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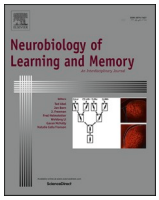

Review

Threat Acquisition and Extinction Differences Between Patients With Panic Disorder or Specific Phobia and Non-Clinical Controls: A Systematic Review

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ABSTRACT

The study of threat conditioning and extinction processes in anxiety disorders (AD) may further our understanding of the genesis, maintenance, and treatment of these conditions. As it stands, there have been multiple systematic reviews carried out in this area. Patient-control differences in threat acquisition and extinction have been investigated in relation to ADs, obsessive–compulsive disorder (OCD), and social anxiety disorder (SAD). However, this remains to be investigated in either panic disorder (PD) or specific phobia (SP). In this paper, a narrative systematic review was carried out to collate and critically assess the literature investigating patient-control differences in threat acquisition, extinction, and extinction retention processes in relation to PD and SP separately. Specifically, across fMRI, EEG, EMG, SCR, and self-report. This resulted in the inclusion of 14 PD studies and 7 SP studies. Across PD studies, the review identified reliable evidence for lowered discrimination between conditioned threat and safety cues, and mixed evidence for increased responding to the threat cue, during acquisition in PD patients vs. non-anxious controls. Across SP studies, the review identified strong evidence for heightened discrimination between conditioned threat and safety cues during acquisition, and strong evidence for heightened responding to the threat cue during extinction, in SP patients vs. non-anxious controls. In both PD and SP studies, patient-control differences were identified more frequently in relation to subjective, as opposed to physiological, measures. The findings of this review are then critiqued and compared to the wider literature. Finally, implications, limitations, and directions for future research are discussed.

1. Introduction

The ability to discriminate between threatening and non-threatening stimuli is essential for survival. Such identification allows one to prepare for and contend with both implied and actual danger, hence reducing risk of harm (Mobbs et al., 2015). Interestingly, the presence of anxiety or fear is largely dictated by current proximity to threat: whereas anxiety occurs in situations with implied danger, fear occurs in situations with current danger (Gray & McNaughton, 2003). Consequently, it is theorised that the function of anxiety is to encourage the anticipation, and avoidance, of potential or implied threat, whereas the function of fear is to encourage the escape from, or confrontation of, current threat (Gray & McNaughton, 2003). These emotional states then produce behavioural responses that increase one's chance of survival in each situation i.e., hypervigilance/behavioural inhibition in response to anxiety (potential threat), and escape or aggression in the case of fear (current threat) (Gray & McNaughton, 2003; Gross & Hen, 2004; Misslin, 2003). Yet, both emotional responses, and their adaptive survival benefits, are predicated on one's ability to successfully discriminate between threat and safety cues within their environment.

Contemporary Pavlovian conditioning paradigms have long been utilised by researchers to study the recognition of, and differentiation between, conditioned threat and safety cues in humans and animals, alongside the emotional and physiological experiences associated with both the learning and unlearning of fear in relation to specific stimuli (Delamater, 2004; Hermans et al., 2006; Lonsdorf et al., 2017). Drawing on classical conditioning principles (Pavlov, 1927), threat conditioning experiments consist of at least two distinct phases; threat acquisition and threat extinction. Said phases are designed to elucidate the processes associated with both the learning, and unlearning, of specific stimulus-fear associations (Beckers et al., 2023; Craske et al., 2014, 2022; Vervliet & Boddez, 2020). The threat acquisition phase involves repeatedly pairing a neutral stimulus (CS+; conditioned stimulus, such as a shape) with an aversive stimulus (US; unconditioned stimulus, such as an electric shock). Through repeated pairing, the CS+ begins to elicit emotional experiences and defensive reactions similar to that of the US,

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thereafter, signalling guaranteed or potential threat i.e., a threat stimulus. This learned reaction is referred to as the 'conditioned response' and the associated process of acquiring said conditioned responding is known as 'threat acquisition' (Lonsdorf et al., 2017). Additionally, threat conditioning procedures typically include an unconditioned control stimulus (CS-), which is never paired with the aversive stimulus, hence, unlike the CS+, the CS- signals safety from threat i.e., a safety stimulus. The function of the CS- is to differentiate between conditioned threat and safety responses (Lonsdorf et al., 2017). Following the acquisition phase, participants undergo a threat extinction phase, which may occur immediately post-acquisition, or after a delay e.g., 24 h. During this phase, both the CS+ and CS- are presented without the US. Over time, this leads to a reduction in conditioned responding towards the CS+; a process referred to as 'extinction learning' or 'threat extinction' (Hermans et al., 2006; Lonsdorf et al., 2017; Milad & Quirk, 2012). Additionally, some procedures also include an 'extinction retention' phase, otherwise known as a 'retention/recall test', which is typically identical to that of the extinction phase but occurs after, at least, a 24-hour delay. Extinction retention phases assess whether the extinction effect persists over time, or whether the original threat response returns upon re-exposure to the CS+ known as 'spontaneous renewal' or a 'return of fear' (Lonsdorf et al., 2017). Researchers typically assess threat acquisition, extinction, and extinction retention by measuring the differential responses to CS+ and CS-, using physiological indicators e.g., skin conductance response (SCR), fear potentiated startle (FPS), functional magnetic resonance imaging (fMRI) or behavioural ratings e.g., perceived expectancy of US presentation (EXP), anxiety/distress (affect) (Lonsdorf et al., 2017).

Researchers have theorised that extinction learning is underpinned by a process known as inhibitory learning (Bouton, 2004; Bouton et al., 2021; Delamater et al., 2004; Myers & Davis, 2007). During extinction learning, a new safety association is formed in relation to the CS+ (CS+/no-US) which then competes with the older threat association (CS+/US). Through repeated CS+/no-US pairings the newer safety association begins to dominate the older threat association, thus inhibiting the experience and expression of fear (Craske et al., 2012). Furthermore, it is argued that threat conditioning and extinction principles provide an effective framework for understanding the genesis, maintenance, and treatment of pathological fear and anxiety (Mineka & Zinbarg, 2006). Specifically, threat acquisition models the genesis and development of anxious and fearful responding (Mineka & Oehlberg, 2008; Mineka & Zinbarg, 2006; Öhman & Mineka, 2001), and extinction learning represents the unlearning of previously acquired anxiety, fear, or disgust responses akin to typical patterns of patient responding during exposure-based treatments (Dunsmoor et al., 2015; Milad & Quirk, 2012; Vervliet et al., 2013). Additionally, the 'return of fear' effect seen during extinction retention (Lornsdorf et al., 2017) is both qualitatively and practically similar to the experience of clinical relapse after successful exposure treatment (Levy et al., 2021; Vervliet et al., 2013). Hence, threat conditioning research is thought to represent a translational bridge between empirical behavioural research and clinically oriented research and practice (Craske et al., 2018). Indeed, it is well-established within clinical research that exposure-based therapies are explicitly based on classical conditioning and extinction principles (Boschen et al., 2009; Foa & McLean, 2016; Rachman, 2015). Yet, despite the concrete finding that exposure therapies are both efficacious and effective treatments for anxiety and stressor-related disorders (Hofmann & Smits, 2008; Norton & Price, 2007), and that exposure forms a key part of the treatment effect (Carpenter et al., 2018), they are also characterised by high rates of treatment failure and low-to-moderate relapse rates (Bandelow et al., 2017; Levy et al., 2021; Lorimer et al., 2021; Springer et al., 2018). As a result, clinical researchers have suggested that further examination of threat acquisition and extinction in relation to clinical anxiety disorders is both warranted and essential when it comes to improving exposure-based therapies for the benefit of future patients (Craske et al., 2012, 2014, 2022).

Over the last two decades there has been a large proliferation of studies investigating threat conditioning and extinction differences between individuals with and without anxiety-related disorders (ADs) (Craske et al., 2022). Said research generally finds evidence of patient-control differences in such processes, although results vary in relation to certain factors (Duits et al., 2015; Kausche et al., 2025). For instance, Duits et al., (2015) carried out a *meta*-analysis on studies comparing patients with ADs (anxiety disorders, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD)) and non-clinical control subjects in relation to indices of conditioned and differential responding during both threat acquisition and extinction. The analysis revealed that AD patients, compared to controls, had higher responses to the CS-, yet comparable responses to the CS+, during acquisition. Further, patients displayed heightened responses to the CS+, but not the CS-, during extinction. In sum, this suggests that AD patients tend to generalise threat responses from threatening to non-threatening stimuli or display muted safety learning in relation to safety stimuli, whilst also displaying impaired, or muted, extinction learning. A more recent review and *meta*-analysis by Kausche et al. (2025) on the same topic has replicated, contradicted, and extended these findings. Like Duits et al., (2015), this analysis demonstrated heightened patient responding to the CS- during acquisition via multiple different conditioning measures (FPS, EXP, and affect ratings). However, AD patients also reported higher affect ratings towards the CS+ during acquisition (Kausche et al., 2025), hence contradicting previous findings slightly (Duits et al., 2015). Further, the review also demonstrated heightened patient responding to the CS+ (affect ratings) and CS- (EXP and affect ratings) during extinction hence both corroborating and contradicting previous findings. Extending previous research, the analysis revealed heightened patient responding to the CS- (EXP and affect ratings) and CS+ (affect ratings) during extinction retention; although said results may be thwarted by publication bias (Kausche et al., 2025). In sum, these results suggest that AD patients have a tendency to display heightened threat acquisition, muted safety learning/threat generalisation, and prolonged or muted extinction learning/continued heightened responding to safety stimuli during both the extinction and retention phases. Hence, these findings provide strong evidence for the presence of altered conditioning processes within individuals with ADs. However, despite the presence of such effects across ADs in general, variation was found in relation to specific ADs. For instance, said analyses revealed differences between PTSD patients and other anxiety disorders/OCD patients (patient group consisting of those diagnosed with an anxiety disorder or OCD) in conditioning effects, as well as unique patient-control effects per subgroup e.g., larger FPS responses to the CS+ and larger CS+/CS- discrimination scores in relation to PTSD patients, but not within the anxiety disorder/OCD group (Kausche et al., 2025). Similarly, multiple individual studies have found similar unique patient-control differences in conditioning indices per specific ADs (Lissek et al., 2010; Otto et al., 2014; Rabinak et al., 2017). Hence, it would appear that individual ADs may possess their own unique associations with threat acquisition, extinction learning, and extinction retention processes that warrant further attention.

Currently, there has been two systematic reviews published that explicitly investigate patient-control differences in threat conditioning within specific ADs: Cooper and Dunsmoor (2021) for OCD, and Wake et al. (2024) for social anxiety disorder (SAD). OCD-control differences were investigated via a narrative systematic review which found mixed evidence for increased patient responses to the CS+ during acquisition, and strong evidence of increased CS+ responses and larger CS+/CS- discrimination scores in patients during the extinction and retention phases respectively (Cooper & Dunsmoor, 2021). Hence, largely mirroring the effects found in relation to ADs in general i.e., heightened patient responding although with some incongruent and omitted effects (Kausche et al., 2025). On the other hand, the *meta*-analysis carried out by Wake et al. (2024) found little evidence of SAD-control differences in conditioned or differential responding during both acquisition and

extinction. Therefore, demonstrating high inter-diagnostic variation in patient-control differences in threat acquisition and extinction processes. Investigating this variability may result in the identification of disorder-specific knowledge which possesses potential clinical utility. Therefore, further investigation of conditioning processes in relation to specific diagnostic categories is warranted. Despite the long-standing centrality of Pavlovian conditioning principles within psychopathological models of specific phobia (SP; Davey, 1992; Field, 2006), and the large prevalence of panic disorder (PD) patients within conditioning research (Kausche et al., 2025), there has not yet been a systematic review focussing on patient-control differences in threat conditioning for either of these disorders. This represents a major gap in the threat conditioning literature given that both PD and SP are associated with specific threat-stimulus associations. For instance, those with PD often fear specific internal physical sensations such as increased heart rate, stomach distress, light-headedness etc (American Psychiatric Association (APA), 2022). Similarly, SPs are diagnosed on the basis of there being a specific threat-stimulus association that causes clinically significant distress such as a fear of spiders in the case of arachnophobia or a fear of heights in the case of acrophobia (APA, 2022). Due to this, patient-control differences in conditioning processes may be particularly relevant to these disorders as opposed to other non-reviewed disorders, hence warranting further inquiry.

