University of Southampton

Faculty of Environmental and Life Sciences

School of Psychology

Threat Conditioning in Anxiety-Related Disorders: An Empirical Study and Systematic Review

by

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Abstract

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Anxiety disorders (AD) are a prevalent form of psychological disorder with far-ranging negative consequences for those suffering with them. Recent efforts have utilised human threat conditioning procedures to gain further understanding of how individuals with ADs respond to conditioned threat and safety cues. Research in this area is at the vanguard of optimising exposure-based treatments and recent developments have yielded promising results. Yet, exposure-based treatments are still marred with lower-than-desired remission rates and higher-than-desired relapse rates, hence further investigation of the factors that may inhibit the success of exposure-based therapies is needed. In chapter two, the reader will be introduced to the concept of intolerance of uncertainty (IU) and its suspected role in inhibiting extinction learning which has potential clinical implications. The empirical study within this chapter describes a two-day threat conditioning procedure using a student sample (N=101) with the aim of investigating the relationship between IU and extinction learning whilst controlling for diagnostic measures. The results demonstrate a null association between these two variables contradicting previous findings. In chapter three, the reader will be introduced to the relevant literature regarding threat conditioning and extinction processes in those with ADs. Although ADs and other specific anxiety-related conditions have had recent systematic reviews on this topic, there is a lack of synthesis in relation to panic disorder (PD) and specific phobia (SP). Hence, a systematic review was carried out focussing on patient-control differences in threat conditioning processes in relation to both PD and SP separately. The review uncovered interesting, yet tentative, patterns of results which indicate key patient-control alterations in threat acquisition in PD patients, and alterations in threat acquisition and extinction in SP patients. The results of both studies have meaningful clinical and academic implications which are outlined and discussed further.

Keywords: Anxiety Disorders, Exposure-Based Treatments, Threat Conditioning, Intolerance of Uncertainty, Panic Disorder, Specific Phobia

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Research Thesis: Declaration of Authorship

Print name: KANE STEGGLES

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I declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

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3. Where I have consulted the published work of others, this is always clearly attributed;
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7. None of this work has been published before submission

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Abbreviations

ACC .....Anterior Cingulate Cortex

ACQ .....The threat acquisition phase within a typical conditioning protocol

ACT .....Acceptance and Commitment Therapy

AD .....Anxiety Disorder

AI .....Artificial Intelligence

ANX .....Anxiety ratings

ARO .....Arousal ratings

bl .....Bilateral

BNST .....Bed Nucleus of Stria Terminalis

CBT .....Cognitive-Behavioural Therapy

cm .....Centromedial

CON .....Non-clinical control participants

COVID-19 .....An infectious Coronavirus disease caused by the SARS-CoV-2 virus which proliferated globally in 2019/2020

CS- .....A control (safety) stimulus employed in a typical conditioning protocol

CS+ .....A conditioned (threat) stimulus paired either continuously or intermittently with an unconditioned aversive stimulus within a typical conditioning protocol

CSdiff .....A difference score calculated by subtracting the CS- from the CS+, otherwise known as a ‘discrimination score’

d .....Dorsal

DSM .....Diagnostic and Statistical Manual of Mental Disorders

EMG .....Electromyography

EPHPP .....Effective Public Health Practice Project Research Quality Tool

ERP .....Event-Related Potentials

ET .....Exposure-Based Treatments

EXP .....US (unconditioned stimulus) Expectancy Ratings

EXT .....A threat extinction phase within a typical conditioning protocol

fMRI .....Functional Magnetic Resonance Imaging

FPS .....Fear-Potentiated Startle Response

GAD .....Generalised Anxiety Disorder

GAD-7 .....7-Item Generalised Anxiety Disorder symptom scale

HiPPC .....Hippocampus

HV .....Hyperventilation

IU .....Trait Intolerance of Uncertainty

IUS-12 .....12-item Intolerance of Uncertainty scale

l .....Lateral

m .....Medial

MDD .....Major Depressive Disorder

MDSQ .....Multi-Dimensional Mood State Questionnaire

MLM .....Multi-Level Modelling analysis

NPU .....'No-Predictable-Unpredictable' procedure/task otherwise known as a 'threat predictability task'

OCD .....Obsessive-Compulsive Disorder

OCI-R .....18-Item Obsessive Compulsive Disorder Symptom scale

PCL-5 .....20-Item PTSD Symptom scale

PD .....Panic Disorder

PDSS-SR.....7-Item Panic Disorder Symptom scale

PFC .....Pre-frontal Cortex

PHQ-9 .....9-Item Major Depressive Disorder Symptom scale

PPI .....Psychophysiological Interaction analysis

PRISMA .....Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines

PTSD .....Post-Traumatic Stress Disorder

RET ..... An extinction retention phase within a typical conditioning protocol

ROI .....Region of Interest fMRI analysis

SAD .....Social Anxiety Disorder

SCR .....Skin Conductance Response otherwise known as ‘electrodermal activity (EDA)’ or a ‘Galvanic skin response (GSR)’

SIPS .....14-Item Social Anxiety Disorder Symptom scale

SNRI .....Serotonin and Noradrenaline Reuptake Inhibitor

SP .....Specific Phobia

SSRI .....Selective Serotonin Reuptake Inhibitor

STAI-T .....Shortened 5-Item Trait Anxiety scale

SWiM .....Synthesis without Meta-Analysis guidelines

TA .....Threat Acquisition

TE .....Threat Extinction

US .....An unconditioned aversive stimulus employed within a typical conditioning protocol

VAL .....Valence Ratings

Vm .....Ventromedial

Chapter 1

Title: Bridging Chapter - An Overview of Threat Conditioning Research in Relation to Anxiety-Related Disorders and Exposure-Based Treatments

Word Count (excluding references): 2270

Bridging Chapter

The nature of human emotion has long piqued the interest of theologians, philosophers, naturalists, and, more recently, psychologists (Adolphs, 2010; Barrett, 2016; Panksepp, 2004). In particular, fear and anxiety have been the focus of much scientific research and debate due to their role in ensuring survival, safety, and self-preservation (Blanchard et al., 2008). It is well-established that fear and anxiety encourage vigilance to threat which allows one to respond in a manner that increases the likelihood of successfully navigating dangerous environments (Mobbs et al., 2015). However, despite their perceived conceptual and functional similarities, both anxiety and fear have distinct functions in relation to their proximity to threat; whereas anxiety occurs in situations with potential threat, fear is reserved for situations with imminent threat (Gray & McNaughton, 2003). Further, the optimal behavioural responses within each circumstance are largely distinct. Whereas escape and/or aggression is beneficial under imminent threat i.e., fear (Misslin, 2003), the optimal responses to potential threat i.e., anxiety are more complex as, in addition to potential threats, such environments are likely to contain potential rewards (Corr, 2013). Hence, in these circumstances approach-avoidance conflicts emerge that require one to approach specific contexts whilst cautiously scanning for threats and preparing for the execution of escape behaviours i.e., anxious responding (Gray & McNaughton, 2003). Yet, despite their inherent survival value, negative emotions, including fear and anxiety, can and do produce their own difficulties which, in their extreme form, cause prominent distress and dysfunction (American Psychiatric Association (APA), 2022).

Anxiety disorders (AD) refer to a set of psychiatric conditions characterised by frequent and intense bouts of affective symptoms such as anxiety, nervousness, and fear, alongside physical symptoms such as perceived heart palpitations, shortness of breath, gastric distress, and hypertonia etc. (APA, 2022; Bandelow et al., 2017). Anxiety and fear represent symptoms of an anxiety disorder when the frequency and intensity of these experiences cause significant distress and dysfunction in relation to important areas of life e.g., work, social life

etc. (APA, 2022). Indeed, ADs are often associated with poorer physical health (Harter, Conway, & Merikangas, 2003), interpersonal (Pankiewicz, Majkowicz et al., 2012), and occupational outcomes (Deady et al., 2022), alongside high levels of comorbidity with other anxiety disorders and major depressive disorder (MDD) (Brown et al., 2001; Goldstein-Piekarski et al., 2016). Hence, ADs tend to be associated with prevalent negative outcomes which impact one's quality of life in multiple domains. The term anxiety disorder is an umbrella term encompassing multiple related disorders such as generalised anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD) etc. (APA, 2022). Although conceptualised as distinct entities, ADs are known to share similar diagnostic features such as worry and avoidance (Herr et al., 2014). Epidemiological studies estimate that the global point-prevalence of ADs ranges from 4.05% to 7.3%, with a moderate degree of cross-cultural variation i.e., of 5.3% and 10.4% in African and European/Anglicised cultures, respectively (Baxter et al., 2013; Javaid et al., 2023). Indeed, ADs are the most common psychiatric disorder in Europe and the second most common in the United States, behind MDD (Kessler et al., 2012; Wittchen et al., 2011). Further, prevalence rates have remained relatively stable in recent times, however, there has been a slight reported increase following the COVID-19 pandemic (Baxter et al., 2014; Santomauro et al., 2021). Additionally, incidences of AD generally decrease with old age, and, overall, women are twice as likely to be diagnosed with an AD in comparison to men (Bandelow & Michaelis, 2015).

