tolerance of uncertainty has identified as an important driver of abnormal fear learning processes across anxiety disorders.[39] Within OCD, early work has demonstrated a poor tolerance of uncertainty in individuals with OCD,[40,41] with evidence indicating that the severity of intolerance to uncertainty is equivalent between generalized anxiety disorder and OCD.[42–44]

While not all children and adults with OCD may experience this impairment,[20] there are potentially beneficial interventions for those who do (particularly as these patients may be less responsive to evidence-based treatments).[24] Attention-bias modification to threat (ABMT) is a therapeutic strategy focused on targeting threat-related biases to reduce anxiety. Preliminary data indicate that ABMT (alone or as a CBT-augmentation strategy) is helpful for combatting automatic, excessive attention to threatening stimuli in anxiety spectrum disorders across development.[45,46] ABMT could potentially be helpful for individuals with OCD who display deficits in threat discrimination in the context of uncertainty by training patients to better differentiate threat-related stimuli. Indeed, early reports indicate success in reducing negative attentional biases and OCD symptom severity in both children[47] and adults.[48] This therapeutic approach could be initiated before exposures in CBT to help those patients with threat discrimination difficulties accurately distinguish stimuli during exposures and fully benefit from evidence-based CBT.

In regard to pharmacotherapy to augment extinction processes, D-cycloserine (DCS) is an *N*-methyl-D-aspartate receptor partial agonist that showed early promise to enhance extinction learning in OCD and related disorders.[49,50] While later studies found inconsistent clinical benefit from augmenting CBT with DCS, multiple methodological factors such as timing, dose, frequency, co-occurring SSRI use, and achievement of extinction learning during exposures complicate these findings.[51,52] Moreover for OCD, multiple mechanisms are implicated in OCD symptoms (eg, fear, disgust, not-just-right sensations). Given its potential to enhance inhibitory associations among even non–fear-based disorders,[53] further research on DCS-augmented treatment is critical to understand its effect on extinction learning and related mechanism for individuals with OCD.

Across fear learning, extinction learning/recall, and reversal learning paradigms, neuroimaging data consistently

highlight the underperformance of the vmPFC, particularly when processing safety signals.[17,20,25] Recent work using inhibitory transcranial direct stimulation of the vmPFC revealed a causal relationship between vmPFC hyporeactivity and pathological fear generalization in healthy adults.[54] Clinically, vmPFC structure and function have been tied to aberrant extinction processes across several anxiety disorders[55–57] and in individuals with high intolerance to uncertainty.[58] For patients with OCD, a CBT response has been linked to amygdala-vmPFC connectivity, with decreased connectivity shown to predict improved CBT efficacy.[59] Even more compellingly, a recent systematic review concluded that stimulation to the vmPFC had the most potential to improve fear extinction in anxiety-spectrum disorders.[60] Consequently, the vmPFC serves as prime target for neuromodulation interventions to enhance treatment outcomes for patients with OCD. In fact, early data show support for vmPFC neuromodulation techniques to improve clinical outcomes in OCD. A recent multicenter, double-blind, randomized controlled trial of mPFC deep transcranial magnetic stimulation (TMS) in OCD patients demonstrated significant symptom improvement that sustained at least 1 month after treatment concluded.[61] Similarly, preliminary data with transcranial direct current stimulation demonstrated improved safety learning in patients with OCD and decreased distress with exposures.[62] Thus, neuromodulation is proving a promising area of research to precisely target and resolve impairments in neural mechanisms underlying OCD. Moreover, this approach holds considerable potential for patients who may have difficulty with (or are resistant to) completing exposures in CBT.

Limitations

The studies conducted to date have overall provided a firm foundation describing the aberrancies in associative learning processes in OCD, though several limitations should be noted. The lack of neuroimaging or extinction recall data in pediatric studies limits our ability to fully consider developmental differences in OCD pathophysiology. Additionally, differences in methodology, both within[23] and across studies, are problematic for drawing extensive conclusions. Confounders such as variable task tolerability, measurement parameters, contingency pairing rates, and medication inclusion also limit the conclusions drawn across studies. Future research should focus on standardizing methodologies for greater ease of comparison across studies.[63] Additionally, there is limited variability in the physiologic markers used in identified studies. Notably, the inclusion of FPS[21] was a welcome addition to allow for more direct generalizability to animal models. Abnormalities in these markers have been reported in anxiety spectrum disorders and posttraumatic stress disorder.[64–67] Thus, the inclusion of other physiological markers in the OCD literature would be useful.

OCD is often comorbid with other mental health conditions.[68] Given that OCD often presents alongside anxiety spectrum disorders, it is likely that the physiological and neuroimaging findings would hold true across fear-based conditions due to shared deficits in extinction learning[69,70] and neural circuitry.[71] Clearly, future research is needed to investigate this question. However, evidence suggests that the occurrence of autism spectrum disorders (ASDs) alongside OCD might likely influence clinical characteristics[72] and treatment outcomes.[73] Despite initial promising studies examining associative learning mechanisms in patients with ASD,[74,75] future research is needed to investigate the mechanism of fear conditioning, extinction learning, and reversal learning and its implications for treatment in the context of ASDs.

CONCLUSION

Despite the limitations, the early literature examining the relationship between OCD symptoms and Pavlovian fear conditioning neural and psychophysiological correlates provides helpful insight into the development and maintenance of distressing OCD behaviors. While an emerging field of inquiry, the evidence points to developmental difference in extinction processes in children and adults with OCD. While youth displayed impaired extinction learning and safety signal discrimination, adults largely showed deficits in extinction recall. Across learning processes, neuroimaging data implicated the importance of the vmPFC.

This article highlights the importance of multimodal measures of fear learning, including measures of autonomic arousal and neuroimaging. Each metric has its own unique benefit. For example, FPS is most directly comparable to animal studies,[65] while SCR has been commonly used in prior research and thus its use facilitates comparison to prior human research. Additionally, the use of neuroimaging provides information on the neural circuitry that may be contributing to the abnormal learning and physiologic responses. Future studies should also aim to include subjective units of distress (SUDs) in study designs. Beyond clarifying the relationship between autonomic arousal and consciously experienced distress, it can help connect the experimental and clinical literature. Indeed, SUDs are commonly used in clinical practice to measure fear levels within and between sessions in CBT.[76,77] Thus, when performed in concert, multimodal assessments provide more complete information regarding the underlying pathophysiology of OCD. Taken together, these findings highlight the potential for novel and targeted therapeutic strategies that precisely address identified impairment to improve treatment outcomes (eg, inhibitory learning exposures, ABMT, neuromodulation). Clearly, more research is needed and ideally would incorporate individual-level patient outcomes that longitudinally measure change over the course of evidence-based treatment. Ultimately such an approach could clarify the timing for fear abnormalities to resolve from specific evidence-based treatment (ie, time to resolve impairments in extinction learning, time to resolve aberrant activation of vmPFC) and ultimately inform personalized treatment recommendations for patients with OCD.

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