The aim of the present study was to carry out a narrative systematic review to investigate patient-control differences in conditioned responding within human threat conditioning studies for both SP and PD separately. The current review synthesises findings in patient-control differences in CS+ responding, CS- responding, and CS+/CS- discrimination across all three conditioning phases (acquisition, extinction, and retention). Further, this review discusses these differences in relation to the main conditioning measures used within threat conditioning research e.g., FPS, fMRI, SCR, behavioural ratings etc. Further, key study characteristics were sought and reported to further contextualise the findings e.g., country of study, reinforcement rates, instruction protocols utilised etc. For clarity, this review defines both PD and SP in accordance with the most recent diagnostic and statistical manual (DSM-V-TR; APA, 2022). Namely, that PD is characterised by recurrent panic attacks and persistent concern/worry, or excessive avoidance, at the prospect of further panic attacks which causes clinically significant impairment or distress. And SP is characterised by marked and disproportionate fear/anxiety in relation to a specific object or situation that causes clinically significant distress or impairment (APA, 2022). Contrary to previous reviews on this topic, the current review includes 'no-predictable-unpredictable threat' designs (NPU; Schmitz & Grillon, 2012) as examples of threat-conditioning, due to the conceptual and practical overlap between the 'No' and 'Predictable' conditions and CS- and CS+ stimuli respectively. Even though threat conditioning (Lonsdorf et al., 2017) and NPU procedures (Schmitz & Grillon, 2012) are similar in design and implications, the two subfields have rarely been examined together. Hence, the inclusion of these studies should increase the breadth of data collected, and consequently, improve the scientific and clinical significance of the conclusions of this review.

2. Method

This review was designed and implemented in accordance with best-practice guidelines for quantitative systematic reviews without a *meta*-analytic component (PRISMA, Page et al., 2021; SWiM, Campbell et al., 2020). The main author pre-registered the study with the international prospective register of systematic reviews (PROSPERO) prior to commencing the review (CRD42024583051). Initially, both PubMED and Web of Science were searched for articles published up to the 23rd of August 2024. Screening was carried out using Rayyan AI software (Ouzzani et al., 2016). A separate search was carried out for panic disorder and specific phobia per database. Titles and abstracts were searched using the following search terms (("Panic" OR "Panic Disorder*" OR "Panic Patient*") AND ("Conditioning" OR "Conditioned" AND ("Fear" OR "Aversive" OR "Classical" OR "Pavlovian" OR "Associative" OR "Extinction" OR "Acquisition" OR "Differential" OR "Evaluative") OR "Associative learning" OR "NPU" OR "predictable threat" OR "unpredictable threat" OR "threat predictability")) NOT (Review)) for panic disorder, and (("Specific phobia*" OR "Phobi*" OR "Phobic disorder*" NOT "Social") AND ("Conditioning" OR "Conditioned" AND ("Fear" OR "Aversive" OR "Classical" OR "Pavlovian" OR "Associative" OR "Extinction" OR "Acquisition" OR "Differential" OR "Evaluative") OR "Associative learning" OR "NPU" OR "predictable threat" OR "unpredictable threat" OR "threat predictability")) NOT (Review)) for specific phobia.

The resultant titles and abstracts were then subject to Rayyan's automatic duplicate detection function. All potential duplicates were manually checked by the primary reviewer (KS) and removed as necessary. The remaining studies were screened in accordance with the following PICO criteria:

- Population: Adult humans (18 + years) that meet diagnostic criteria for either panic disorder or specific phobia via standardised clinical interview.
- Intervention/exposure: Classical threat conditioning task or unpredictable threat paradigm task with a discernible CS+ and CS-.
- Comparator/control: Adult human (18 + years) non-clinical control participants.
- Outcome: Ratings or indices of distress, valence, or learning associated with both a CS+ and CS- per group.

Ultimately, experimental studies comparing conditioned responding to both a CS+ and CS- within either a threat conditioning or unpredictable threat task between PD or SP patients and non-clinical controls were sought. The following types of articles were excluded: animal studies, studies on children or adolescent humans (17 years or lower), qualitative studies, case studies, existing reviews, non-English language studies, and articles published before 1975. Screening was carried out by three independent reviewers (KS, JM, EB) who screened the title, abstract, and, if needed, the full text of each article simultaneously to determine suitability. Reviewers regularly discussed discrepancies in screening and/or ambiguous articles to reach a final screening decision via consensus. Post-screening, full-text reviewing commenced which included reading each paper's method and results section in detail to apply the previously mentioned criteria a second time (see Fig. 1 for flowchart). Alongside this, the reviewers transferred the study characteristics of each included article to a shared excel sheet to facilitate data extraction (see Table 1). The primary (KS) and senior (JM) reviewers were in complete agreement regarding all screening decisions by the end of this process. Finally, each paper was assessed for research quality using an adapted version of the Effective Public Health Practice Project tool (EPHPP; Thomas et al., 2004) i.e., sections C, D, and G were removed as they were not relevant to the studies sought within this review. The adapted EPHPP tool included sections A, B, E, F, and H which rated quality on the basis of selection bias, study design, data collection methods, handling of withdrawal/drop out, and appropriateness of analyses respectively. The primary reviewer assessed all studies independently using the EPHPP tool and regularly sought advice from the senior reviewer when necessary. This allowed the primary reviewer to benefit from the senior reviewer's expertise in assessing research quality whilst simultaneously prioritising practicality and feasibility. Ultimately, all quality ratings were overseen by the senior reviewer. Due to there being a sole rater, inter-rater agreement was not assessed. Each study was rated as strong, moderate, or weak in quality (see Table 1).

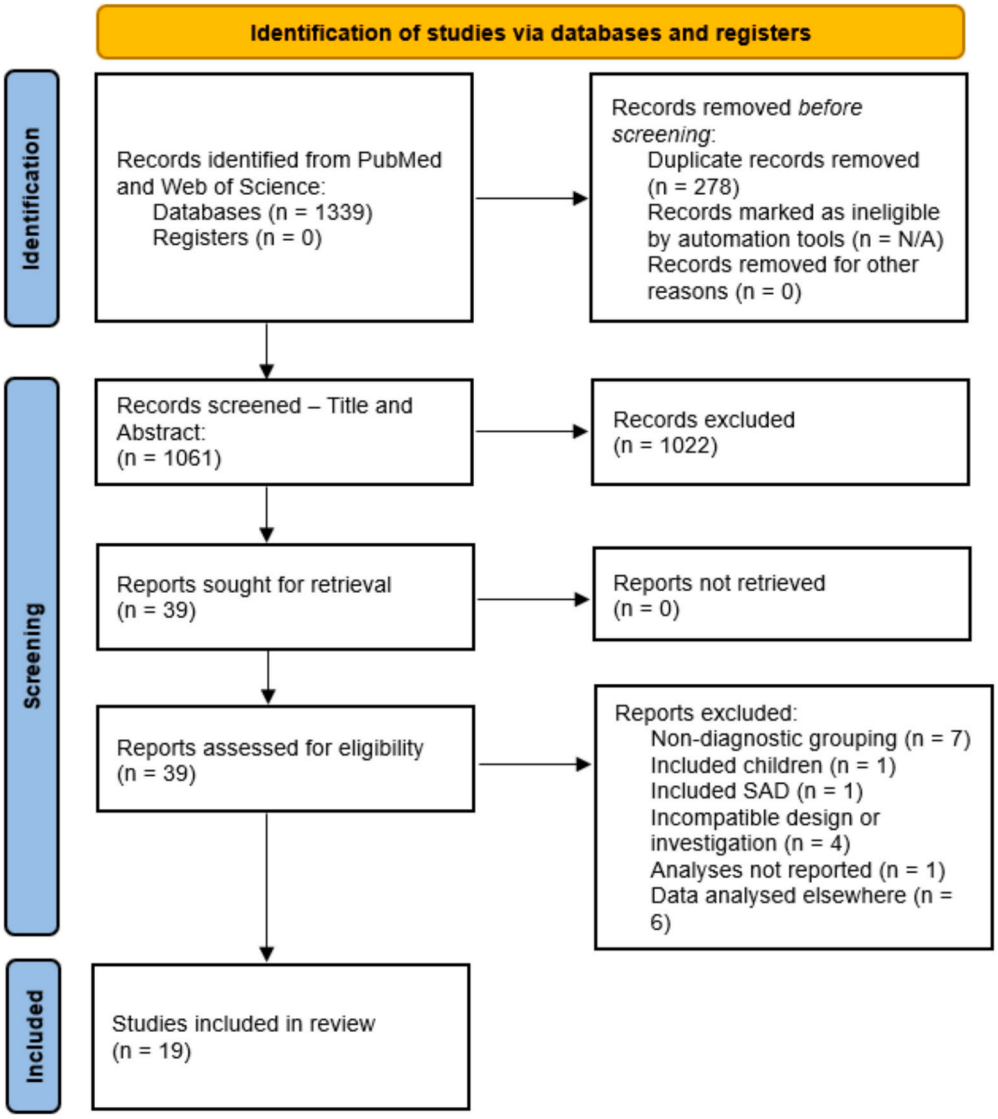

Fig. 1. A Figure demonstrating the Identification and Screening of Study Articles. Note. Flowchart template was downloaded from the PRISMA guidelines for Systematic Review (Page et al., 2021). Also, Rayyan's auto-duplicate detection tool was used to highlight possible duplicates; KS removed all duplicates by hand. 'Data analysed elsewhere' = secondary analysis of parent study already included in review.

3. Results

3.1. Study Characteristics

The full screening and reviewing process resulted in a total of 19 studies that met the inclusion criteria for the current review out of the original 1,061 studies eligible for screening (Fig. 1). Within the final sample, 12 studies utilised a threat-conditioning paradigm, five studies utilised an NPU experimental paradigm, and one study outlined a mixed procedure with elements of both paradigms (see Table 1 for overview of study characteristics). Of the 12 threat-conditioning studies, two described evaluative conditioning procedures (Schienle et al., 2005; Schweckendiek et al., 2011), one employed a cue-in-context component (Marin et al., 2020), and another included an avoidance task component (De Kleine et al., 2023). The previously mentioned avoidance and contextual variables were shared equally across both the patient and control groups, and did not interfere directly with the presentation of CS stimuli, therefore these studies were not excluded. Each remaining threat-conditioning study outlined a relatively typical approach. Of the five NPU studies, one experiment included a modified NPU design where the interim between the CS+ and the US presentation was interspersed with random facial stimuli (Klahn et al., 2017). Further, another study included a modified NPU design which was characterised by elongated (3 min) CS+ and CS- trials with the presentation of one single US at the offset of each CS+ trial (Benke et al., 2023). Despite these peculiarities, both studies were included in the review as the CS+ and CS- stimuli represented the anticipation of threat and safety respectively, hence satisfying our inclusion criteria. Each remaining NPU study outlined a relatively typical approach. Lastly, the mixed-procedure (Siminski et al., 2021) consisted of an instructed threat-conditioning paradigm alongside stimuli that cued either the exact or random timing of the US presentation, hence representing predictable and unpredictable cues typically included within NPU studies (Schmitz & Grillon, 2012). However, this study was ultimately included in the review as the predictable and unpredictable effects were balanced across both CS stimuli and experimental groups.

Ultimately, the final sample included 12 studies with PD samples, five with SP samples, and two with both PD and SP samples, in comparison to non-clinical controls. As per our inclusion/exclusion criteria, each study included explicitly clinical, as opposed to sub-clinical, PD and/or SP patients. Most studies reported the utilisation of appropriate and validated structured-clinical interviews to establish a primary

Table 1
Final sample of included studies and their associated characteristics.