Despite the high prevalence, morbidity, and chronicity associated with ADs, multiple effective pharmacological and psychotherapeutic treatments exist (Bandelow et al., 2014). For instance, both selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) reduce anxiety symptomatology and increase day-to-day functioning (Bandelow et al., 2017). Further, cognitive-behavioural therapy (CBT), a form of psychotherapy, has demonstrated efficacy and effectiveness in treating anxiety disorders as evidenced in an extensive number of meta-analyses and randomised controlled trials across both controlled and naturalistic settings (Asnaani et al., 2020; Hofman & Smits, 2008; Norton

& Price, 2007; Carpenter et al., 2018). On top of this, CBT has been shown to outperform anxiolytic medications (Roshanaei-Moghaddam et al., 2011), psychodynamic therapy (Bandelow et al., 2014), and third-wave therapies such as acceptance and commitment therapy at follow-up (ACT; Forman et al., 2012) when treating ADs specifically. As a result, CBT is often the treatment of choice for the treatment of ADs by clinical practitioners (Bandelow et al., 2014). It has long been argued that exposure represents the main active ingredient responsible for the effect that CBT has in reducing anxiety symptomatology (Craske et al., 2014; Foa & Kozak, 1986). Briefly, exposure is a therapeutic technique characterised by guiding patients to voluntarily engage with specific fear and/or anxiety inducing stimuli which, over time, leads to a reduction in the level of fear and anxiety expressed in the presence of said stimuli (Barlow, 2021). Indeed, much research has shown that the exposure component is the most effective element of CBT in reducing anxiety specifically (Carpenter et al., 2018; Whiteside et al., 2020). Similarly, exposure theorists and researchers have suggested that, regardless of the modality, all anxiety-focussed treatments should include and emphasises an element of exposure (Foa & Kozak, 1986). Moreover, the clinical application of exposure-based treatments for ADs is well understood as evidenced by the development of multiple specific exposure protocols that have been successfully utilised in clinical practice (Kaplan & Tolin, 2011). Despite this, just under half of patients exhibit a lack of remission in response to exposure treatments, and post-exposure relapse rates range from 14% to 23.8% (Levy et al., 2021; Lorimer et al., 2021; Springer et al., 2018). Similarly, due to the demanding nature of exposure treatment, such therapeutic practices have high rates of treatment refusal and attrition which reduce their overall effectiveness (Haby et al., 2006; Issakidis & Andrews, 2004). Hence, further improvement in the short-term and long-term outcomes exposure-based treatments would be of extensive benefit to future AD patients.

It is well-established that exposure-based treatments are modelled on classical conditioning principles (Boschen et al., 2009; Foa & McLean, 2016; Rachman, 2015). Classical, or Pavlovian, conditioning refers to the process by which the frequent pairing of a

neutral stimulus and an aversive stimulus (US; unconditioned stimulus) eventually causes the neutral stimulus to evoke responses similar to that observed in response to the aversive stimulus (Pavlov, 1927). Since Ivan Pavlov's seminal research on this subject (Pavlov, 1927), conditioning processes have been extensively studied in humans culminating in the production of modern human threat conditioning experiments (Lonsdorf et al., 2017). Such experiments have been used to study the processes by which human beings learn and unlearn specific stimulus-stimulus associations (Delameter, 2004; Hermanns et al., 2006; Lonsdorf et al., 2017). Briefly, such experiments consist of two, but sometimes three, phases: Within the acquisition phase, participants are presented with two stimuli (CS+ and CS-). The CS+ is paired with an aversive stimulus e.g., an electric shock (US) whereas the CS- is not. Throughout this phase, the CS+ begins to elicit defensive responding regardless of whether there was a CS+/US pairing within that particular trial; this learning process is referred to as 'threat acquisition learning' (Lonsdorf et al., 2017). Next, in the extinction phase, both the CS+ and CS- are presented to participants without the presentation of a single US. Over time, the defensive responding to the CS+ reduces until there is no observable difference in responding to the CS+ and CS-, a process known as 'threat extinction learning' (Lonsdorf et al., 2017). Lastly, some experiments include a third 'recall' or 'retention' phase which is identical to the extinction phase except it takes place after a delay of at least 24 hours. This phase tests the retention of extinction learning over time (Lonsdorf et al., 2017). Such threat conditioning experiments have been used as a framework for the understanding of the processes associated with the acquisition and treatment of pathological anxiety and/or fear (Mineka & Zinbarg, 2006). Specifically, threat acquisition is said to represent the genesis and development of anxiety disorders (Mineka & Oehlberg, 2008; Mineka & Zinbarg, 2006; Ohman & Mineka, 2001). And threat extinction and retention are said to represent the treatment of anxiety, and the maintenance of treatment gains post-exposure treatment, respectively (Dunsmoor et al., 2015; Levy et al., 2021; Milad & Quirk, 2012; Vervliet et al., 2013). Indeed, threat conditioning experiments have been used to inform contemporary

clinical psychological practice in relation to the treatment of ADs (Craske et al., 2014, 2018, 2022). Similarly, clinically-oriented researchers have long postulated that exposure-based treatments may be further improved by studying the nature of conditioning and extinction processes, within the context of threat conditioning experiments, in relation to ADs specifically (Craske et al., 2012, 2014, 2022). The current doctoral thesis will focus solely on this topic. Namely, investigating the nature of threat acquisition and extinction processes in relation to anxiety to further our understanding of the genesis, maintenance, and treatment of ADs. Both the empirical project (chapter two) and the systematic review (chapter three) outline two different avenues of furthering this area of research.

Within chapter two, the reader will be introduced to the concept of intolerance of uncertainty (IU) which refers to a trait-level tendency to experience distress and discomfort in relation to uncertainty/ambiguity (Carelton, 2016). IU is conceptualised as a transdiagnostic factor, subsumed by trait neuroticism (Carleton, 2016; Hong & Cheung, 2015; McEvoy & Mahoney, 2012), to which there is mounting evidence of its clinical relevance. For instance, IU has been shown to account for significant variance in anxiety and depression symptoms (Mahoney & McEvoy, 2012), and SAD symptoms specifically (McEvoy & Mahoney, 2011). More recently IU has been shown to account for individual differences in threat extinction learning within threat conditioning experiments whilst controlling for trait anxiety (Morriss et al., 2021). Given the previously mentioned conceptual overlap between threat extinction learning and exposure-based treatments this suggests that IU may have potential clinical utility, however little is currently known as to whether IU accounts for threat extinction differences whilst controlling for psychopathological symptoms. Therefore, the empirical project outlines a typical two-day threat conditioning experiment (acquisition, extinction, and retention): a student sample was recruited to examine whether individual differences in self-reported IU account for differences in threat extinction learning whilst controlling for common psychiatric symptom measures. Elucidating this question will have direct clinical implications. For instance, if IU is found to be specifically associated with threat extinction

learning in this context, it would warrant a further attempt to replicate these findings in a clinical sample, which, if successful could motivate further research into the role of IU in moderating exposure therapy outcomes. Ultimately, if IU is found to moderate exposure outcomes, then explicit focus on IU within exposure-based treatment may yield better results than traditional exposure treatment. Indeed, a specific clinical focus on IU has been successfully implemented when treating GAD (Robichaud et al., 2019). Further, a recent meta-analysis found that effective psychological treatment directly lowers trait IU in those seeking treatment for ADs (Miller & McGuire, 2023). However, whether IU directly impedes exposure treatment itself is still unknown.

Within chapter three, the reader will be guided through the current state of the literature surrounding threat acquisition and extinction processes in relation to ADs. More specifically, there have been multiple meta-analyses examining whether AD patients differ to non-clinical controls in threat acquisition and extinction learning (Duits et al., 2015; Kausche et al., 2024; Lissek et al., 2005). The most comprehensive review demonstrates heightened patient responding to both CS stimuli throughout acquisition, extinction, and retention in comparison to controls (Kausche et al., 2024). Yet, within this meta-analysis there has been high inter-diagnostic variability reported i.e., different anxiety disorders seem to possess different conditioning and extinction signatures to one another (Kausche et al., 2024). Indeed, OCD and SAD have been investigated in this regard via systematic reviews and both disorders differ to one another, and to ADs in general, in their specific conditioning alterations compared to controls (Cooper & Dunsmoor, 2015; Wake et al., 2024). However, a systematic review has not been carried out for either specific phobia (SP) or panic disorder (PD) hence demonstrating a large gap in the literature. Consequently, a systematic review was carried out to examine patient-control differences in threat acquisition, extinction learning, and extinction retention in relation to SP and PD separately. Again, further elucidation of this question would have wide-ranging implications for our understanding of pathological anxiety, conditioning, and by extension, exposure-based treatments. Given the aforementioned conceptual overlap

between threat acquisition/extinction/retention and the genesis and treatment of ADs (Mineka & Zinbarg, 2006), further information on the conditioning signatures associated with these disorders could further elucidate their associated risk and/or maintaining factors. Similarly, information about aberrant extinction processes could further our understanding of potential methods of improving exposure treatments for individuals with these specific disorders. Indeed, the rejection of previous habituation-based models for more recent inhibitory-learning models of exposure occurred on the basis of threat conditioning research findings (Craske et al., 2012). This innovation has produced further recommendations for clinicians on how to optimize exposure treatment as informed by inhibitory learning (Craske et al., 2014). Hence, further understanding of threat conditioning pertaining to anxiety disorders could lead to similar disorder-specific innovations.