Study	Diagnostic Group	*n* (Group)	Presence of Comorbidity	Paradigm	CS Type and Number	US Type	CS+/US Contingency	Instruction Type	Relevant Phases	CR Measures	Study Quality
Benke et al., (2023)	PD/AG	73 (PD/AG), 52 (CON)	Unspecified	NPU	Coloured slides: 2 CS+, 2 CS-	Shock + HV-Induction Task	100%	Instructed	ACQ	FPS (EMG), Ratings (ANX, DSM-4 Panic Symptoms)	Strong
Brinkmann et al., (2017)	PD and PD/AG	17 (PD), 19 (CON)	Yes	CC	Hash or percentage sign: 1 CS+, 1 CS-	Aversive Scream	100%	Instructed	ACQ	fMRI (ROI: amygdala, insula, ACC, and PFC (lateral, medial), and PPI: BNST and amygdala), Ratings (VAL, ANX, ARO)	Strong
De Kleine et al., (2023)	PD/AG	40 (PD/AG), 47 (CON)	Yes (1 case)	CC[b]	Office image with different coloured lamps: ACQ 1 (2 CS+. 1 CS-), ACQ 2 (1 CS+, 1 CS-)	Aversive Images	100%	Instructed	ACQ 1, ACQ 2[b]	Ratings (EXP)	Strong
Gorka et al., (2017)	SP	24 (SP), 41 (CON)	Yes (1 case)	NPU	Text and visual countdown: 1 CS+, 1 CS-	Shock	100%	Instructed	ACQ	FPS (EMG)	Strong
Klahn et al., (2017)	PD, SP	20 (PD), 20 (SP), 20 (CON)	No	NPU	Triangle and tone, and absence of cue: 1 CS+, 1 CS-	Monster Video and Aversive Scream	100%	Instructed	ACQ	Ratings (Discomfort (agitation, and mood))	Moderate
Li & Graham (2016)	SP (spider)	34 (SP), 26 (CON)	Yes	CC	Spider images: 1 CS+, 1 CS-	Shock	62.50%	Unspecified	ACQ, EXT, RET	SCR, Ratings (EXP, VAL)	Moderate
Lissek et al., (2009)	PD and PD/AG	24 (PD with and without AG), 24 (CON)	Yes	CC	Bowl or mug image: 1 CS+, 1 CS-	Shock	100%	Uninstructed	ACQ, EXT	FPS (EMG), Ratings (ANX)	Strong
Lissek et al., (2010)	PD and PD/AG	19 (PD with and without AG), 19 (CON)	Yes	CC	Large and small circular rings : 1 CS+, 1 CS-	Shock	75%	Unspecified	ACQ	FPS (EMG), Ratings (EXP (risk), ANX)	Strong
Lueken et al., (2014)	PD/AG	60 (PD), 60 (CON)	Permitted, but not reported	CC	Coloured Shapes: 1 CS+, 1 CS-	Aversive Tone	50%	Unspecified	ACQ, EXT	FMRI (whole-brain analysis, and ROI: Amygdala) Ratings (VAL, ARO)	Strong
Marin et al., (2020)	PD, SP	18 (PD), 20 (SP), 21 (CON)	Unspecified	CC[d]	Desk or bookshelf image with different coloured lamps: 1 CS+, 1 CS-	Shock	62.50%	Unspecified	ACQ, EXT, RET	fMRI (ROI: Amygdala, HiPPC, Insular, dACC, vmPFC), SCR	Strong
Michael et al., (2007)	PD and PD/AG	39 (PD with and without AG), 33 (CON)	Yes	CC	Coloured Rorschach inkblots: 1 CS+, 1 CS-	Shock	100%	Partially Instructed	ACQ, EXT	SCR, Ratings (VAL)	Strong
Otto et al., (2014)	PD and PD/AG	21 (PD with and without AG), 96 (CON)	Yes	CC	Yellow circle or white square: 1 CS+, 1 CS-	Shock	100%	Uninstructed	ACQ[e]	SCR	Strong
Schienle et al., (2005)	SP(BII)	23 (SP), 20 (CON)	Unspecified	CC[c]	Neutral pictures: 2 CS+, 1 CS-	Aversive (Fear, Disgust) Images	100%	Unspecified	ACQ	Ratings (VAL)	Strong
Schwarzmeier et al., (2019)	PD	10 (PD), 10 (CON)	Permitted, but not reported	CC	Neutral faces: 1 CS+, 1 CS-	Aversive Scream	100%	Unspecified	ACQ, EXT, RET	fMRI (Whole-brain analysis), SCR, Ratings (VAL, ARO)	Strong
Schweckendiek et al., (2011)	SP (spider)	15 (SP), 14 (CON)	No	CC[c]	Grey shapes: 2 CS+, 1 CS-	Aversive (fear-relevant, fear-irrelevant) Images	100%	Uninstructed	ACQ[e]	fMRI (Whole-brain analysis, ROI: bilateral amygdala, ACC, mPFC, bilateral OFC, bilateral thalamus and bilateral insula), SCR, Ratings (Fear, Disgust, ARO, VAL)	Strong

(*continued on next page*)

Table 1 (*continued*)

Study	Diagnostic Group	*n* (Group)	Presence of Comorbidity	Paradigm	CS Type and Number	US Type	CS+/US Contingency	Instruction Type	Relevant Phases	CR Measures	Study Quality
Shankman et al., (2013)	PD, PD/MDD, MDD	28 (PD), 58 (PD/MDD), 40 (MDD), 65 (CON)	Yes	NPU	Different coloured shapes: 1 CS+, 1 CS-	Shock	37.50%	Instructed	ACQ	FPS (EMG), Ratings (ANX)	Strong
Siminski et al., (2021)	SP (spider)	21 (SP), 21 (CON)	MDD or other SP diagnosis permitted, but not reported	CC/PU	Letters A or B: 1 CS+, 1 CS-	Spider Images	100%	Instructed	ACQ	fMRI (ROI: BNST and centromedial amygdala)	Strong
Stevens et al., (2018)[a]	PD, PD/MDD, MDD	27 (PD), 56 (PD/MDD), 37 (MDD), 61 (CON)	Yes	NPU	Different coloured shapes: 1 CS+, 1 CS-	Shock	37.50%	Instructed	ACQ	ERP	Strong
Tinoco-Gonzalez et al. (Study 1, 2015)	PD/AG	16 (PD/AG), 16 (CON)	Specific secondary diagnoses permitted (non-MDD, PTSD, psychosis, or bipolar), but not reported	CC	Neutral faces: 1 CS+, 1 CS-	Critical facial expression and verbal insult	100%	Unspecified	ACQ, EXT	FPS, Ratings (ARO, ANX, VAL)	Moderate

Note. This table represents the study characteristics associated with each included study as it pertains to our research question i.e. any information not relevant to this research question has been excluded from the table and can be accessed by visiting the original study. Abbreviations: PD = Panic disorder, AG = Agoraphobia, SP = Specific Phobia, CON = non-clinical control, BII = Blood, Injury, and Injection, MDD = Major Depressive Disorder, CC = Classical/Threat Conditioning Experiment, NPU = No-Predictable-Unpredictable Threat Task, CC/PU = Mixture of both Paradigms, CS = Conditioned Stimuli, CS+ = Conditioned Threat Stimulus, CS- = Conditioned Safety Stimulus, US = Unconditioned Stimulus, Shock = Electric Shock, HV = Hyperventilation, ACQ = Threat Acquisition Phase, EXT = Threat Extinction Phase, RET = Extinction Retention/Recall Phase, FPS = Fear-Potentiated Startle, EMG = Electromyography, DSM = Diagnostic-Statistical Manual, ANX = Anxiety, EXP = US Expectancy, VAL = Valence, ARO = Arousal, SCR = Skin Conductance Response, fMRI = Functional Magnetic Resonance Imaging, ROI = Region of Interest Analysis, PPI = Psychophysiological Interaction Analysis, ACC = Anterior Cingulate Cortex, OFC = Orbitofrontal Cortex, PFC = Prefrontal Cortex, HiPPC = Hippocampus, BNST = Bed Nucleus Stria Terminalis, ERP = Event-Related Potential, MDSQ = Multidimensional Mood State Questionnaire.

[a] ERP analysis of Shankman et al. (2013) data.

[b] Avoidance task component included.

[c] Evaluative conditioning task.

[d] Cue-in-context component included.

[e] Extra phases included but not analyses or reported.

diagnosis of either PD or SP, two studies stated the primary diagnosis without disclosing the method of assessment (Schwarzmeier et al., 2019; Schweckendiek et al., 2011), and one study used prior diagnosis as the basis for inclusion (Marin et al., 2020). All studies included true non-clinical control samples with no current evidence of psychiatric morbidity, except for Shankman et al. (2013) and Stevens et al. (2018) as both included individuals with major depressive disorder (MDD) in their control samples (dual analyses of the same participant data). Shankman et al. (2013) and Stevens et al. (2018) were ultimately included as participant MDD was present in both the clinical and non-clinical groups in similar proportions, hence any MDD-specific effects should occur equally in both groups. Each study included either an explicit or procedurally concordant threat acquisition phase and reported analyses appropriate to our research question. Further, 6 studies (1 SP, 4 PD, 1 PD/SP) outlined an appropriate threat extinction phase alongside analyses that related to our review question, and 3 studies (1 SP, 1 PD, 1 PD/SP) reported review-appropriate analyses in relation to an extinction retention/recall phase. Using the modified EPHPP tool (Thomas et al., 2004), 16 studies were rated as strong, and the remaining 3 as moderate, in research quality hence suggesting a reasonably high standard of research in this area. As a result, individual studies were not deprioritised or removed from the synthesis on the basis of low quality.

3.1.1. CS Type

Across the PD sample, different CS stimuli were employed: shapes or symbols ($k = 7$), facial stimuli ($k = 2$), image of scene with different coloured lamps ($k = 2$), neutral images ($k = 1$), combined shape and sound stimulus ($k = 1$), and coloured slides ($k = 1$). The SP sample had more variation in the use of CS stimuli: Shapes or symbols ($k = 1$), text and numerical countdown ($k = 1$), disorder-specific fear-relevant images ($k = 1$), image of scene with different coloured lamps ($k = 1$), neutral images ($k = 1$), combined shape and sound stimulus ($k = 1$), and alphabetical letters ($k = 1$) (see Table 1 for more details).

3.1.2. US Type

Across the PD sample, different US stimuli were employed: Electric shock stimulus ($k = 8$), aversive scream or sound ($k = 3$), hyperventilation induction task ($k = 1$), aversive images ($k = 1$), negative facial stimuli/insults ($k = 1$), and threatening video/aversive scream ($k = 1$). The SP sample employed the following US stimuli: Electric shock stimulus ($k = 3$), aversive images ($k = 2$), fear-relevant images ($k = 2$), and threatening video/stimulus ($k = 1$) (see Table 1 for more details).

3.1.3. CS+/US Reinforcement Rate

Most PD studies employed a continuous reinforcement schedule ($k = 9$) as opposed to an intermittent reinforcement schedule ($k = 5$). Similarly, most SP studies also employed a continuous reinforcement schedule ($k = 5$) as opposed to an intermittent reinforcement schedule ($k = 2$) (see Table 1 for more details).

3.1.4. Conditioning Measures

The following conditioning measures relevant to the review question were used across the final sample of PD studies: anxiety ratings ($k = 6$), valence ratings ($k = 5$), FPS ($k = 5$), SCR ($k = 4$), arousal ratings ($k = 4$), fMRI ($k = 4$), US expectancy ratings ($k = 2$), panic symptoms ($k = 1$), and ERP ($k = 1$). Similarly, the following conditioning measures were used across the final sample of SP studies: SCR ($k = 3$), valence ratings ($k = 3$), fMRI ($k = 3$), FPS ($k = 1$), US expectancy ratings ($k = 1$), arousal ratings ($k = 1$), fear ratings ($k = 1$), and disgust ratings ($k = 1$) (see Table 1 for more details). A *meta*-analysis was not employed as the included studies rarely listed the appropriate effect sizes, which is essential for carrying out such an analysis (Field & Gillett, 2010). As a result, each possible stage within this review would fail to meet the generally accepted threshold of at least five studies with comparable measures to justify the addition of a *meta*-analytic component (Myung, 2023).

3.1.5. Instruction Type

Conditioning studies differ regarding the level of instruction participants are given about the CS-US contingency: participants can be fully instructed about the CS-US contingency (instructed), partially instructed (partial), or not instructed at all about the CS-US contingency (uninstructed). Across the PD sample, instruction type varied between studies with 6 studies employing an instructed protocol, 1 study employing a partial protocol, 2 studies employing an uninstructed protocol, and 5 studies not specifying their instruction protocol. Further, across the SP sample, 4 studies employed an instructed protocol, 1 study employed an uninstructed protocol, and 3 studies did not specify their instruction protocol.

3.1.6. Context

Within the PD sample, most research took place in either the United States ($k = 6$) or Germany ($k = 5$), however research also took place in Switzerland ($k = 1$), the Netherlands ($k = 1$), and Spain ($k = 1$). Similarly, within the SP sample, research took place in Germany ($k = 4$), the United States ($k = 2$), and Australia ($k = 1$).

In summary, the current systematic review represents a valid basis for the investigation of patient-control differences in threat acquisition, extinction, and extinction retention in relation to panic disorder and specific phobia. Please note that not all of the effects, analyses, or results associated with each of the included studies are outlined in this review as many aspects did not relate to our review question.

3.2. Collation and Synthesis of Key Results

Each included study was read in close detail and all results pertaining to patient-control differences in CS+ responding, CS- responding, and CS+/CS- discrimination were retrieved. These results were then collated and tabulated to produce absolute frequencies of significant vs. null differences between groups per disorder, per conditioning phase, per outcome measure type. Study outcome measures were collated into the following subcategories: US expectancy ratings, distress ratings (anxiety, fear, disgust, negative mood, symptoms), valence ratings, arousal ratings, FPS, SCR, and miscellany. These subcategories were then collated into two superordinate categories: physiological measures (FPS, SCR, Miscellany) and subjective measures (US expectancy, distress, valence, and arousal ratings). fMRI results were synthesized separately to these superordinate categories as such data do not fit neatly into either physiological or subjective arousal i.e., neurological activity can indicate learning, inhibition etc. Additionally, the included fMRI studies had a wide variety of regional foci and differed in the level of conservatism of their analyses i.e., ROI vs whole-brain analyses which precludes them from any meaningful comparison to one another. Due to this, fMRI research is explored narratively and was not subjected to the formation of absolute frequencies of significant vs. null results. The following section is structured as follows: a table of key results in relation to each of the included studies followed by text outlining the absolute frequencies of significant vs. non-significant effects in relation to both superordinate categories per conditioning phase and an overall summary. Key results per each of the subcategories are then outlined in text. Followed lastly by a description of the results associated with each of the included fMRI studies per conditioning phase followed directly by a summary of said findings. This structure is outlined first for panic disorder and then for specific phobia. Results not included in the key results tables (Tables 2 and 4) are also outlined in text where necessary. For ease, fMRI results have been bullet pointed and arranged alphabetically whilst simultaneously outlining subcortical structures first and cortical structures second.

3.2.1. Panic Disorder

Across the final pool of studies, key results were tabulated to provide an overview of PD-control differences in CS+ and CS- responding, alongside differences in CS+/CS- discrimination, within each of the

Table 2
Overview of key results in relation to the included panic disorder studies.

Study	Conditioning Phase	Measure and Analysis Details	PD vs. CON		
			CS+	CS-	CSdiff
Benke et al. (2023)	ACQ	FPS	PD>CON	NR	-
		ANX	PD>CON	PD>CON	-
		Panic Symptoms	PD>CON	PD>CON	-
Brinkmann et al. (2017)	ACQ	VAL	CON>PD	ns	-
		ANX	PD>CON	PD>CON	-
		ARO	PD>CON	ns	-
		fMRI (Amygdala)	-	-	PD>CON
		fMRI (Insula)	-	-	PD>CON
		fMRI (ACC)	-	-	PD>CON
		fMRI ((l/m)PFC)	-	-	PD>CON
		fMRI (BNST)	-	-	PD>CON
De Kleine et al. (2023)	ACQ 1	EXP	ns	ns	-
	ACQ 2	EXP	ns	ns	-
Klahn et al. (2017)	ACQ	Discomfort (MDSQ)	PD>CON	PD>CON	-
Lissek et al. (2009)	ACQ	FPS	ns	PD>CON	CON>PD
		ANX	ns	ns	ns
	EXT	FPS	ns	ns	ns
		ANX	ns	PD>CON	ns
Lissek et al. (2010)	ACQ	FPS	ns	ns	ns
		EXP	PD>CON	CON>PD	CON>PD
		ANX	CON>PD	PD>CON	CON>PD
Lueken et al. (2014)	ACQ	VAL	CON>PD	CON>PD	CON>PD[a]
		ARO	PD>CON	PD>CON	CON>PD[a]
		fMRI (Amygdala)	-	-	ns
		fMRI (Amygdala) *E*	-	-	ns
		Whole brain	-	-	*In text*
	EXT	VAL	CON>PD	CON>PD	ns[b]
		ARO	PD>CON	PD>CON	ns[b]
		fMRI (Amygdala)	-	-	ns
Marin et al. (2020)	ACQ	SCR	ns	ns	-
		fMRI (Amygdala)	-	-	ns
		fMRI (HiPPC)	-	-	ns
		fMRI (Insula)	-	-	ns
		fMRI (dACC)	-	-	ns
		fMRI (vmPFC)	-	-	ns
	EXT	SCR	CON>PD	CON>PD	
		fMRI (Amygdala) *E*	-	-	ns
		fMRI (HiPPC) *E*	-	-	ns
		fMRI (Insula) *E*	-	-	ns
		fMRI (dACC) *E*	-	-	ns
		fMRI (vmPFC) *E*	-	-	ns
		fMRI (Amygdala) *L*	-	-	ns
		fMRI (HiPPC) *L*	-	-	ns
		fMRI (Insula) *L*	-	-	ns
		fMRI (dACC) *L*	-	-	ns
		fMRI (vmPFC) *L*	-	-	ns
	RET	SCR	ns	ns	-
		fMRI (Amygdala)	-	-	ns
		fMRI (HiPPC)	-	-	ns
		fMRI (Insula)	-	-	ns
		fMRI (dACC)	-	-	ns
		fMRI (vmPFC)	-	-	CON>PD
Michael et al. (2007)	ACQ	SCR	ns	ns	-
		VAL	ns	ns	-
	EXT	SCR	PD>CON	ns	-
		VAL	CON>PD	ns	-
Otto et al. (2014)	ACQ	SCR	ns	NR	ns
Schwarzmeier et al. (2019)	ACQ	SCR	ns	ns	-
		VAL	ns	ns	-
		ARO	ns	ns	-

(*continued on next page*)

Table 2 (*continued*)

Study	Conditioning Phase	Measure and Analysis Details	PD vs. CON		
			CS+	CS-	CSdiff
		fMRI (Whole brain)	-	-	*In Text*
	EXT	SCR	ns	ns	-
		VAL	ns	ns	-
		ARO	ns	ns	-
		fMRI (Whole brain)	-	-	*In Text*
	RET	SCR	ns	ns	-
		VAL	ns	ns	-
		ARO	ns	ns	-
		fMRI (Whole brain)	-	-	*In Text*
Shankman et al. (2013)	ACQ	FPS	-	ns	PD>CON
		ANX	-	ns	NR
Stevens et al. (2018)	ACQ	ERP (N100)	-	-	ns
		ERP (P300)	-	-	ns
Tinoco-Gonzalez et al. (2015) (Study 1)	ACQ	FPS	-	-	ns
		ANX	ns	ns	-
		VAL	ns	ns	-
		ARO	ns	ns	-
	EXT	ANX	ns	ns	-
		VAL	ns	ns	-
		ARO	ns	ns	-

Note. CS + and CS- refer to average scores or baseline/corrected change scores e.g., Michael et al. (2007). CSdiff refers to CS + -CS- discrimination scores. PD > CON and CON > PD refer to statistically significant differences between groups in the specified direction. All fMRI results refer to region of interest (ROI) analyses; whole-brain and PPI analyses are outlined in text. Abbreviations/key: PD = Panic Disorder, CON = Non-Clinical Controls, ns = Non-Significant Differences, Hyphen (–) = Analyses not Performed, NR = Analyses Performed but not Reported, Overall = Whole Phase, Early = Early Subsection of Phase, Late = Late Subsection of Phase.
[a] Statistical CS+/CS- discrimination observed in control group but not PD group.
[b] Discrimination not observed in either group.

Table 3
Overview of Frequencies and Percentages of Significant vs Non-Significant Group Comparisons across CS + responding, CS- responding, and CS+/CS- Discrimination for Physiological Measures and Ratings Separately for all PD Studies.

Phase	Metric	Physio			Ratings		
		PD > CON	CON > PD	ns	PD > CON	CON > PD	ns
ACQ	CS+	1(14.29)	0	6(85.71)	9(47.37)	1(5.26)	9(47.37)
	CS-	1(16.67)	0	5(83.33)	7(35)	1(5)	12(60)
	CS Diff	1(14.29)	1(14.29)	5(71.43)	0	4(80)	1(20)
EXT	CS+	1(25)	1(25)	2(50)	3(33.33)	0	6(66.67)
	CS-	0	1(25)	3(75)	3(33.33)	0	6(66.67)
	CS Diff	0	0	1(100)	0	0	3(100)
RET	CS+	0	0	2(100)	0	0	2(100)
	CS-	0	0	2(100)	0	0	2(100)
	CS Diff	–	–	–	–	–	–

Note. Frequency of effects displayed in cell. Percentage of effects in relation to all studies represented in parentheses. – indicates a lack of analyses carried out in this domain. VAL effects have been reversed for the sake of congruence with other measures i.e., CON > PD has been listed as an example of heightened responding in the PD group as it indicates a heightened dislike of the stimulus and vice versa. Physio category includes FPS, SCR, and ERP, whereas ratings category includes all ratings. Please note that an individual study may contain multiple analyses that contribute to the absolute frequencies associated with the physio and ratings categories.

included studies (Table 2).

3.2.1.1. Threat Acquisition. Across all physiological outcomes, there is strong evidence for a lack of patient-control differences in CS+/CS- discrimination, CS+ responding, and CS- responding with 5 out of 7, 6 out of 7, and 5 out of 6 analyses finding null group differences respectively (Table 3). Alternatively, for subjective outcomes, there is strong evidence for heightened CS+/CS- discrimination within non-clinical controls with 4 out of 5 analyses finding heightened discrimination (observed between groups or demonstrated statistically) within the control group. Further, there is mixed evidence for heightened patient responses to the CS+ with 9 out of 18 analyses finding heightened CS+ ratings in patients vs. controls and the same number of analyses finding null group differences. Whereas there is stronger evidence for a lack of patient-control differences in CS- responding with 12 out of 18 analyses finding a null effect.

3.2.1.2. Threat Extinction. Across all physiological outcomes, there is strong evidence for a lack of patient-control differences in CS+/CS- discrimination and CS- responding with 1 out of 1 and 3 out of 4 analyses finding null group differences respectively (Table 3). Further, the balance of evidence suggests a lack of patient-control differences in CS+ responding also with 2 out of 4 analyses finding null comparisons vs. 1 analysis finding heightened CS+ scores in patients and controls each. Similarly, across subjective measures, there is strong evidence for a lack of patient-control differences in CS+/CS- discrimination, CS+

Table 4
Overview of key results in relation to the included specific phobia studies.

Study	Conditioning Phase	Measure and Analysis Details	SP vs. CON		
			CS+	CS-	CS Diff
Gorka et al. (2017)	ACQ	FPS	-	-	ns
Klahn et al. (2017)	ACQ	Discomfort (MDSQ)	ns	ns	-
Li and Graham (2016)	ACQ	EXP	ns	ns	-
		VAL	CON>SP	CON>SP	-
		SCR	SP>CON	SP>CON	-
	EXT	EXP	SP>CON	ns	-
		VAL	CON>SP	CON>SP	-
		SCR	ns	ns	-
	RET	EXP	ns	ns	-
		VAL	CON>SP	CON>SP	-
		SCR	ns	ns	-
Marin et al. (2020)	ACQ	SCR	ns	ns	-
		fMRI (Amygdala)	-	-	ns
		fMRI (HiPPC)	-	-	ns
		fMRI (Insula)	-	-	ns
		fMRI (dACC)	-	-	ns
		fMRI (vmPFC)	-	-	ns
	EXT	SCR	CON>SP	CON>SP	-
		fMRI (Amygdala) *E*	-	-	ns
		fMRI (HiPPC) *E*	-	-	ns
		fMRI (Insula) *E*	-	-	ns
		fMRI (dACC) *E*	-	-	ns
		fMRI (vmPFC) *E*	-	-	ns
		fMRI (Amygdala) *L*	-	-	ns
		fMRI (HiPPC) *L*	-	-	ns
		fMRI (Insula) *L*	-	-	ns
		fMRI (dACC) *L*	-	-	ns
		fMRI (vmPFC) *L*	-	-	ns
	RET	SCR	ns	ns	-
		fMRI (Amygdala)	-	-	ns
		fMRI (HiPPC)	-	-	ns
		fMRI (Insula)	-	-	ns
		fMRI (dACC)	-	-	ns
		fMRI (vmPFC)	-	-	CON>SP
Schienle et al. (2005)	ACQ	VAL		ns	
		VAL (Fear CS+)	ns		-
		VAL (Disgust CS+)	ns		-
Schweckendiek et al. (2011)	ACQ	Fear		-	
		Fear (F-rel CS+)	-		SP>CON
		Fear (F-irrel CS+)	-		NR
		Disgust		-	
		Disgust (F-rel CS+)	-		SP>CON
		Disgust (F-irrel CS+)	-		NR
		ARO		-	
		ARO (F-rel CS+)	-		SP>CON
		ARO (F-irrel CS+)	-		NR
		VAL		-	
		VAL (F-rel CS+)	-		SP>CON
		VAL (F-irrel CS+)	-		NR
		SCR		-	
		SCR (F-rel CS+)	-		SP>CON
		SCR (F-irrel CS+)	-		NR
		fMRI (blAmygdala; F-rel CS+) *E*	-	-	ns
		fMRI (ACC; F-rel CS+) *E*	-	-	ns
		fMRI (mPFC; F-rel CS+) *E*	-	-	SP>CON
		fMRI (blOFC; F-rel CS+) *E*	-	-	ns
		fMRI (bl Thalamus; F-rel CS+) *E*	-	-	ns
		fMRI (bl Insula; F-rel CS+) *E*	-	-	SP>CON
		fMRI (All ROIs; F-rel CS+) *L*	-	-	ns
		fMRI (All ROIs; F-irrel CS+) *E*	-	-	ns
		fMRI (All ROIs; F-irrel CS+) *L*	-	-	ns
		fMRI (Whole Brain; F-rel and F-irrel)	-	-	*In text*
Siminski et al. (2021)	ACQ	fMRI (BNST)	-	-	ns
		fMRI (cmAmygdala)	-	-	ns

Note. CS + and CS- represent either average scores or baseline/corrected change scores e.g., Schienle et al. (2005). CSdiff refers to CS + -CS- discrimination scores. SP > CON and CON > SP refer to statistically significant differences between groups in the specified direction. All fMRI results refer to region of interest (ROI) analyses;

whole-brain and PPI analyses outlined in text. Fear Relevant and Fear-Irrelevant CS + effects are represented on different lines within same column. Abbreviations/key: SP = Specific Phobia, CON = Non-Clinical Controls, ns = Non-Significant Differences, Hyphen (−) = Analyses not Performed, NR = Analyses Performed but not Reported, Early = Early Subsection of Phase, Late = Late Subsection of Phase, F-rel = Fear Relevant, F-irrel = Fear Irrelevant.

responding, and CS- responding with 3 out of 3, 6 out of 9, and 6 out of 9 analyses finding null group differences respectively.