Ultimately, this thesis will contribute to our understanding of threat conditioning in relation to anxiety disorders and their associated treatments. Given the courage that AD patients show when actively confronting fear, anxiety, and discomfort during exposure (Rachman, 2010), further research on the optimization of these techniques in the pursuit of further therapeutic gains is the least that the clinical psychology profession can do to repay their bravery and tenacity.

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Chapter 2

Title: Investigating whether Intolerance of Uncertainty is Specifically Associated with Threat Extinction over Diagnostic Measures of Anxiety-Related Conditions

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Abstract

Modern exposure-based therapies operate on principles of threat conditioning and extinction. Previous research has demonstrated that trait-level intolerance of uncertainty (IU) is specifically associated with worsened extinction learning whilst controlling for trait anxiety. Hence, IU may serve as a useful focus for researchers aiming to improve the effectiveness of exposure-based therapies. Yet, little is known as to whether IU is associated with extinction learning whilst controlling for disorder-specific symptom measures. A two-day Pavlovian conditioning task was carried out, consisting of threat acquisition, extinction, and extinction retention phases. An opportunity sample (N=101) completed IU, trait anxiety, and various disorder-specific symptom questionnaires e.g., generalised anxiety disorder before engaging in the conditioning procedure. Skin conductance magnitudes, and behavioural ratings of anxiety and stimulus expectancy were used as indices of conditioned responding, and extinction by extension. Analyses revealed that successful threat conditioning was observed for all three measures during threat acquisition, yet extinction was not observed during both the extinction and retention phases. IU was not specifically associated with individual differences in extinction as indexed by differential SCR magnitudes, contradicting prior research. Further, IU was specifically associated with differential stimulus expectancy and anxiety ratings within extinction and retention respectively, whilst controlling for symptom measures. Lastly, IU was not associated with any other extinction measure. Exploratory examinations of traits/symptom measures revealed null associations with CS+/CS- difference scores. Yet, trait/symptom measures did correlate frequently with overall arousal and individually to conditioned stimuli. Interpretations, limitations, and future research are discussed in relation to IU and extinction learning.

Key words: Uncertainty, Threat Conditioning, Extinction, Retention, Anxiety-Related Disorders.

Introduction

Anxiety is a negative affective state characterised by specific behavioural and physiological responses such as avoidance, hypervigilance, and physiological arousal (Gross & Hen, 2004). Anxious responding arises in situations characterised by perceived danger; hence such responding is thought to serve the function of enabling the identification of, and escape from, species-specific threats (Gray & McNaughton, 2003). Overall, anxiety is considered a normal and adaptive response allowing one to effectively anticipate, prepare for, and contend with future problems (Davey, 2021). Anxiety disorders, however, refer to psychiatric conditions characterised by frequent and intense bouts of anxiety, fear, and worry, alongside physical symptoms such as heart palpitations, breathlessness, dizziness, and increased muscle tension etc. (Bandelow et al., 2017). Anxiety meets diagnostic thresholds when it produces significant distress and/or impairment in multiple domains of daily functioning e.g., social, occupational, or other important aspects of life (American Psychiatric Association (APA), 2022).

Anxiety disorders have a global prevalence ranging from 4.05% to 7.3%, with a moderate degree of cross-cultural variation (Baxter et al., 2012; Vos et al., 2017; Javaid et al., 2023; Kessler et al., 2012; Wittchen et al., 2011). Further, as outlined in the most-recent diagnostic and statistical manual (DSM-V-TR; APA, 2022), the term ‘anxiety disorder’ encompasses multiple related conditions such as generalised anxiety disorder (GAD), panic disorder (PD), and social anxiety disorder (SAD). These conditions are frequently comorbid with one another and other depressive disorders e.g., major depressive disorder (Brown et al., 2001; Goldstein-Piekarski et al., 2016). Interestingly, seemingly distinct anxiety disorders share similar diagnostic features such as excessive worry and frequent avoidance of feared situations (Herr et al., 2014). Indeed, recent research on transdiagnostic models emphasises the presence of shared underlying mechanisms amongst anxiety disorders e.g., attentional biases to threat, anxiety-sensitivity (Norton & Paulus, 2017). Despite this, individual anxiety disorders are distinguishable from one another in the types of stimuli that induce fear and/or anxiety in each condition. For instance, individuals with SAD tend to fear negative social

evaluation and ridicule, whereas those with PD tend to fear the prospect of dying or losing one's mind as a result of an impending panic attack (APA, 2022). Therefore, individuals with SD and PD are both likely to experience excessive worry, however the content of said worry is likely to differ significantly with respect to their associated diagnoses.

It has long been argued that an element of exposure to feared, or anxiety-provoking, situations is essential when treating anxiety disorders (Foa & Kozak, 1986). Within exposure-based treatments, the therapist facilitates the voluntary engagement of the patient with a series of objects or situations that they find anxiety or fear inducing. Paradoxically, upon repeated instances of exposure, the previously avoided objects begin to elicit less fear/anxiety which then produces a reduction in anxiety symptomatology (Barlow, 2021). Exposure therapies vary widely in their clinical application, for instance exposure can be graded or non-graded i.e., flooding, employed in vivo or with imaginal feared stimuli, utilise internal or external stimuli, and be used with or without relaxation techniques e.g., diaphragmatic breathing (Kaplan & Tolin, 2011). It is now well-established that exposure-based therapies are highly effective for treating anxiety disorders (Kaplan & Tolin, 2011). Indeed, multiple meta-analyses have demonstrated that cognitive behavioural therapy (CBT), of which exposure is a key component, outperforms wait-list control, pill placebo, and psychological placebo groups within clinical trials (Hofman & Smits, 2008; Norton & Price, 2007; Carpenter et al., 2018). It is thought that exposure may directly and predominantly underpin the effectiveness of CBT in reducing anxiety symptomatology given its centrality within established protocols (Craske et al., 2014; Foa & Kozak, 1986). Indeed, it has been shown that exposure-based therapies produce larger effect sizes than those that do not utilise exposure when treating anxiety disorders (Carpenter et al., 2018). Despite the illustrated efficacy of exposure-based therapies, treatment responses in naturalistic settings are varied with approximately 49% of patients failing to reach clinical remission by the end of treatment (Springer et al., 2018). Similarly, 14% of patients with successful treatment outcomes experience relapse post-treatment (Levy et al., 2021). Although higher relapse rates have been recorded elsewhere in the literature e.g.,

23.8% (Lorimer et al., 2021). Such differences are likely due to varying definitions of relapse and follow-up. Additionally, exposure protocols produce high rates of treatment refusal and attrition (Haby et al., 2006; Issakidis & Andrews, 2004). Therefore, it is important to understand the variables that may inhibit the success of exposure-based treatments for the benefit of future patients.

Exposure treatments can be understood via principles of classical conditioning (Boschen et al., 2009). Within human threat-conditioning experiments, and during the 'threat acquisition phase', a neutral stimulus (CS+; conditioned stimulus e.g., a shape) is repeatedly paired with an aversive stimulus (US; unconditioned stimulus e.g., an electric shock). After repeated pairings, the CS+ begins to evoke a response analogous to the unconditioned stimulus i.e., defensive responding, otherwise known as the conditioned response (Lonsdorf et al., 2017). Additionally, conditioning procedures often include a control stimulus (CS-) that is not paired with the US to outline differential responding to conditioned and unconditioned stimuli (Lonsdorf et al., 2017). Typically, this phase is followed by either an immediate or delayed/repeated 'threat extinction' phase. In the threat extinction phase, both the CS+ and the CS- are presented to the participant without the presence of the aversive stimulus which leads to a reduction in the magnitude/frequency of conditioned responding to the CS+, this process is known as 'extinction learning' (Hermans et al., 2006; Lonsdorf et al., 2017). Threat acquisition and extinction tend to be indexed via differential CS+/CS- response measurements in either physiological data e.g., skin conductance responses, or behavioural ratings e.g., expectancy of aversive stimulus presentation or perceived distress (Lonsdorf et al., 2017). Threat acquisition is said to represent the mechanism by which pathological anxiety/fear responses may be acquired (Mineka & Oehlberg, 2008; Mineka & Zinbarg, 2006; Ohman & Mineka, 2001). Whereas threat extinction learning is thought to represent the central mechanism underpinning exposure-based treatments i.e., the unlearning of previously acquired CS+/US associations (Dunsmoor et al., 2015; Milad & Quirk, 2012, Vervliet et al, 2013; Rachman, 1989). Multiple explanatory mechanisms of extinction learning have been

proposed, however recent research supports the inhibitory learning model (Craske et al., 2012). This model suggests that threat extinction learning leads to the formation of new safety associations in relation to the conditioned stimulus which compete with, but do not erase, the older threat associations (Bouton, 2004; Delamater, 2004).

Interestingly, recent research has demonstrated distinct differences in conditioned responding between those with and without clinical anxiety disorders. Such research has been undertaken to elucidate potential differences in threat conditioning between clinical and non-clinical groups with the hope of improving future treatments (Jacoby & Abramowitz, 2016). For instance, a recent meta-analysis found that anxiety patients show stronger responses to the CS-, but not the CS+, during acquisition in comparison to non-clinical controls. Additionally, anxiety patients displayed heightened responding to the CS+, but not the CS-, compared to controls during extinction (Duits et al, 2015). These results suggest that individuals with anxiety disorders transfer learned threat associations to non-threatening stimuli during threat acquisition, whilst also demonstrating difficulty in extinguishing previously learned CS+/threat associations during extinction. Although utilizing a general anxiety disorder category, most of the studies within Duits et al. (2015) examined patient-control differences in relation to post-traumatic stress disorder (PTSD) hence these effects may be more specific to this disorder. Interestingly, a more recent study carried out by Abend et al. (2020) found patient-control differences in the magnitude of responding to both the CS+ and CS- (heightened patient responding to both stimuli compared to controls) throughout the entirety of the conditioning procedure i.e., both acquisition and extinction. This suggests that anxiety disorders are associated with heightened arousal throughout threat acquisition and extinction, as opposed to showing differences specific to either conditioning phase or stimulus type. Further, OCD patients also demonstrate heightened responding to the CS+ in extinction compared to controls, however this effect was stronger in studies that utilised delayed extinction protocols (see Cooper & Dunsmoor, 2021 for review). Yet, unlike anxiety disorders in general, individuals with OCD display heightened conditioned responding to the

CS+ during threat acquisition in comparison to controls (Cooper & Dunsmoor, 2021). This may suggest that individuals with OCD acquire stronger, or more rapid, threat associations with the CS+ in comparison to anxiety-related disorders in general. Further, it appears that individuals with SAD display little evidence of group-level differences in threat conditioning (Wake et al., 2024). Hence, although patient-control differences in threat conditioning have been found in relation to anxiety-related disorders as a general category (Duits et al., 2015; Abend et al., 2020), there is also evidence of inter-diagnostic variation in both the presence and/or nature of these effects with respect to specific anxiety-related conditions (Cooper & Dunsmoor, 2021; Wake et al., 2024).

On another note, disparate lines of academic enquiry have outlined the emerging importance of intolerance of uncertainty (IU) in accounting for both anxiety disorder symptomatology (Mahoney & McEvoy, 2012) and altered threat extinction learning (Morriss et al., 2021a). IU is defined as "an individual's dispositional incapacity to endure the aversive response triggered by the perceived absence of salient, key, or sufficient information, and sustained by the associated perception of uncertainty" (Carleton, 2016a). Essentially, IU represents an aversion to uncertainty similar to the notion of "fearing the unknown"; an experience associated with multiple anxiety disorders (Carleton, 2016b). IU is said to represent a lower-order transdiagnostic factor which is subsumed by neuroticism (Carleton, 2016a, Carleton, 2016b; Hong & Cheung, 2015; McEvoy & Mahoney, 2012; Paulus et al., 2015), a higher-order personality trait indexed via an increased tendency to experience negative emotion, otherwise known as negative affectivity (Watson & Clark, 1984). In cross-sectional research, IU has been shown to account for unique variance in social anxiety whilst controlling for neuroticism (McEvoy & Mahoney, 2011). Similarly, IU mediates the well-established relationship between neuroticism and various anxiety disorders and depression (McEvoy & Mahoney, 2012). In relation to human threat conditioning, a recent meta-analysis revealed that higher IU is associated with poorer threat extinction learning whilst controlling for other measures of trait anxiety that are similar to neuroticism (Morriss et al., 2021a). It is

posited that those with high IU find the contingency uncertainty during extinction more distressing than those with low IU, and this, in turn, maintains heighted conditioned responding to the CS+ during extinction (Morriss & van Reekum, 2019). If true, this may suggest that a clinical focus on IU within exposure-based therapies is warranted to enhance extinction learning specifically (Morriss, 2025).

Indeed, there is strong evidence that IU can be clinically altered via evidence-based treatments for anxiety disorders such as CBT (Miller & McGuire, 2023). Pertinently, it appears that CBT interventions which target IU specifically are more effective at reducing IU (Wilson et al., 2023). Such targeted approaches included further psychoeducation about IU, worry awareness training, behavioural experiments aimed at re-evaluating IU-related beliefs etc. (Robichaud et al., 2019; Hebert & Dugas, 2019). However, to fully understand the clinical utility of IU as a transdiagnostic dimension, it is important to address whether IU is associated with extinction learning, over and above anxiety-, stress- and depression-related symptomatology as such constructs have not yet been controlled for in prior research. This would allow us to demonstrate whether the predictive effect of IU upon extinction learning is subsumed by anxiety-, stress-, and depression-related symptomatology or whether it represents an association that may translate across different types of symptomatology.

The current study aimed to investigate IU in relation to threat extinction learning whilst controlling for disorder-specific measures. The study employed a two-day classical threat conditioning task consisting of three distinct phases: threat acquisition (acquisition), same-day threat extinction (extinction), and next-day extinction retention (retention). Behavioural ratings of anxiety, stimulus expectancy, and skin conductance responses (SCR) were used as indices of conditioned responding as per standard practice in threat conditioning research (Lonsdorf et al., 2017). Similar to previous research, the specificity of IU was assessed whilst controlling for trait-level anxiety and an array of common mental health disorder symptoms e.g., SAD, GAD, PTSD etc. Considering previous research, we hypothesised the following:

1. During acquisition, we predicted significantly heightened responding to the CS+, vs. the CS-, for both the behavioural ratings (anxiety and stimulus expectancy) and SCR, demonstrating conditioning to the CS+.
2. During extinction, we predicted a continuation of significantly heightened responding (behavioural ratings and SCR) to the CS+, vs. CS-, within the first half of the extinction phase. However, within the latter half we predicted equal responding (SCR and behavioural ratings) between the CS+ and CS-, demonstrating extinction learning.
3. During retention, we predicted slightly yet significantly heightened responding to the CS+, vs. the CS-, (SCR and behavioural ratings) in the first half of the retention phase demonstrating a 'return of fear' (Lonsdorf et al., 2017). Within the latter half, we predicted equal responding (SCR and behavioural ratings) between the CS+ and CS-, demonstrating extinction retention.
4. With regards to individual differences in IU, we predicted that high IU will be associated with continued heightened responding to the CS+, vs. the CS-, during both extinction and retention whilst controlling for trait anxiety (Morriss et al., 2021b). Additionally, we predicted that high IU will be specifically associated with poorer extinction learning (heightened responding to CS+ vs. CS-) in both phases whilst controlling for disorder-specific symptom measures.
5. Based on recent work showing patient-control differences in responding to the CS+ and CS- in clinical samples with anxiety and OCD (Duits et al., 2015; Cooper & Dunsmoor, 2021), we anticipated that symptom measures may be associated with differences between the CS+ and CS- (CS+-CS- difference scores) during acquisition, extinction, and retention.
6. Given the clinical research by Duits et al (2015) and Abend et al. (2020), we explored whether trait (IU and trait anxiety (TA)) and symptom measures were associated with overall arousal levels (behavioural ratings/SCR across entire phase), as well as individually to the CS+ and CS- during all three phases.

Method

Participants

An opportunity sample of 101 participants (76 females, 25 males; 54 White, 38 Asian, 6 black, and 3 multi-ethnic; 68 heterosexual, 24 lesbian/gay/bisexual, 9 sexual orientation not reported) was recruited for the study. Participants were between the ages of 18 and 40 (M = 23.13, SD = 5.79). The sample consisted predominantly of students enrolled at the University of Southampton recruited via word of mouth or the University's student research recruitment website (SONA). Each participant was remunerated for their time via the payment of 24 SONA credits (required for those enrolled on an undergraduate Psychology course) or £20 in cash. This study was granted ethical approval by the Psychology ethics sub-committee within the University of Southampton Research Ethics Committee (UREC; Ethical Approval Number: 78272).

Inclusion criteria

The pre-specified age range was between 18 and 40 due to theoretical differences in safety learning and retention in relation to the hormonal profiles and experiences of people above and below this age range (Lonsdorf & Merz, 2017). Additionally, participants were excluded if they had a history of traumatic brain injury due to its effect in producing emotion processing and regulation differences (Salas et al., 2019). Similarly, participants were excluded if they were currently taking psychotropic medications as such treatments are known to alter internal experiences and psychophysiological responsiveness (Siepmann et al., 2007).

Power Analysis

Although multi-level modelling (MLM) was the main analysis in this study, an a-priori power analysis was carried out to estimate the minimum sample size required to detect IU-differential responding (CS+ minus CS-) correlations. This method was employed given the lack of well-established methods for estimating sample sizes for MLMs (Peugh, 2010; Snijders, 2005). The power analysis was carried out using G*Power version 3.1.9.7 (Faul et

al., 2007) with an estimated effect size of r = 0.28 (the IU-differential responding correlation effect size across 18 studies; Morriss et al., 2021a). The additional parameters used within the analysis were: a two-tailed hypothesis, an alpha value of = 0.05, and Power (1- error probability) = 0.8. This produced a required sample size of N = 97. Therefore, the obtained sample size of N = 101 is adequate to test the study hypotheses using MLMs.

Conditioning Task

Eprime 3.0 software was used to design and run the condition task procedure (Psychology Software Tools Ltd., Pittsburgh, PA). Participants were positioned approximately 60cm from the computer screen. During the experiment, visual shape stimuli (blue and yellow squares) were presented on the screen with visual angles of 6.16 X 9.07 degrees. The aversive sound stimulus was administered using headphones. The sound stimulus used throughout the experiment was that of a high-pitched female scream at 90 decibels. This sound was based on a sample from the International Affective Digitised Sounds Battery (IADS-2; Bradley & Lang, 2007) and has been used in similar research (Morriss et al., 2020). The volume of the aversive stimulus was kept consistent across participants; experimenters used an audiometer to measure the volume prior to each experiment and adjusted as necessary.