3.2.1.3. Extinction Retention. Within physiological measures, there is strong evidence for a lack of patient-control differences in CS+ and CS- responding with 2 out of 2 analyses finding null group differences for both CS types (Table 3). Similarly, across subjective measures, there is strong evidence for a lack of patient-control differences in CS+ and CS- responding with 2 out of 2 analyses finding null group differences for both CS types. There is a dearth of evidence for patient-control differences in CS+/CS- discrimination for both physiological and subjective measures.

3.2.1.4. Summary. In sum, these results provide tentative evidence for altered threat acquisition, but not threat extinction or extinction retention, in panic patients via reduced discrimination between the CS+ and CS- stimuli, and heightened CS+, but not CS-, responding. This suggests that panic patients possess heightened CS+ responding alongside a tendency to poorly discriminate between the CS+ and CS- during acquisition i.e., poorer threat acquisition, yet these effects only seem to materialize at the subjective level.

3.2.1.5. Sub-Categories

3.2.1.5.1. Threat Acquisition. US Expectancy Ratings: During threat acquisition, one (Lissek et al., 2010) out of three analyses demonstrated heightened expectancy ratings to the CS+ in patients compared to controls (De Kleine et al., 2023; Lissek et al., 2010). Similarly, expectancy ratings to the CS- were heightened in controls compared to patients in one (Lissek et al., 2010) out of three of these analyses. Only one of these studies investigated patient-control differences in discrimination and demonstrated heightened CS+/CS- discrimination of US expectancy scores in controls compared to patients (Lissek et al., 2010).

Valence Ratings: During threat acquisition, two (Brinkmann et al., 2017; Lueken et al., 2014) out of five analyses demonstrated lowered valence (heightened dislike) ratings to the CS+ in patients compared to controls (Brinkmann et al., 2017; Lueken et al., 2014; Michael et al., 2007; Schwarzmeier et al., 2014; Tinoco-Gonzalez et al., 2015). Similarly, one (Lueken et al., 2014) out of five of these analyses found lowered valence ratings (heightened dislike) to the CS- in patients compared to controls. Only one of these analyses investigated discrimination differences (Lueken et al., 2014) and found that the control group showed statistical discrimination between the CS+ and CS- whereas the patient group did not. However, it is worth noting that one of the studies that found null effects for both the CS+ and CS- did not achieve conditioning in valence scores hence its ability to detect group differences may have been thwarted (Schwarzmeier et al., 2019).

Arousal Ratings: During threat acquisition, two (Brinkmann et al., 2017; Lueken et al., 2014) out of four analyses demonstrated heightened arousal ratings to the CS+ in patients compared to controls (Brinkmann et al., 2017; Lueken et al., 2014; Schwarzmeier et al., 2019; Tinoco-Gonzalez et al., 2015). Further, one (Lueken et al., 2014) of these analyses demonstrated heightened arousal ratings to the CS- in patients compared to controls. Again, only Lueken et al. (2014) investigated differences in discrimination and found statistical discrimination between the CS+ and CS- in the control group, but not the patient group.

Distress Ratings: During threat acquisition, four (Benke et al., 2023; Brinkmann et al., 2017; Klahn et al., 2017) out of seven analyses found heightened distress ratings towards the CS+ in patients compared to controls, whereas one (Lissek et al., 2010) found heightened distress towards the CS+ in the control group (Benke et al., 2023; Brinkmann et al., 2017; Klahn et al., 2017; Lissek et al., 2009; Lissek et al., 2010; Tinoco-Gonzalez et al., 2015). Similarly, five (Benke et al., 2023; Brinkmann et al., 2017; Klahn et al., 2017; Lissek et al., 2010) out of eight found heightened distress to the CS- in patients compared to controls (Benke et al., 2023; Brinkmann et al., 2017; Klahn et al., 2017; Lissek et al., 2009; Lissek et al., 2010; Shankman et al., 2013; Tinoco-Gonzalez et al., 2015). One (Lissek et al., 2010) out of two of these analyses investigated discrimination differences and found that controls had higher discrimination scores in CS+/CS- distress ratings compared to patients.

FPS: During threat acquisition, one (Benke et al., 2023) out of four analyses found heightened FPS towards the CS+ in patients compared to controls (Benke et al., 2023; Lissek et al., 2009; Lissek et al., 2010; Tinoco-Gonzalez et al., 2015). Interestingly, this effect only occurred when the CS+ was paired with a disorder-relevant hyperventilation task, as opposed to an electric shock (Benke et al., 2023). Further, one (Lissek et al., 2009) out of four analyses found heightened FPS towards the CS- in patients compared to controls (Lissek et al., 2009; Lissek et al., 2010; Shankman et al., 2013). Of the two analyses that investigated discrimination, one (Lissek et al., 2009) found heightened discrimination in controls compared to patients, and the other (Shankman et al 2013) found heightened discrimination in patients compared to controls. Interestingly, Lissek et al. (2009) found that patients started to discriminate towards the end of the acquisition phase whereas the control group discriminated between CS stimuli much earlier.

SCR: During threat acquisition, four out of four analyses found a lack of group differences in SCRs to the CS+ (Marin et al., 2020; Michael et al., 2007; Otto et al., 2014; Schwarzmeier et al., 2019). Three of these analyses investigated SCRs towards the CS- and similarly found no group differences between patients and controls. Similar to valence ratings, Schwarzmeier et al. (2019) saw a lack of conditioning in SCR hence the studies ability to detect a true group effect may have been thwarted. None of these studies investigated group differences in CS+/CS- discrimination in relation to SCR.

Miscellany: Stevens et al. (2018) investigated patient-control differences in CS+/CS- discrimination in relation to N100 and P300 event-related potentials (ERP) and found no group differences. Said ERPs were not investigated by another study within the final sample.

3.2.1.5.2. Threat Extinction. Valence Ratings: During threat extinction, one (Michael et al., 2007) out of four analyses found evidence of increased valence ratings towards the CS+ in patients, whereas another study (Lueken et al., 2014) found increased valence ratings towards the CS+ in controls (Lueken et al., 2014; Michael et al., 2007; Schwarzmeier et al., 2019; Tinoco-Gonzalez et al., 2015). Regarding the CS-, one (Lueken et al., 2014) out of the four analyses found heightened responding in controls compared to patients; the same article was the only study to investigate CS+/CS- discrimination in valence ratings and found that both groups did not discriminate between stimuli during extinction. Again, Schwarzmeier et al. (2019) did not see evidence of conditioning in valence ratings hence group differences in extinction may have been difficult to detect.

Arousal Ratings: During extinction, one (Lueken et al., 2014) out of three analyses found heightened arousal ratings to the CS+ in patients compared to controls (Lueken et al., 2014; Schwarzmeier et al., 2019; Tinoco-Gonzalez et al., 2015). Whereas all three analyses found a lack of patient-control differences in arousal ratings towards the CS-. Further, Lueken et al. (2014) was the only study to investigate discrimination and found a lack of patient-control differences in CS+/CS- discrimination in relation to arousal ratings.

Distress Ratings: During extinction, two out of two analyses found a lack of patient-control differences in distress ratings towards the CS+ (Lissek et al., 2009; Tinoco-Gonzalez et al., 2015). However, one (Lissek et al., 2009) of these analyses found heightened distress ratings towards

the CS- in patients vs. controls. Only Lissek et al., (2009) investigated differences in CS+/CS- discrimination in relation to distress (anxiety) ratings and found no group difference during extinction.

FPS: Similarly, Lissek et al. (2009) was the only study to investigate patient-control differences in FPS during threat extinction. They found a lack of significant group differences in FPS responses towards the CS+, CS-, or CS+/CS- discrimination scores.

SCR: During extinction, one (Michael et al., 2007) out of three analyses found increased SCRs towards the CS+ in patients compared to controls, whereas one (Marin et al., 2020) of these analyses also found the opposite effect i.e., CON>PD (Michael et al., 2007; Marin et al., 2020; Schwarzmeier et al., 2019). Similarly, one (Marin et al., 2020) out of three of these analyses found heightened SCRs towards the CS- in controls compared to patients. Differences in SCR CS+/CS- discrimination were not investigated by any study. Again, Schwarzmeier et al (2019) found no evidence of conditioning in relation to their SCR data hence this study's ability to detect a true effect may have been thwarted.

3.2.1.5.3. Extinction Retention. Valence Ratings: Only Schwarzmeier et al. (2019) investigated group differences in valence ratings during extinction retention. This study found a lack of patient-control differences in valence ratings towards either the CS+ or CS-. Additionally, group differences in valence rating discrimination scores were not analysed. Again, it has been noted that this study did not find initial conditioning effects in relation to valence ratings hence this may have affected its ability to detect group differences during extinction retention.

Arousal Ratings: Similarly, only Schwarzmeier et al. (2019) investigated group differences in arousal ratings during extinction retention. This study found a lack of patient-control differences in arousal ratings towards either the CS+ or CS-. Additionally, group differences in arousal rating discrimination scores were not analysed.

SCR: Both Marin et al. (2020) and Schwarzmeier et al. (2019) were the only studies to investigate group differences in SCR during extinction retention, yet both analyses found a lack of such differences in relation to both the CS+ and CS-. Again, group differences in SCR discrimination scores were not investigated by either study. Once more, Schwarzmeier et al. (2019) did not find evidence of initial conditioning in relation to SCR, hence this may have affected this result also.

3.2.1.6. Neuroimaging Findings

3.2.1.6.1. Threat Acquisition. Specific region of interest (ROI) analyses (Brinkmann et al., 2017; Lueken et al., 2014; Marin et al., 2020) and separate whole-brain analyses (Lueken et al., 2014; Schwarzmeier et al. 2019) were carried out to investigate group differences in differential neural responding (CS+ - CS- contrast) during threat acquisition:

- Amygdala: Brinkmann et al. (2017) found heightened differential responding in the amygdala (right central and basolateral) for PD patients vs. controls during acquisition, whereas a lack of such an effect was found by Marin et al. (2020). Similarly, Lueken et al. (2014) failed to find such an effect during both early and overall acquisition. The effect demonstrated by Brinkmann et al. (2017) was found to be specific to the "phasic" (1 s post-CS presentation), as opposed to the "sustained" (full CS presentation), epoch. Interestingly, PPI analyses revealed that the central amygdala "seed region" was associated with heightened phasic connectivity with the left amygdala, dACC, and multiple insula regions in patients vs. controls. Similarly, the basolateral amygdala seed region was associated with heightened phasic connectivity with the rostral ACC and reduced phasic connectivity with the anterior insula and dorsolateral PFC in patients vs. controls (Brinkmann et al., 2017). Further, whole-brain analyses found heightened differential activation in the right amygdala for patients vs. controls (Schwarzmeier et al. 2019).
- BNST: Brinkmann et al. (2017) found heightened differential neural responding in the BNST for patients vs. controls during acquisition which was specific to the sustained epoch. Additionally, PPI analyses showed that the right BNST seed region was associated with heightened sustained connectivity with the rACC and multiple PFC areas, alongside reduced sustained connectivity with the dorsolateral PFC, in patients vs. controls (Brinkmann et al., 2017).
- Hippocampus: Marin et al. (2020) found a lack of differential neural activation in this area between patients and controls during acquisition.
- Insula: Brinkmann et al. (2017) found heightened differential neural responding in the insula cortex for PD patients vs. controls during acquisition and this effect was present during both the "phasic" and "sustained" epochs. Whereas Marin et al. (2020) found no group differences in differential neural responding in this area. Additionally, whole-brain analyses also found heightened differential activation in the left insula in patients vs. controls (Schwarzmeier et al. 2019).
- ACC: Brinkmann et al. (2017) found heightened differential neural responding in the dACC for PD patients vs. controls during acquisition which was specific to the phasic epoch. Whereas Marin et al. (2020) did not find group differences in differential activation in this area.
- PFC: Brinkmann et al. (2017) found heightened differential neural responding in multiple areas within the PFC for PD patients vs. controls during acquisition; these effects were present during both the phasic and sustained epochs. Whereas Marin et al. (2020) did not find group differences in differential neural activation in this area. Whole-brain analyses also found differential neural activation in the same direction within prefrontal areas i.e., the bilateral dorsal inferior frontal gyrus and right superior frontal gyrus (Lueken et al., 2014), yet differential activation was also found to be higher in the right middle frontal gyrus (amongst others) in controls vs. patients (Schwarzmeier et al., 2019).
- Other: Whole-brain analyses revealed heightened differential neural activation in the left fusiform gyrus in patients vs. controls during early acquisition (Schwarzmeier et al., 2019).