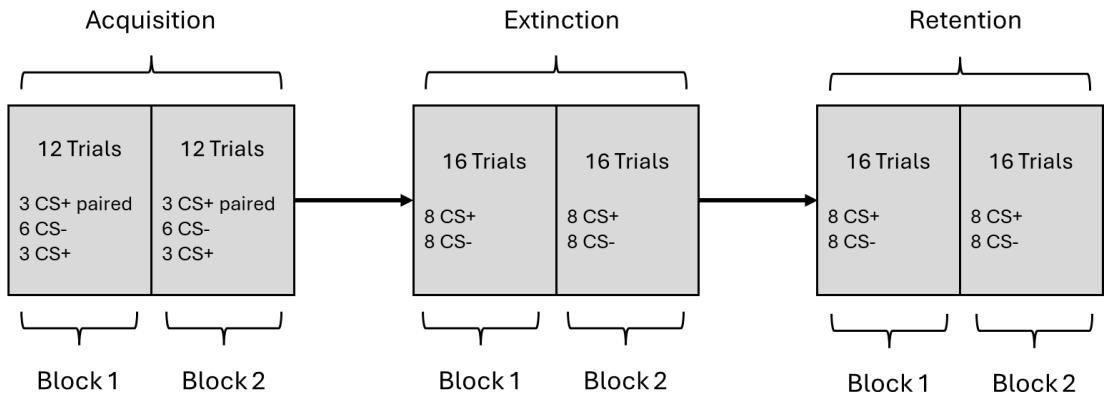
The main conditioning task was a differential cue conditioning protocol (Lonsdorf et al., 2017) consisting of three distinct learning phases: threat acquisition (acquisition), threat extinction (extinction), and extinction retention (retention). During acquisition, one of the coloured squares (yellow or blue) was paired with the aversive sound stimulus 50% of the time (CS+), the other coloured square was not paired with the aversive stimulus (CS-). Such partial reinforcement rates are known to prolong extinction learning in human samples therefore are considered optimal for extinction-specific investigations such as the current study (Haselgrove et al., 2004; Lonsdorf et al., 2017). The CS+ stimuli were counterbalanced; an equal number of participants had a blue or yellow square as the CS+ to avoid any potential

confounding colour effects. During both extinction and retention, the CS+ was not paired with the aversive stimulus. Participants were not aware that the experiment consisted of different phases, nor did they receive any differing instructions per phase. Additionally, participant instructions did not outline the reinforcement contingencies in any way, hence representing an "uninstructed procedure" (Lonsdorf et al., 2017).

Acquisition consisted of 24 trials (6 CS+ paired, 12 CS-, and 6 CS+ unpaired). Both extinction and retention consisted of 32 trials each (16 CS+ unpaired, and 16 CS-). Experimental trials underwent pseudo-randomisation; this ensured that the first trial of the acquisition phase was a CS+ trial. The shape stimuli were presented for a total of 4000ms, and the aversive sound stimulus was presented for the final 1000ms of the shape stimuli presentation (within paired trials i.e., CS+ paired). This ensured a degree of anticipation and unpredictability. Subsequently, a blank screen was presented for 6000ms to 8800ms after each stimulus presentation (Morriss et al., 2019a; Morriss & Van Reekum, 2019). Each experimental phase was split into two equal experimental blocks consisting of the same number of trials per block i.e., the acquisition phase consisted of two blocks of 12 trials whereas the extinction and retention phases consisted of two blocks of 16 trials (Figure 1). Behavioural rating scales were presented to the participants after each experimental block (see 'Rating Scales'). Pseudo-randomisation ensured that each block had an equal proportion of CS+ and CS- stimuli, and a maximum of 2 CS+ or 3 CS+ unpaired/3 CS- were presented consecutively.

Figure 1

A diagram depicting progression through the experimental procedure in terms of experimental phases and their constituent blocks.



Questionnaires

The following questionnaires were used to collect construct-specific data per participant.

Intolerance of Uncertainty Scale (IUS-12; Carleton et al., 2007)

The IUS-12 consists of 12 items measuring trait IU on a 5-point Likert scale (score range: 12 – 60). For instance, example item *"One should always look ahead so as to avoid surprises"* is rated from 1 (Not at all characteristic of me) to 5 (Entirely characteristic of me). The IUS-12 possesses an 'excellent' level of internal consistency (α = .91). The IUS-12 does not have an established clinical cut-off.

Trait Anxiety Shortened (STAI-T; Zsido et al, 2020)

The STAI-T consists of 5 items measuring trait anxiety on a 4-point Likert scale (score range: 5 - 20). For instance, example item *"I worry too much over something that really doesn't matter"* is rated from 1 (Not at all) to 4 (Very much so). This scale possesses a 'good' level of internal consistency (α = 0.82). The STAI-T does not have an established clinical cut-off.

Generalised Anxiety Disorder Questionnaire (GAD-7; Spitzer et al., 2006)

The GAD-7 is a routinely utilised measure for symptoms of GAD. It consists of 7 items measured on a 4-point Likert scale (score range: 0 - 21). For instance, example item

"Over the last 2 weeks, how often have you been bothered by any of the following problems?... Feeling nervous, anxious or on edge?" is rated from 0 (Not at all) to 3 (Nearly every day). The internal consistency of the GAD-7 is considered 'excellent' (α = .92), and test-retest reliability was also 'good' (α = 0.83). Similarly, the GAD-7 is considered to have good criterion, factorial, construct, and procedural validity. The GAD-7 has three categorical cut-offs at total scores of 5, 10, and 15 which represent mild, moderate, and severe levels of generalised anxiety respectively. A clinical cut off score of 10 or above is said to represent a clinical level of GAD.

Patient Health Questionnaire (PHQ-9; Kroenke et al, 2001)

The PHQ-9 measures symptoms of depression (MDD). It consists of 9 items rated on a 4-point Likert scale (score range: 0 - 27). For instance, *"Over the last 2 weeks, how often have you been bothered by any of the following problems?... Feeling down, depressed, or hopeless?"* is rated from 0 (not at all) to 3 (nearly every day). The PHQ-9 has demonstrated a 'good' level of internal consistency (α = 0.89) and satisfies the criteria for construct and criterion validity. The PHQ-9 has four categorical cut-offs at total scores of 5, 10, 15, and 20 which represent mild, moderate, moderately severe, and severe levels of depression respectively. A clinical cut off score of 10 or above is said to represent a clinical level of depression.

Obsessive Compulsive Inventory - Revised (OCI-R; Foa et al., 2002)

The OCI-R measures symptoms of obsessive-compulsive disorder (OCD). It consists of 18 items rated on a 5-point Likert scale (score range: 0 - 72). For instance, example item *"I check things more often than necessary"* is rated from 0 (not at all) to 4 (extremely). The OCI-R has achieved an 'excellent' level of internal consistency (α = .90) as well as a good range for test-retest reliability and convergent validity. A clinical cut-off score of 21 or above is said to represent a clinical level of OCD.

Panic Disorder Severity Scale (PDSS-SR; Shear et al., 1997)

The PDSS-SR measures symptoms of panic disorder. It consists of 7 items rated on a 5-point Likert scale (score range: 0 - 28). For instance, example item *"How many panic and limited symptoms attacks did you have during the week?"* is rated from 0 (No panic or limited symptom episodes) to 4 (Extreme: full panic attacks occurred more than once a day, more days than not). The PDSS-SR possesses 'excellent' level of internal consistency (α = .92), as well as demonstrating 'good' convergent validity and sensitivity to change. A clinical cut-off score of 8 or above is said to represent a clinical level of panic disorder (Shear et al., 2001).

Social Interaction Phobia Scale (SIPS; Carleton et al., 2009)

The SIPS measures symptoms of social anxiety disorder. It consists of 14 items rated on 5-point Likert scale (score range: 0 - 56). For instance, example item "I am tense mixing in a group" is rated from 0 (not at all characteristic of me) to 4 (entirely characteristic of me). The SIPS has been shown to contain an 'excellent' level of internal consistency (α = .92). A clinical cut-off score of 21 is said to represent a clinical level of social anxiety.

Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5; Weathers, 2013)

The PCL-5 measures symptoms of post-traumatic stress disorder (PTSD). It consists of 20 items rated on a 5-point Likert scale (score range: 0 - 80). For instance, example item *"Below is a list of problems and complaints that people sometimes have in response to stressful life experiences. How much you have been bothered by that problem IN THE LAST MONTH… Feeling jumpy or easily startled?"* is rated from 0 (not at all) to 4 (extremely). The PCL-5 possesses 'excellent' internal consistency (α = .94), and strong test-retest (r = .82), convergent (r = .74 - .85) and discriminant (r = .31 - .60) validity (Blevins et al., 2015). A clinical cut-off score of 31 is said to represent clinical levels of PTSD in community populations (Ashbaugh et al., 2016; Forkus et al., 2023).