3.2.1.6.2. Threat Extinction. Specific region of interest (ROI) analyses (Lueken et al., 2014; Marin et al., 2020) and separate whole-brain analyses (Lueken et al., 2014; Schwarzmeier et al. 2019) were carried out to investigate group differences in differential neural responding (CS+ - CS- contrast) during threat extinction:

- Amygdala: Lueken et al. (2014) found no group differences in differential neural activation in the amygdala during extinction, and Marin et al. (2020) found the same null effect during both early and late extinction.
- Hippocampus: Marin et al. (2020) found no group differences in differential neural activation within the hippocampus during extinction.
- Insula: Marin et al. (2020) found no group differences in differential neural activation within the insula cortex during extinction.
- ACC: Marin et al. (2020) found no group differences in differential neural activation within the dACC region during extinction.
- PFC: Marin et al. (2020) found no group differences in differential neural activation within the vmPFC region during extinction. However, whole-brain analyses revealed heightened differential neural activation in the superior frontal gyrus in controls vs. patients during extinction (Schwarzmeier et al., 2019).
- Other: Whole-brain analyses revealed heightened differential neural activation in the left medial temporal gyrus, left midcingulate cortex and supplementary motor area in controls vs. patients during extinction (Schwarzmeier et al., 2019).

3.2.1.6.3. Extinction Retention. Specific region of interest (ROI) analyses (Marin et al., 2020) and separate whole-brain analyses (Schwarzmeier et al. 2019) were carried out to investigate group differences in differential neural responding (CS+ - CS- contrast) during extinction retention:

- Amygdala: Marin et al. (2020) found no group differences in differential neural activation within the amygdala during retention.
- Hippocampus: Marin et al. (2020) found no group differences in differential neural activation within the hippocampus during retention.
- Insula: Marin et al. (2020) found no group differences in differential neural activation within the insula cortex during retention. Whereas whole-brain analyses revealed heightened differential neural activation in the insula cortex during the mid-retention period in patients vs. controls (Schwarzmeier et al., 2019).
- ACC: Marin et al. (2020) found no group differences in differential neural activation within the dACC during retention.
- PFC: Unlike preceding phases, Marin et al. (2020) found heightened differential neural activation in the vmPFC in control subjects vs. patients during retention. Whereas whole-brain analyses revealed heightened differential neural activation in the inferior frontal operculum and inferior frontal gyrus during the mid-retention period in patients vs. controls (Schwarzmeier et al., 2019). However, the middle frontal gyrus was more differentially activated in controls vs. patients.
- Other: Whole-brain analyses revealed heightened differential neural activation in the supramarginal gyrus in controls vs. patients during retention (Schwarzmeier et al., 2019).

3.2.1.6.4. Summary. Taken together, this collation of results tentatively suggests that panic patients, relative to controls, exhibit heightened activation towards the CS+ vs. CS- in the amygdala, insula, ACC, BNST, and prefrontal cortex regions during threat acquisition, lowered differential activation in specific PFC areas during extinction, and heightened and lowered differential activation in the insula/specific PFC regions and the vmPFC respectively during retention. Although, it must be noted that all neuroimaging effects are supported by either mixed or uncorroborated evidence.

3.2.2. Specific Phobia

Key results were tabulated to provide an overview of SP-control differences in CS+ and CS- responding, alongside differences in CS+/CS- discrimination, within each of the included studies (Table 4).

3.2.2.1. Threat Acquisition. Across all physiological outcomes, there is mixed evidence for heightened CS+/CS- discrimination in SP patients vs. controls with 1 out of 2 analyses finding heightened discrimination and 1 out of 2 analyses finding no group differences (Table 5). Further, there is mixed evidence for heightened CS+ and CS- responding in patients vs. controls with 1 out of 2 analyses finding heightened discrimination and 1 out of 2 analyses finding no group differences. On the other hand, across subjective measures, there is strong evidence to suggest heightened CS+/CS- discrimination in patients vs. non-clinical controls with 4 out of 4 analyses demonstrating such differences. However, there is relatively strong evidence for a lack of patient-control differences in both CS+ and CS- responding with 4 out of 5, and 3 out of 4 analyses demonstrating null effects respectively.

3.2.2.2. Threat Extinction. Across all physiological outcomes, there is mixed evidence for heightened CS+ and CS- responding in controls vs. patients with 1 out of 2 analyses showing heightened CS responses in controls (Table 5). However, across subjective rating outcomes, there is strong evidence for heightened CS+ responding in patients vs. controls with 2 out of 2 analyses showing such differences. However, there is mixed evidence for heightened CS- responding in patients vs. controls with 1 out of 2 analyses finding heightened scores and 1 out of 2 analyses finding null effects. There is a dearth of research on patient-control differences in CS+/CS- discrimination for both physiological and subjective measures.

3.2.2.3. Extinction Retention. Across all physiological outcomes, there is strong evidence for a lack of patient-control differences in CS+ and CS- responding with 2 out of 2 analyses finding null effects (Table 5). Further, across all subjective outcomes, there is mixed evidence for heightened CS+ and CS- responding in patients vs. controls with 1 out of 2 analyses finding heightened CS scores and 1 out of 2 analyses finding null effects. There is a dearth of research on patient-control differences in CS+/CS- discrimination for both physiological and subjective measures.

Table 5
Overview of Frequencies and Percentages of Significant vs Non-Significant Group Comparisons across CS + responding, CS- responding, and CS+/CS- Discrimination for Physiological Measures and Ratings Separately for all SP Studies.

Phase	Metric	Physio			Ratings		
		SP > CON	CON > SP	ns	SP > CON	CON > SP	ns
ACQ	CS+	1(50)	0	1(50)	1(20)	0	4 (80)
	CS-	1(50)	0	1(50)	1(25)	0	3 (75)
	CS Diff	1(50)	0	1(50)	4(100)	0	0
EXT	CS+	0	1(50)	1(50)	2(100)	0	0
	CS-	0	1(50)	1(50)	1(50)	0	1 (50)
	CS Diff	–	–	–	–	–	–
RET	CS+	0	0	2 (100)	1(50)	0	1 (50)
	CS-	0	0	2 (100)	1(50)	0	1 (50)
	CS Diff	–	–	–	–	–	–

Note. Frequency of effects displayed in cell. Percentage of effects in relation to all studies represented in parentheses. – indicates a lack of analyses carried out in this domain. VAL effects have been reversed for the sake of congruence with other measures i.e., CON > SP has been listed as an example of heightened responding in the SP group as it indicates a heightened dislike of the stimulus and vice versa. Physio category includes FPS and SCR, whereas ratings category includes all ratings. Please note that an individual study may contain multiple analyses that contribute to the absolute frequencies associated with the physio and ratings categories.

3.2.2.4. Summary. In sum, and accounting for the most reliable effects across the review, these results provide tentative evidence for increased CS+/CS- discrimination in phobic patients during threat acquisition, and increased CS+ responding, across subjective measures specifically, during extinction. This suggests that phobic patients possess heightened responsiveness to the CS-US contingency during acquisition, and may imply muted extinction learning during extinction. Again, patient-control differences seem most detectable in relation to subjective, as opposed to physiological, outcome measures generally.

3.2.2.5. Sub-Categories

3.2.2.5.1. Threat Acquisition. US Expectancy Ratings: Only Li and Graham (2016) studied patient-control differences in expectancy ratings. They found a lack of group differences in expectancy ratings towards both the CS+ and CS-. Differences in CS+/CS- discrimination were not investigated throughout the SP sample of studies.

Valence Ratings: During threat acquisition, one (Li & Graham, 2016) out of three analyses found lowered valence ratings (increased dislike) towards the CS+ in patients vs. controls (Li & Graham, 2016; Schienle et al., 2005). Further, one (Li & Graham, 2016) out of two of these analyses found lowered valence ratings towards the CS- in patients vs. controls. Only one study investigated CS+/CS- discrimination, finding that patients had higher discrimination scores than control subjects in relation to CS+ paired with fear-relevant stimuli, whereas fear-

irrelevant CS+ effects were investigated but not reported (Schweckendiek et al., 2011).

Arousal Ratings: Only Schweckendiek et al., (2011) studied patient-control differences in arousal ratings during acquisition and found that patients had higher CS+/CS- discrimination scores in response to CS+ paired with fear-relevant stimuli (fear-irrelevant CS+ effects were not reported). Differences in CS+ and CS- responding were not investigated throughout the SP sample of studies.

Distress Ratings: Only Klahn et al. (2017) studied patient-control differences in distress (discomfort) ratings towards the CS+ and CS- during acquisition and found a lack of such differences. Further, only Schweckendiek et al. (2011) studied CS+/CS- discrimination in relation to distress ratings (fear and disgust) and found that two out of two analyses showed heightened CS+/CS- discrimination scores in response to fear-relevant CS+ stimuli in patients vs. controls (fear-irrelevant CS+/CS- discrimination differences were not reported).

FPS: Only Gorka et al. (2017) studied patient-control differences in FPS responses in CS+/CS- discrimination and found a lack of difference between patients and controls during acquisition. None of the included studies investigated patient-control differences in FPS responses to individual CS stimuli.

SCR: During threat acquisition, one (Li & Graham, 2016) out of two analyses found heightened SCRs to the CS+ in patients vs. controls (Li & Graham, 2016; Marin et al., 2020). Further, one (Li & Graham, 2016) out of two of these analyses found heightened SCRs towards the CS- in patients vs. controls. Lastly, only Schweckendiek et al. (2011) studied group differences in SCR CS+/CS- discrimination, finding that patients had higher SCR discrimination scores compared to controls in response to fear-relevant CS+ stimuli (fear-irrelevant CS+/CS- discrimination not reported).

3.2.2.5.2. Threat Extinction. US Expectancy Ratings: Only Li and Graham (2016) studied patient-control differences in expectancy ratings during extinction. They found higher expectancy ratings towards the CS+, but not the CS-, in patients vs. controls. CS+/CS- discrimination differences in expectancy ratings were not investigated by any study.

Valence Ratings: Only Li and Graham (2016) studied patient-control differences in expectancy ratings during extinction. They found lowered valence ratings (increased dislike) for both the CS+ and CS- in patients vs. controls. Interestingly, they also found that phobic patients had higher change-in-valence rates towards the CS- in comparison to controls i.e., patients exhibited greater increases in the liking (increased valence) of the CS- compared to controls hence demonstrating a safety learning effect in the extinction phase, as opposed to the acquisition phase where it is typically observed (Lonsdorf et al., 2017). CS+/CS- discrimination differences in valence ratings were not investigated by any study.

SCR: During extinction, one (Marin et al., 2020) out of two analyses found heightened SCRs towards the CS+ in control subjects vs. patients (Li & Graham, 2016; Marin et al., 2020). Within these same studies, one (Marin et al., 2020) out of two analyses showed heightened SCRs towards the CS- in control subjects vs. patients within extinction. CS+/CS- discrimination differences in SCR were not investigated by any study.

3.2.2.5.3. Extinction Retention. US Expectancy Ratings: Only Li and Graham (2016) studied patient-control differences in expectancy ratings during extinction retention. They found a lack of such group differences in expectancy ratings towards both the CS+ and CS-. CS+/CS- discrimination differences in expectancy ratings were not investigated by any study.

Valence Ratings: Only Li and Graham (2016) studied patient-control differences in valence ratings during extinction retention. They found lowered valence ratings (increased dislike) in response to both the CS+ and CS- in patients vs. controls during the retention phase. Interestingly, this study also found that phobic patients had higher change-in-valence rates towards the CS+ compared to controls i.e., phobic patients exhibited greater increases in the liking (valence) of CS+ stimuli compared to controls, hence demonstrating a continued threat extinction effect during the retention phase. This implies that phobic patients experience slowed, as opposed to impaired, threat extinction in comparison to controls. CS+/CS- discrimination differences in valence ratings were not investigated by any study.

SCR: During extinction retention, two out of two analyses found that patients and controls did not differ in their SCRs towards both the CS+ and CS- stimuli (Li & Graham, 2016; Marin et al., 2020). CS+/CS- discrimination differences in SCRs were not investigated by any study.

3.2.2.6. Neuroimaging Findings

3.2.2.6.1. Threat Acquisition. Specific region of interest (ROI) analyses (Marin et al., 2020; Schweckendiek et al., 2011; Siminski et al., 2021) and separate whole-brain analyses (Schweckendiek et al., 2011) were carried out to investigate group differences in differential neural responding (CS+ - CS- contrast) during threat acquisition:

- Amygdala: Both Marin et al. (2020) and Siminski et al. (2021) found a lack of group differences in differential neural activation within the amygdala across the entire acquisition phase. Similarly, Schweckendiek et al. (2011) found a comparable lack of differential activation in the amygdala during both the early and late acquisition phases for both fear-relevant and fear-irrelevant CS+ stimuli.
- BNST: Siminski et al. (2021) found a lack of group differences in differential neural activation within the BNST during acquisition.
- Hippocampus: Marin et al. (2020) found a lack of group differences in differential neural responding within the hippocampus across the entire acquisition phase.
- Insula: Marin et al. (2020) found a lack of group differences in differential neural responding within the amygdala across the entire acquisition phase. Whereas Schweckendiek et al. (2011) found heightened differential neural activation within the insula cortex during the early acquisition phase in patients vs. controls in relation to fear-relevant CS+ stimuli. However, no group differences were found for fear-relevant CS+ stimuli during late acquisition, or for fear-irrelevant CS+ stimuli during both early and late acquisition.
- Thalamus: Schweckendiek et al. (2011) found a lack of group differences in differential neural responding within the thalamus during both early and late acquisition across both fear-relevant and fear-irrelevant stimuli.
- ACC: Marin et al. (2020) found a lack of group differences in differential neural responding within the dACC across the entire acquisition phase. Similarly, Schweckendiek et al. (2011) found the same null group differences in the ACC across both early and late acquisition for both fear-relevant and fear-irrelevant CS+ stimuli.
- OFC: Schweckendiek et al. (2011) found a lack of group differences in differential neural responding within the OFC during both early and late acquisition across both fear-relevant and fear-irrelevant stimuli.
- PFC: Marin et al. (2020) found a lack of group differences in differential neural responding within the vmPFC across the entire acquisition phase. Whereas Schweckendiek et al. (2011) found heightened differential neural activation within the mPFC during the early acquisition phase in patients vs. controls in relation to fear-relevant CS+ stimuli. However, no group differences were found for fear-relevant CS+ stimuli during late acquisition, or for fear-irrelevant CS+ stimuli during both early and late acquisition.

3.2.2.6.2. Threat Extinction. Specific region of interest (ROI) analyses (Marin et al., 2020) were carried out to investigate group differences in differential neural responding (CS+ - CS- contrast) during threat extinction:

- Amygdala: No group level differences were found in differential neural activation within the amygdala during extinction (Marin et al., 2020).

- Hippocampus: No group level differences were found in differential neural activation within the hippocampus during extinction (Marin et al., 2020).
- Insula: No group level differences were found in differential neural activation within the insula cortex during extinction (Marin et al., 2020).
- ACC: No group level differences were found in differential neural activation within the dACC during extinction (Marin et al., 2020).
- PFC: No group level differences were found in differential neural activation within the vmPFC during extinction (Marin et al., 2020).

3.2.2.6.3. Extinction Retention. Specific region of interest (ROI) analyses (Marin et al., 2020) were carried out to investigate group differences in differential neural responding (CS+ - CS- contrast) during extinction retention:

- Amygdala: No group level differences were found in differential neural activation within the amygdala during retention (Marin et al., 2020).
- Hippocampus: No group level differences were found in differential neural activation within the hippocampus during retention (Marin et al., 2020).
- Insula: No group level differences were found in differential neural activation within the insula cortex during retention (Marin et al., 2020).
- ACC: No group level differences were found in differential neural activation within the dACC during retention (Marin et al., 2020).
- PFC: Unlike preceding phases, heightened differential neural activation was demonstrated in the vmPFC in control subjects vs. patients hence mirroring results achieved for PD patients within the analogous phase (Marin et al., 2020).

3.2.2.6.4. Summary. Taken together, these results tentatively suggest that phobic patients, relative to controls, exhibit heightened differential activation towards the CS+ vs. CS- in both the insula cortex and mPFC but only in relation to fear-relevant CS+ stimuli during acquisition, and lowered activation in the vmPFC during extinction retention. Again, it must be noted that all these neuroimaging effects are supported by either mixed or uncorroborated evidence.

4. Discussion

This systematic review aimed to elucidate the presence and nature of patient-control differences in threat conditioning and extinction processes in panic disorder and specific phobia separately. The review identified 14 PD studies and 7 SP studies therefore demonstrating a larger body of evidence for panic disorder compared to specific phobia. Regardless, both the PD and SP samples represent relatively small bodies of research hence the conclusions of this review should be evaluated cautiously by the reader. The following paragraphs will critique and contextualise our findings in relation to the wider literature.

In general, the conditioning findings in relation to PD and SP tend to both corroborate and contradict the findings associated with general, and specific, ADs in other reviews. Firstly, Kausche et al. (2025) found heightened AD patient responding (all ADs in one category vs. controls) to the CS+ and CS- throughout acquisition, extinction, and retention, coupled with a general lack of patient-control differences in CS+/CS- discrimination. This is at odds with the findings of this review in relation to PD, which found strong evidence of lowered CS+/CS- discrimination in PD patients coupled with a general lack of group differences in CS- responding during acquisition. Additionally, this review found a lack of PD-control differences in CS+ and CS- responding across both extinction and retention. Hence, demonstrating vast incongruity between the findings of this review and those of Kausche et al. (2025). On the other hand, our findings demonstrated mixed evidence of heightened CS+ responding in the PD group during acquisition and a lack of PD-control group differences in CS+/CS- discrimination in extinction which matches the findings of Kausche et al. (2025). Hence, it appears that, on the basis of this review, PD differs from the general AD category in relation to patient-control differences in CS+ and CS- responding during threat extinction and retention, coupled with an increased tendency to poorly discriminate between the CS+ and CS- during acquisition. Further, it appears that PD patients differ to both OCD and SAD patients in relation to conditioning and extinction processes. Whereas OCD is characterised by strong evidence of heightened CS+ responding and CS+/CS- discrimination during extinction and retention respectively (Cooper & Dunsmoor, 2021), this does not appear to be the case for PD. Similarly, SAD patients have been characterised by a lack of patient-control differences in conditioning and extinction processes (Wake et al., 2024), whereas the current review has demonstrated strong and mixed evidence of poorer stimulus discrimination and enhanced threat acquisition learning, respectively, during acquisition in PD patients. Further, the results of this review suggest that PD and SP are characterised by differences in conditioning signatures. Whereas PD was associated with reduced CS+/CS- discrimination during acquisition, SP was associated with increased patient-control differences in CS+/CS- discrimination. Further, SP received mixed evidence for heightened CS+ responses during extinction whereas the evidence for PD suggested a lack of patient-control differences in CS+ responding during this phase. Hence, it appears that the conditioning signatures associated with PD are relatively distinct to that of other ADs.

Regarding SP, this review finds both distinguishing and corroborating effects in relation to the conditioning signatures associated with general, and specific, ADs found by other reviews. Firstly, the finding that SP patients possess heightened CS+/CS- discrimination in comparison to controls during acquisition directly contradicts the entire corpus of literature in relation to ADs which generally shows either a lack of such differences or trend effects in the opposite direction (Cooper & Dunsmoor, 2021; Duits et al., 2015; Kausche et al., 2025; Wake et al., 2024). Indeed, poorer discrimination during acquisition is considered largely pathognomonic of anxiety disorders as it demonstrates an inability to distinguish between threat and safety cues (Duits et al., 2015; Lissek et al., 2005). Therefore, this finding would suggest that SP patients are more aware of the CS-US contingency, either explicitly or implicitly, than non-clinical control participants. At face value this effect is difficult to comprehend considering the wider literature. Upon closer inspection, however, it appears that this effect is driven entirely by one study (Schweckendiek et al., 2011). This study was the only experiment that differentiated between fear-relevant and fear-irrelevant CS-US pairings; the increased CS+/CS- discrimination effect in SP patients was driven solely by fear-relevant CS+ stimuli (CS+ stimuli paired with a fear-relevant US) (Schweckendiek et al., 2011). Therefore, it may be the case that this finding is driven by an increased learning effect that is specific to fear-relevant stimuli. Given that Schweckendiek et al. (2011) did not report the fear-irrelevant CS+ effects we cannot, at this stage, deduce whether this represents a generalised, or fear-specific, heightened ability to discriminate between CS stimuli. Indeed, prior research has found that fear-relevant interpersonal CS stimuli produce larger differential responses when compared to neutral stimuli, hence such stimuli may produce larger between-group differences in this instance also (Ney et al., 2022). Additionally, across physiological measures, this review found mixed evidence for heightened CS+ responding in phobic patients during acquisition which matches the findings for ADs in general (Kausche et al., 2025) and OCD (Cooper & Dunsmoor, 2021), but not SAD (Wake et al., 2024). Similarly, mixed evidence was found for heightened CS- responding in patients during acquisition which matches the findings associated with ADs in general, but not OCD. Further, in light of this review, SP patients were characterised by heightened CS+ responding in relation to subjective ratings during extinction which coalesces with the effects found for both ADs in general (Kausche et al., 2025) and OCD (Cooper & Dunsmoor, 2021), but not SAD (Wake et al., 2024). Further, there is mixed evidence for heightened CS- responding during extinction, and CS+ and CS- responding during retention, in relation to subjective ratings in SP patients which matches the findings

by Kausche et al. (2025), but not Cooper and Dunsmoor (2021) or Wake et al. (2024). Lastly, the results obtained by this review regarding heightened physiological responding to both CSs in control subjects during extinction largely contradict the wider literature; however, these effects came from a single study. Overall, the results of this review, in relation to both PD and SP, seem to highlight the large degree of inter-diagnostic variability within ADs in relation to threat conditioning and extinction processes. Indeed, such heterogeneity in conditioning findings has been mentioned elsewhere in the literature (Duits et al., 2015; Kausche et al., 2025).

These findings enable us to further our understanding of conditioning processes in relation to PD and SP which has potential conceptual and clinical implications. Regarding PD, our strongest review finding was evidence of poorer discrimination between the CS+ and CS- during acquisition in panic patients compared to controls indicating poorer threat acquisition. Yet, there was mixed evidence for heightened CS+ responding, but not heightened CS- responding, in panic patients vs. controls during acquisition indicating a heightened sense of threat towards the CS+ compared to controls. Specifically, however, panic patients did seem to report heightened distress ratings, as opposed to other subjective measures, towards both the CS+ and CS- during acquisition. Taken together, this suggests that those with PD may discriminate less between threat and safety cues within ecological learning contexts e.g., new situations, and acquire CS+/threat associations strongly (Duits et al., 2015). Further, this may elucidate the process by which panic disorder develops from a single panic attack i.e., the sense of threat generated by the panic-inducing stimulus is transferred to neutral stimuli resulting in a heightened concern of panic attacks across a multitude of stimuli. If accurate, this process may also partially explain the phenomenon whereby a single panic attack first develops into panic disorder and then, eventually, agoraphobia (Klein & Gorman, 1987; Lelliot et al., 1989; Margraf et al., 1986). In relation to treatment, our findings lend credence to clinical recommendations in relation to exposure therapy that emphasizes the generalization of learning via utilizing multiple contexts (de Jong et al., 2019). In particular, it may be beneficial for exposure therapists to focus on utilizing exposure protocols in multiple environments and in relation to a variety of panic-specific stimuli i.e., multiple physical sensations e.g., increased heart rate, sweating, faintness, to ensure that extinction learning counteracts this tendency to transfer threat associations to benign stimuli.