Behavioural Rating Scales

The behavioural rating scales were presented after each experimental block. There were two behavioural rating scales used throughout the experiment that related to both of the shape stimuli presented: expectancy i.e., *"Please rate how much you expect the sound to occur when you see this colour square?"* which was rated on a 101-point Likert scale (0 = Didn't expect it, 100 = Did expect it), and anxiety i.e., *"Please rate how anxious you feel when you see this colour square?"* which was also rated on a 101-point Likert scale (0 = Not at all anxious, 100 = Anxious). These scores were used to calculate the mean score for each stimulus type. For instance, the mean rating for both the CS+ and CS- was calculated for the acquisition phase, and for both experimental blocks within the extinction and retention phases (see Figure 1). This resulted in 5 mean behavioural scores per stimulus i.e., CS+ and CS-, per behavioural construct i.e., expectancy and anxiety ratings for acquisition, early extinction (block 1), late extinction (block 2), early retention (block 1), and late retention (block 2).

Skin Conductance Responses (SCR)

Skin conductance data was recorded via a BIOPAC MP160 machine (Biopac Systems Inc., Goleta, CA) and processed using Acknowledge software (v4.2). The skin conductance data was measured in microsiemens (μS) at a rate of 2000 samples per second. After data acquisition, the data was downsampled to 20 samples per second. The full skin conductance signal was split into sections that were experiment-relevant and irrelevant sections. The sections that were relevant were known as epochs; each epoch denoted the signal recorded between 1 and 4s post-stimulus presentation, per trial. Within each epoch, the highest peak was identified and baseline corrected by subtracting the mean skin conductance value from 1s pre-stimulus to stimulus presentation (Pineles et al., 2009). To be counted as a valid SCR, the difference between the baseline and peak had to be at least 0.03 μS (Dawson et al., 2000). Trials with no discernable SCR were given a value of 0.

CS+ trials that were paired with the aversive stimulus were excluded from the analysis to prevent sound-based confounds. Therefore, each participant produced a total of 82 epochs per experiment: 6 CS+ and 12 CS- in acquisition, and 16 CS+ and 16 CS- in both extinction and retention. These epochs were visually inspected to check for movement-based artefacts and total loss of signal. Zero artefacts were detected. The data were square root transformed to normalize the distributions in accordance with previous literature (Braithwaite et al., 2013). Separate SCR magnitudes were then created by calculating the mean number of SCRs per stimulus type, per phase i.e., SCR magnitudes for CS+ and CS- during threat acquisition, extinction, and extinction retention.

Procedure

On the first day of testing (day 1), the experimenter verbally introduced the participant to the outline of the experiment. The participant then read the information sheet and signed the consent form. Participants were given time to ask any questions prior to signing the consent form. Once consent was obtained, the participant was instructed to listen to an example soundbite that was similar in nature and volume to the aversive stimulus used in the experiment. At this point, the participant's consent to continue was reassessed by the experimenter. To ensure participant safety, the experimenters were trained to recognise signs of distress and to terminate the experiment early if necessary. Following this, the experiment began with the participant completing all questionnaires.

Next, participants were instructed to wash their hands with warm water prior to the conditioning task. Participants were instructed not to use soap when washing their hands to prevent excessive removal of surface salt as it can negatively impact skin conductance data (Shaffer et al., 2016). The skin conductance electrodes were attached to the distal phalanges of the index and middle fingers on the participant's left hand. The participant was instructed to rest their left hand upon a polystyrene block to allow their fingers to float over the edge, hence minimizing disruption to electrode positioning throughout the experiment. The

participant was instructed to assume a comfortable position, to attempt to keep their left hand as still as possible, and to avoid crossing or bouncing their legs during the experimental procedure to reduce movement-based artefacts in the data (Boucsein, 2012). Before commencing, the experimenter checked the quality of the skin conductance data by instructing the participant to take a deep breath; if a skin conductance response (SCR) was observed the experiment commenced. If an SCR was not observed, the electrodes were readjusted to ensure valid recording of data.

Subsequently, the main conditioning task commenced. The conditioning task was presented on a computer screen whilst skin conductance and behavioural data were collected simultaneously. On day one, participants were instructed to maintain attention to the experimental stimuli i.e., squares and sounds, to respond to the behavioural rating scales, and were reminded to remain still throughout. On day two, participants received a similar set of instructions. Day one and two of testing took approximately one hour and 30 minutes, respectively.

Analysis Plan

Sets of multi-level models (MLMs) were conducted using the mixed procedure in SPSS (IBM inc., Armonk, NY; v28.1.1.0). Raw data and SPSS outputs (supplementary materials) can be accessed via the open science framework at: https://osf.io/y95an/?view_only=8114381c9cff478c962b59285bab7e36. Two separate MLMs (Model 1 and Model 2) were carried out per dependent variable (anxiety, stimulus expectancy, and SCR magnitude), per conditioning phase (acquisition, extinction, and retention), resulting in a total of 18 MLMs. For anxiety ratings, expectancy ratings, and SCR magnitudes during the acquisition phase Stimulus Type (CS+, CS-) was entered at level 1, and individual subjects at level 2. For anxiety ratings, expectancy ratings, and SCR magnitudes during extinction and retention both Stimulus Type (CS+, CS-) and Time (Early:

first 8CS+/CS-, Late: last 8CS+/CS-) were entered into the model at level 1, and individual subjects at level 2.

Each of the above MLMs were run twice in accordance with either Model 1 or Model 2. Within Model 1, IU and STAI-T were entered into the model as covariates. Within Model 2, IU, GAD-7, PCL-5, PDSS-SR, PHQ-9, OCI-R, and SIPS were entered into the model as covariates. The MLMs were run using mean-centred questionnaire scores. Fixed effects included Stimulus Type and Time, and random effects included a random intercept per subject. The maximum likelihood method was utilised within each MLM. Pairwise comparisons were used to follow-up both two-way and three-way interactions using the 'COMPARE' function within SPSS syntax which were adjusted using the least significant differences (LSD) method. Model 1 MLMs were interpreted first, if a significant IU main effect was present this demonstrated a specific association between IU and the dependent variable whilst controlling for trait anxiety, in this case Model 2 was interpreted and reported to assess the specificity of IU over disorder-specific measures. If a significant IU main effect or interaction (e.g., Time-IU*) was observed, follow up partial regression plots were carried out (Level 1: IU, Level 2: STAI-T, GAD-7, PCL-5, PDSS-SR, PHQ-9, OCI-R, SIPS) to ascertain the direction of the IU effect. The partial regression plots were presented graphically in the results section.

Lastly, three sets of bivariate, parametric correlational analyses were carried out in SPSS. All correlations were carried out as two-tailed analyses as they were led by non-directional, exploratory hypotheses. The first set of analyses correlated sample mean questionnaire scores with the conditioned stimulus difference score (CS+ - CS-) per dependent variable (anxiety ratings, stimulus expectancy ratings, SCR magnitudes), per conditioning phase (acquisition, extinction, retention). The second and third sets of analyses followed the same pattern: correlating sample mean questionnaire scores with mean CS+ and

mean CS- scores, and overall arousal scores (mean of CS+ and CS- scores), respectively, per dependent variable, per conditioning phase.

Results

Questionnaires

Descriptive statistics, and the internal consistency, associated with each questionnaire are presented in Table 1. The IUS-12 and STAI-T data were relatively normally distributed, whereas the disorder-specific questionnaire data were positively skewed (see Supplementary Materials).

Table 1

Means, Standard Deviations, and Ranges associated with each Questionnaire

Measure	*M*	*SD*	*α*	Observed Score Range	Possible Range
IUS-12	29.43	8.52	.89	12-54	12-60
STAI-T	11.07	2.89	.75	5-20	5-20
GAD-7	6.67	4.17	.82	0-19	0-21
PCL-5	21.04	15.02	.93	0-54	0-80
PDSS-SR	3.17	3.33	.84	0-15	0-28
PHQ-9	6.84	5.33	.86	0-23	0-27
OCI-R	13.69	9.12	.86	0-45	0-72
SIPS	15.79	11.83	.93	0-52	0-56

Note. '*α'* represents Cronbach's alpha coefficient.

Manipulation Check

As expected, the sound stimulus was rated as both aversive (M = 2.34, SD = 1.30, where 1 = very negative and 9 = very positive) and arousing (M = 6.80, SD = 2, where 1 = calm and 9 = excited) therefore was appropriately used as an unconditioned stimulus.