In relation to SP, our strongest finding suggested the opposite tendency, compared to PD, during acquisition; stronger discrimination between the CS+ and CS- hence indicating heightened threat acquisition in those with SP vs. controls. This implies that those with SP possess a heightened learning/awareness of the CS-US contingency and that such individuals may demonstrate specific attentional biases culminating in heightened threat orientation. Indeed, previous research has emphasised the role of attentional biases in relation to SP (Elsesser et al., 2006; Rinck et al., 2005). Clinically, this finding suggests that exposure therapy for those with SP should focus specifically on the phobic stimulus. Additionally, this review found mixed evidence for heightened CS+ responding during extinction, and heightened CS+ and CS- responding during retention which may suggest muted threat extinction and retention tendencies. Hence, prolonged exposure protocols with a heavy emphasis on follow-up assessment and top-up exposure work may be required to combat these tendencies. Additionally, generic exposure optimization strategies e.g., expectancy violation, deepened extinction etc. (Craske et al., 2014) may be specifically warranted in relation to SP due to this muted extinction and retention effect demonstrated experimentally. However, these clinical implications need further corroboration, both *meta*-analytically and clinically, prior to dissemination as disorder-specific recommendations.

Although direct comparisons between fMRI studies could not be meaningfully executed due to the large heterogeneity in specific analyses and regional foci across studies, the current review did reveal emerging evidence of specific neural correlates associated with conditioning processes in relation to PD and SP. Overall, there has not been much research on this topic (e.g., Duits et al., 2015; Kausche et al., 2025). However, similar to PD, post-traumatic stress disorder (PTSD) has been associated with heightened differential neural activation within the amygdala during acquisition and altered PFC activity during extinction (Suarez-Jimenez et al., 2019). Unlike PD however, PTSD is also associated with aberrant insula and ACC activity during extinction (Suarez-Jimenez et al., 2019), whereas PD found effects relating to the insula during acquisition and extinction retention specifically, and ACC effects within acquisition only. Similarly, like PTSD, SP patients also experienced altered insula activation during acquisition; however, this was specific to fear-relevant CS+ stimuli (Schweckendiek et al., 2011). Interestingly, this review found that both SP and PD were characterised by lowered differential neural activation, relative to controls, within the vmPFC during extinction retention (Marin et al., 2020). Given the well-established role of the vmPFC in safety learning and fear inhibition (Milad & Quirk, 2012; Sangha et al., 2020), this suggests that both SP and PD patients are characterised by inhibited safety learning or fear inhibition in relation to the CS+ vs. CS-, relative to controls, during the retention phase. This corroborates the mixed results of heightened responding during this phase in SP patients but does not corroborate the null effects found in PD patients, across both physiological and subjective measures, within this review. Interestingly, similar vmPFC hypoactivation effects have been found in relation to PTSD during extinction (Suarez-Jimenez et al., 2019) and OCD during both extinction and extinction retention (Cooper & Dunsmoor, 2021). Hence, suggesting that a distinct vmPFC hypoactivation towards the CS+ vs. CS-, relative to controls, within extinction phases may be representative of most ADs, including PD and SP.

The majority of the findings in this review demonstrate patient-control differences within the acquisition phase, as opposed to the extinction phases, which also corroborates the finding that anxiety disorders and OCD are characterised by larger differences in acquisition, whereas PTSD is characterised by larger extinction differences (Kausche et al., 2025). Interestingly, across both SP and PD, this review found that patient-control differences manifested more readily in subjective outcome measures, as opposed to physiological outcome measures. This provides tentative support for the 'two-system account of fear learning' which generally posits that threat conditioning operates upon two separate systems: a rapid and autonomically mediated system generally demonstrated in physiological responses, and a slower, conscious and controlled system generally demonstrated in subjective ratings (Hamm & Vaitl, 1996; Hamm & Weike, 2005; LeDoux & Pine, 2016; Sevenster et al., 2012). Similar patterns have also been found in relation to patient-control differences in ADs in general (Kausche et al., 2025). Therefore, suggesting that anxiety patients are more sensitive to alterations in threat conditioning and extinction within the slower, controlled system as indicated by subjective ratings, at least within the confines of typical threat conditioning experiments. Alternatively, the null findings in relation to physiological outcomes may reflect shortcomings of the physiological measures themselves (E.g., Gatzke-Kopp, 2016). For instance, previous research has shown that AD patients can be differentiated from controls via their differences in subjective, but not physiological, arousal scores (Rosebrock et al., 2016). Suggesting that patients and controls may not be easily distinguished based on their physiological responses. This inability to distinguish patients from controls on the basis of their physiological responses may simply obscure any conditioning-related learning differences even if they were present.

This review demonstrated considerable heterogeneity in relation to the conditioning-specific aspects of study methodology e.g., CS type, US type, reinforcement rates etc. (see 'Study Characteristics'). Upon review of the literature, the authors noted a few methodological differences between studies that may account for the heterogeneity in findings. For instance, it has been noted that certain PD fMRI studies found patient-control differences in differential activation within fear network

regions (Brinkmann et al., 2017; Schwarzmeier et al., 2019) whereas others did not (Lueken et al., 2014; Marin et al., 2020). Interestingly, the studies that found such differences utilised 100 % reinforcement schedules whereas those that did not utilised partial schedules. Given that partial reinforcement schedules are known to produce increased extinction learning and reduced response frequency (Lonsdorf et al., 2017), such schedules may be associated with ceiling and floor effects that increase the likelihood of type 2 errors when carrying out group-level comparisons. Further, Kausche et al. (2025) demonstrated that reinforcement rate significantly moderated conditioning findings, albeit in relation to discrimination in FPS responses specifically. However, given that this has not been investigated in relation to fMRI it cannot be excluded as a potential confounding influence in this review. Further research is needed on this topic. On another note, it has been shown that physiological outcomes can vary widely on the basis of certain statistical corrections e.g., Z transformation vs. range correction (Ben-Shakhar, 1985). Therefore, the mixed findings in relation to physiological outcomes between groups may differ as a function of differences in statistical corrections across studies. Additionally, Tinoco-Gonzalez et al. (2015) produced a large proportion of the null patient-control effects in relation to subjective ratings during both acquisition and extinction; removing this study would have made the heightened CS+ during acquisition finding much stronger/more reliable. Upon further inspection, it was observed that this study utilised facial stimuli and verbal insults as the US; one could argue that this represents a fear-relevant US stimulus specific to SAD, hence is unlikely to produce substantial conditioning in non-SAD patients. As a result, this may have obscured any true panic-control differences in conditioning if they were indeed present (Ney et al., 2022). Relatedly, US type is a known moderator of patient-control differences in ADs (Kausche et al., 2025), and the PD studies in this review that utilised more generic US's e.g., electric shock or aversive scream tended to find increased patient responding in subjective measures (Brinkmann et al., 2017; Leuken et al., 2014; Lissek et al., 2010). Hence, the removal of studies with non-typical US's may produce a more accurate picture of patient-control differences in threat conditioning and extinction processes.

Overall, the current review highlights multiple areas for further research. Firstly, the review found a relatively small body of research in relation to PD, and an even smaller body of research in relation to SP, which highlights the need for further well-sampled studies in threat conditioning for both SP and PD. Interestingly, there were many SP conditioning studies identified during screening that were ultimately excluded on the basis of their use of median/upper-lower quartile splits to determine phobic and non-phobic groups (Hare & Blevings, 1975; Olatunji, 2006; Soares and Öhman, 1993), hence further research in SP is warranted that specifically recruits clinical SP patients. Secondly, there was a significant lack of SP studies investigating extinction and extinction retention, and a similar lack of PD studies investigating extinction retention. Similarly, CS+/CS- discrimination differences in relation to extinction and retention within SP, and retention within PD studies, were not investigated. Hence, in addition to the need for more conditioning research in general, future studies should focus explicitly on these phases and metrics to produce a more comprehensive corpus of knowledge in this domain. Thirdly, upon the proliferation of more research in this area, it will be important for a series of *meta*-analyses to be carried out separately for specific phobia and panic disorder that focus on patient-control differences during acquisition, extinction, and retention. Future *meta*-analyses should consider investigating the moderating influences of methodological characteristics e.g., CS type, US type, reinforcement rates, to improve the interpretation of the findings of this, and any future, review. During the execution of this review, the authors noticed that the included studies rarely stated the appropriate statistics and effect sizes necessary for the execution of *meta*-analyses, therefore both published and future studies should share all the associated inferential statistics, or better yet whole datasets, as per open science practices (Open Science Collaboration, 2015; Persic et al., 2021). Fourthly, future research should seek to further standardize the approach to conditioning studies to reduce the current heterogeneity present within this research area and improve inter-study comparisons (Lonsdorf et al., 2017). For instance, the fMRI studies included in this review demonstrated variability in their use of analyses e.g., ROI vs whole-brain analyses, the specific regions investigated, and whether or not they investigated early and late conditioning blocks which makes it difficult to make direct comparisons. Further, future fMRI research may consider imitating Brinkmann et al. (2017) in demarcating between phasic and sustained responses, as well as including time/block comparisons e.g., early acquisition/late acquisition, as important effects may be obscured by focusing solely on group differences between overall phase scores. Fifth, given our finding that the increased CS+/CS- discrimination effect during threat acquisition for SP patients was driven by fear-relevant CS-US pairings (Schweckendiek et al., 2011) it would be extremely prudent for future research to focus on the potential moderating effect that fear-relevant vs fear-irrelevant CS+ stimuli may have upon patient-control differences in CS+/CS- discrimination in relation to SP. This would enable us to determine whether SP is characterised by a generic, or a fear-specific, threat orientation/awareness, and such research will enable future researchers to further standardise their approach to investigating conditioning in relation to SP.

This systematic review has multiple limitations that should be considered when interpreting the results. Firstly, the results are based on small bodies of literature, especially in relation to SP. Secondly, this review did not include a *meta*-analytic component which limits the robustness, reliability, and validity of its findings. Thirdly, this review did not test/correct for publication bias. Similarly, we did not include grey-literature within this review hence it is likely that the final studies may have been affected by publication bias (file-drawer phenomenon; Rosenthal, 1979). Fourthly, as previously mentioned, there was a large degree of heterogeneity in the methodology associated with the included studies which may confound the effects highlighted in this review. Fifth, the current review excluded single-cue designs (Del-Ben et al., 2001; Grillon et al., 2007), which may have added further data for the investigation of patient-control differences in CS+ responding. Sixth, most studies reported female-dominated samples hence the results and conclusions of this review may not be representative of male-typical responding. Seventh, it was common for studies to forego outlining the ethnic makeup of their respective samples. Given that ethnicity and sex are known to moderate the relationship between psychophysiological processes and behaviour the generalizability of these findings in relation to these variables is unknown (Gatzke-Kopp, 2016). Despite these limitations, one strength of the review relates to the quality of the studies as all were rated as either moderate or high in research quality which increases the credibility of the findings.

In conclusion, despite the small bodies of literature and methodological heterogeneity, the current review provides tentative evidence for specific patient-control alterations in threat acquisition in relation to PD and threat acquisition and extinction in relation to SP. Specifically, there was strong evidence for poorer CS+/CS- discrimination and mixed evidence for heightened CS+ responding in PD patients during acquisition. Further, there was strong evidence for heightened CS+/CS- discrimination in SP patients in comparison to controls during acquisition, although this effect could be specific to fear-relevant CS+ stimuli. Moreover, there was strong evidence for heightened CS+ responding during extinction and mixed evidence for heightened CS+ and CS- responding during extinction retention in SP patients. All effects seem to materialise more readily in relation to subjective measures and the conditioning signatures associated with SP and PD identified within this review largely differentiate themselves from the conditioning effects associated with other disorders e.g., OCD, SAD, and ADs in general. It must be noted that the conclusions of this review are inhibited by the large variability in both the experimental and analytic methods employed within the field. Additionally, there is both a general, and specific i.e., investigating extinction and retention in SP, paucity of

evidence in this research area which makes it difficult to draw robust conclusions. Further, the lack of effect sizes retrieved made it implausible to carry out a *meta*-analysis in this area which also limits the conclusions of this review. These elements require amelioration to further improve the field. Overall, this review has highlighted current gaps in the literature and made recommendations for future research which, if heeded, should facilitate the furthering of scientific understanding of this topic.

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Kane Steggles: Writing – original draft, Visualization, Conceptualization. **Matthew Garner:** Supervision. **Jayne Morriss:** Writing – review & editing, Supervision, Conceptualization.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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