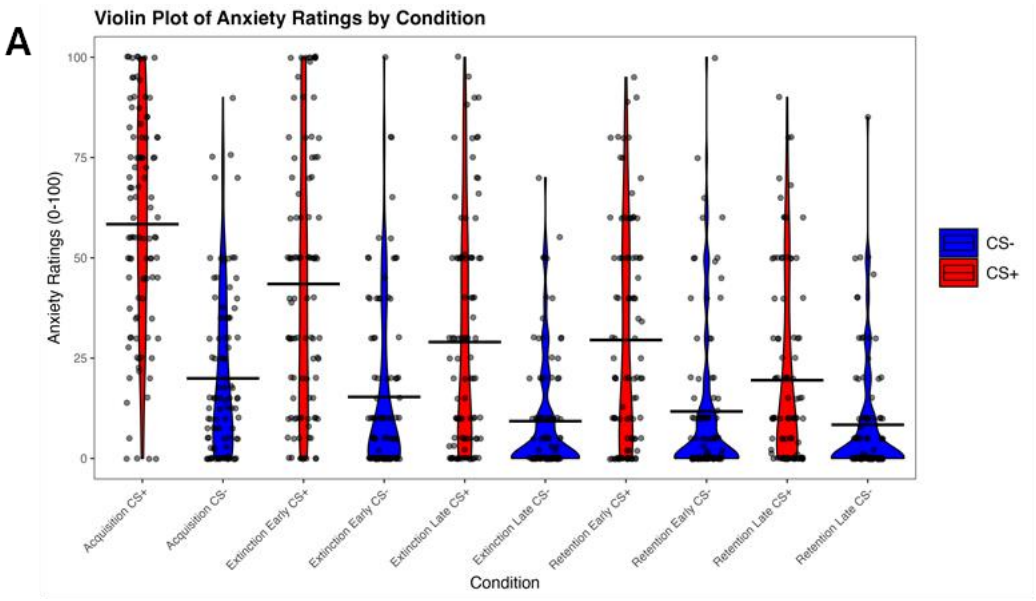
Threat Conditioning Data

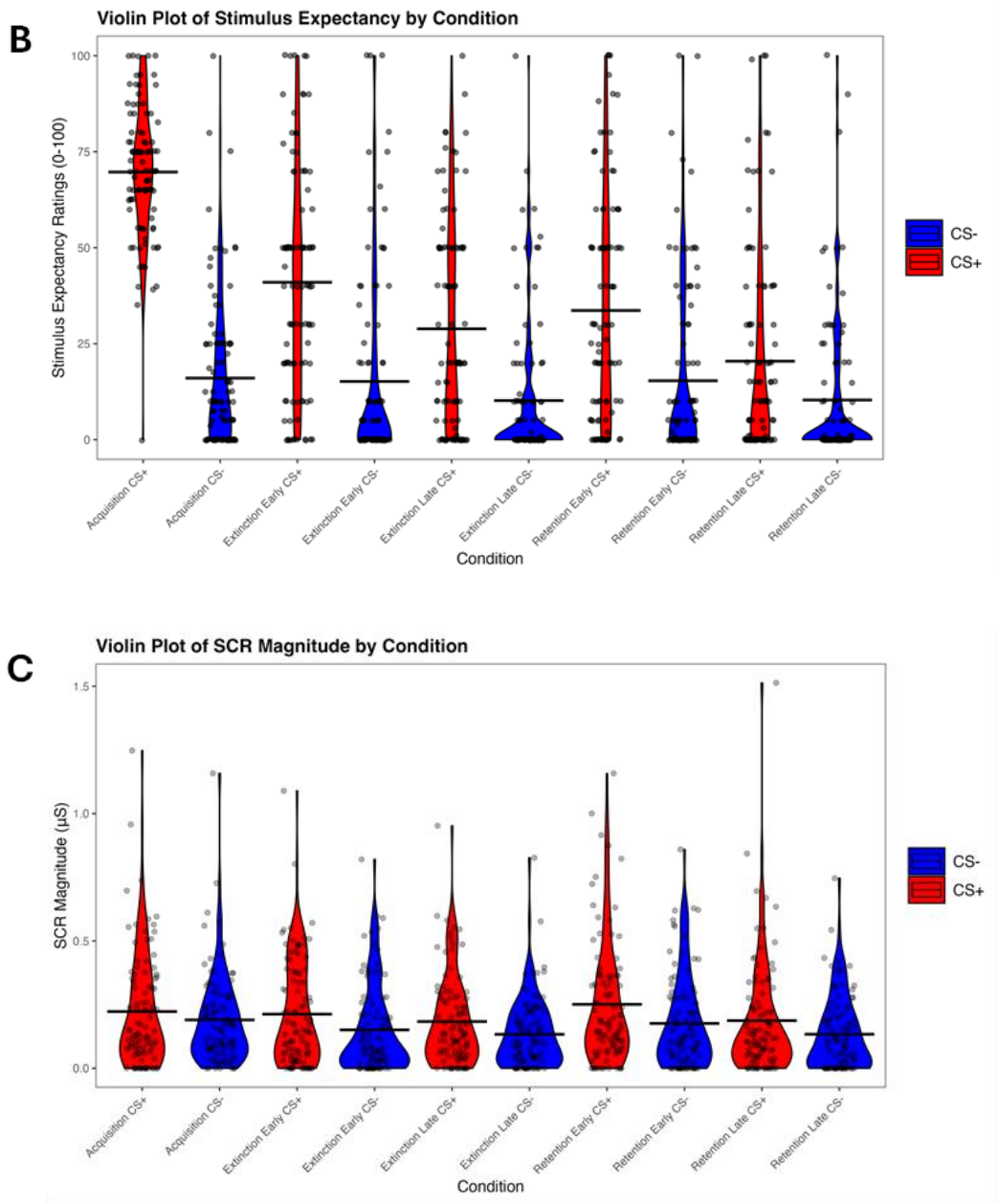
The following results are structured by conditioning phase i.e., acquisition, extinction, and retention and by dependent variable i.e., anxiety ratings, stimulus expectancy ratings, and SCR magnitudes (see Figure 2 for a visualisation of these results). The first set of MLMs

tested for stimulus (CS+ vs. CS-), time (early vs. late extinction and extinction retention), IU, and TA main effects, as well as two-way and three-way interactions between these variables. The first paragraph of each section outlines the stimulus, time, and stimulus-time effects pertaining to hypotheses 1-3. The second paragraph of each section outlines the IU-related main effects and interactions whilst controlling for TA as pertaining to hypothesis 4 (see Table 2). TA-related effects are not outlined within the text but are detailed in Table 2. Similarly, the second paragraph of each section outlines the significant IU-related effects that maintained their significance in the second set of MLMs i.e., whilst controlling for all disorder-specific measures. Said results also pertain to hypothesis 4 and are denoted by bold text within Table 2. The disorder-specific questionnaire effects are not outlined within either the text or table as they were not related to our hypotheses (see remaining MLM effects in supplementary materials). IU-related follow up tests are then presented to ascertain the direction of all significant IU-related main effects and interactions. Lastly, we presented a set of exploratory parametric correlations pertaining to hypotheses 5 and 6.

Figure 2

A set of three violin plots outlining the main effects of Stimulus Type and Time per conditioning phase, per dependent variable.





Note. Each circle represents the participant mean associated with each stimulus type (CS+ or CS-), per time block (early or late), per conditioning phase (acquisition, extinction, or retention). The solid black line represents the sample mean associated with each stimulus type, per time block, per conditioning phase.

Threat Acquisition

Anxiety Ratings. As expected, anxiety ratings were significantly higher in response to the CS+, as opposed to the CS-, within the acquisition phase (Stimulus: $F(1,98) = 204.18$, $p = <.001$).

Further, IU did not significantly predict anxiety ratings (IU: $F(1, 98) = 3.01$, $p = .086$), nor did IU interact with stimulus type whilst predicting anxiety ratings (Stimulus-IU: $F(1, 98) = 0.51$, $p = .477$), within the acquisition phase.

Stimulus Expectancy Ratings. As expected, stimulus expectancy ratings were higher in response to the CS+, as opposed to the CS-, within the acquisition phase (Stimulus: $F(1, 193.83) = 444.32$, $p = <.001$).

Mirroring anxiety ratings within the acquisition phase, IU did not significantly predict stimulus expectancy ratings (IU: $F(1, 193.83) = .544$, $p = .462$), nor did IU interact with stimulus type whilst predicting stimulus expectancy ratings (Stimulus-IU: $F(1, 193.83) = 1.02$, $p = .315$), within the acquisition phase.

SCR Magnitudes[1]. As expected, SCR magnitudes were significantly higher in response to the CS+, as opposed to the CS-, within the acquisition phase (Stimulus: $F(1, 99) = 4.89$, $p = .029$).

Consistent with prior measures, IU did not significantly predict SCR magnitudes (IU: $F(1, 99) = 0.63$, $p = .431$), nor did it interact with stimulus type whilst predicting SCR magnitudes (Stimulus-IU: $F(1,99) = 1.00$, $p = .321$), within the acquisition phase.

[1] Z transformed SCR magnitudes achieved similar results to the square-root transformed SCR magnitudes, hence these results are not outlined for brevity

Threat Extinction

Anxiety Ratings. Interestingly, participants continued to report higher anxiety ratings in response to the CS+, vs. the CS-, across the entire extinction phase (Stimulus: $F(1, 199.36) = 146.41$, $p = <.001$). As expected, anxiety ratings were significantly higher within early vs. late extinction (Time: $F(1, 199.36) = 26.70$, $p =< .001$). Additionally, the analysis revealed a significant stimulus-time interaction (Stimulus-Time: $F(1, 199.36) = 4.58$, $p = .034$). Yet, follow-up pairwise comparisons revealed that anxiety ratings were significantly higher in

response to the CS+, vs. the CS-, during both early and late extinction (Early: $p = <.001$; Late: $p = <.001$). Further, anxiety ratings were significantly higher in early vs. late extinction for both the CS+ and the CS- (CS+: $p = <.001$; CS-: $p = <.001$).

Interestingly, IU scores predicted anxiety ratings throughout the extinction phase (IUS: $F(1, 154.19) = 10.92$, $p = .001$); this effect retained its significance whilst controlling for all disorder-specific measures (IUS Model 2: $F(1, 153.61) = 9.13$, $p = .003$). Please see the 'IU follow up analyses' subsection for the direction of all significant IU related effects. Interestingly, all IU-related interactions were not significant within the extinction phase (Stimulus-IUS: $F(1, 199.36) = 3.51$, $p = .062$; Time-IUS: $F(1, 199.36) = 0.23$, $p = .633$; Stimulus-Time-IUS: $F(1, 199.36) = 0.01$, $p = .964$).

Stimulus Expectancy Ratings. Interestingly, participants continued to report higher stimulus expectancy ratings in response to the CS+, vs. the CS-, across the extinction phase (Stimulus: $F(1, 200.82) = 157.80$, $p = <.001$). As expected, stimulus expectancy ratings were higher during early vs. late extinction (Time: $F(1, 200.82) = 22.82$, $p = <.001$). Similarly, a significant stimulus-time interaction was revealed (Stimulus-Time: $F(1, 200.82) = 3.99$, $p = .047$). Yet, follow-up pairwise comparisons revealed that stimulus expectancy ratings were higher in response to the CS+, vs the CS-, in both early and late extinction (Early: $p = <.001$; Late: $p = <.001$), and higher in early vs. late extinction for both the CS+ and CS- (CS+: $p = <.001$; CS-: $p = .001$).

Interestingly, IU scores did not predict stimulus expectancy ratings within extinction (IUS: $F(1, 121.17) = 3.55$, $p = .062$), however there was a significant interaction between IU and stimulus type (Stimulus-IUS: $F(1, 200.82) = 3.99$, $p = .048$); this effect also retained its significance whilst controlling for disorder-specific measures (Stimulus-IUS model 2: $F(1, 199.22) = 4.07$, $p = .045$). Remaining IU interactions were not significant (Time-IUS: $F(1, 200.82) = 1.17$, $p = .281$; Stimulus-Time-IUS: $F(1, 200.82) = 0.21$, $p = .647$).

SCR Magnitudes[2]. Interestingly, participants continued to exhibit higher SCR magnitudes in response to the CS+, vs. the CS-, across the extinction phase (Stimulus: $F(1, 262.37) = 26.24$, $p = <.001$). As expected, SCR magnitudes were higher for early vs. late extinction (Time: $F(1, 262.37) = 4.62$, $p = .032$). The stimulus-time interaction was not significant in relation to SCR magnitudes within extinction (Stimulus-Time: $F(1, 262.37) = 0.27$, $p = .603$).

Interestingly, all IU-SCR magnitude main effects and interactions were not significant within the extinction phase (IUS: $F(1, 96.83) = 0.48$, $p = .490$; Stimulus-IUS: $F(1, 262.37) = 0.10$, $p = .755$; Time-IUS: $F(1, 262.37) = 2.28$, $p = .132$; Stimulus-Time-IUS: $F(1, 262.37) = 0.28$, $p = .595$).

[2] Z transformed SCR magnitudes achieved similar results to the square-root transformed SCR magnitudes, hence these results are not outlined for brevity

Threat Extinction Retention

Anxiety Ratings. Unexpectedly, participants continued to report higher anxiety ratings in response to the CS+, vs. the CS-, within the retention phase (Stimulus: $F(1, 214.01) = 83.34$, $p = <.001$). In line with expectations, anxiety ratings were higher in early vs. late retention (Time: $F(1, 214.01) = 17.73$, $p = <.001$). Mirroring the earlier extinction phase, there was a significant stimulus-time interaction in predicting anxiety ratings in retention (Stimulus-Time: $F(1, 214.01) = 4.54$, $p = <.034$). Follow-up, pairwise comparisons revealed that anxiety ratings were higher for CS+, vs. the CS-, trials within both early and late retention (Early: $p = <.001$; Late: $p = <.001$). Further, anxiety ratings were significantly higher in early vs. late retention for both the CS+ and CS- (CS+: $p = <.001$; CS-: $p = .030$).

In line with the prior extinction phase, IU scores predicted anxiety ratings throughout the extinction retention phase (IUS: $F(1, 118.03) = 5.02$, $p = .027$) and this effect retained significance when controlling for disorder-specific measures (IUS Model 2: $F(1, 115.73) = 5.09$, $p = .026$). Interestingly, a significant interaction emerged between IU and stimulus type

(Stimulus-IUS: F(1, 214.01) = 6.88, p = .009); this effect also retained its significance whilst controlling for disorder-specific measures (Stimulus-IUS Model 2: $F(1, 216.95) = 8.41$, $p = .004$). The remaining IU-related interactions were not significant (Time-IUS: $F(1, 214.01) = 0.07$, $p = .794$; Stimulus-Time-IUS: $F(1, 214.01) = 0.02$, $p = .883$).

Stimulus Expectancy Ratings. Unexpectedly, participants continued to report higher stimulus expectancy ratings in response to the CS+, as opposed to the CS-, throughout the retention phase (Stimulus: $F(1, 225.84) = 69.59$, $p = <.001$). In line with expectations, higher stimulus expectancy ratings were reported in early vs. late retention (Time: $F(1, 225.84) = 29.04$, $p = <.001$). Mirroring the earlier extinction phase, there was a significant stimulus-time interaction in predicting stimulus-expectancy ratings (Stimulus-Time: $F(1, 225.84) = 5.88$, $p = .016$). Yet, follow-up, pairwise comparisons revealed that stimulus expectancy ratings were higher for the CS+, as opposed to the CS-, within both early and late extinction retention (Early: $p = <.001$; Late: $p = <.001$). Further, stimulus expectancy ratings were higher in early vs. late extinction retention for both the CS+ and CS- (CS+: $p = <.001$; CS-: $p = .006$).

In line with the prior extinction phase, IU scores did not predict stimulus expectancy ratings within the extinction retention phase (IUS: $F(1, 107.55) = 0.12$, $p = .732$). Interestingly, all IU-related interactions were not significant within the retention phase (Stimulus-IUS: $F(1, 225.84) = 2.55$, $p = .111$; Time-IUS: $F(1, 225.84) = 0.38$, $p = .539$; Stimulus-Time-IUS: $F(1, 225.84) = 0.05$, $p = .821$).

SCR Magnitudes[3]. Unexpectedly, participants continued to exhibit larger SCR magnitudes in response to the CS+, vs. the CS-, within the extinction retention phase (Stimulus: $F(1, 255.93) = 28.49$, $p = <.001$). Yet, in line with expectations, higher SCR magnitudes were exhibited within early, vs. late, extinction retention (Time: $F(1, 255.93) = 19.38$, $p = <.001$). Mirroring the prior extinction phase, the stimulus-time interaction was not significant within the retention phase (Stimulus-Time: $F(1, 255.93) = 0.79$, $p = .376$).

Interestingly, yet in line with the prior extinction phase, all IU-SCR magnitude main effects and interactions were not significant within the extinction-retention phase (IUS: $F(1, 87.20) = 0.38$, $p = .541$; Stimulus-IUS: $F(1, 255.93) = 0.06$, $p = .813$; Stimulus-Time-IUS: $F(1, 255.93) = 0.26$, $p = .611$).

[3]Z transformed SCR magnitudes achieved similar results to the square-root transformed SCR magnitudes, hence these results are not outlined for brevity

Table 2

Table Showing IUS-12 and STAI-T Main Effects and Interactions within MLM Analyses per Experimental Phase, per Dependent Variable.

Effect	ACQ			EXT			RET		
	Anx	Exp	SCR	Anx	Exp	SCR	Anx	Exp	SCR
IUS	F(1, 98) = 3.01, p = .086	F(1, 193.83) = 0.54, p = .462	F(1, 99) = 0.63, p = .431	**F(1, 154.19) = 10.92, p = .001**	F(1, 121.17) = 3.55, p = .062	F(1, 96.83) = 0.48, p = .490	**F(1, 118.34) = 5.02, p = .027**	F(1, 107.55) = 0.12, p = .732	F(1, 87.20) = 0.38, p = .541
STAIT	F(1, 98) = 1.12, p = .294	F(1, 193.83) = 6.45, p = .012	F(1, 99) = 0.03, p = .864	F(1, 154.19) = 0.88, p = .351	F(1, 121.17) = 0.06, p = .801	F(1, 96.83) = 0.09, p = .759	F(1, 118.34) = 0.10, p = .748	F(1, 107.55) = 2.08, p = .153	F(1, 87.20) = 0.02, p = .890
Stim x IUS	F(1, 98) = .51, p = .477	F(1, 193.83) = 1.02, p = .315	F(1, 99) = 1.00, p = .321	F(1, 199.36) = 3.51, p = .062	**F(1, 200.82) = 3.96, p = .048**	F(1, 262.37) = 0.10, p = .755	**F(1, 214.01) = 6.88, p = .009**	F(1, 225.84) = 2.55, p = .111	F(1, 255.93) = 0.06, p = .813
Stim x STAIT	F(1, 98) = .80, p = .373	F(1, 193.83) = 3.91, p = .049	F(1, 99) = 3.11, p = .081	F(1, 199.36) = 2.48, p = .117	F(1, 200.82) = 6.47, p = .012	F(1, 262.37) = 0.32, p = .570	F(1, 214.01) = 3.56, p = .061	F(1, 225.84) = 2.97, p = .086	F(1, 255.93) = 1.10, p = .295
Time x IUS	-	-	-	F(1, 199.36) =	F(1, 200.82) =	F(1, 262.37) =	F(1, 214.01) =	F(1, 225.84) =	F(1, 255.93) =

			0.23, p = .633	1.17, p = .281	2.28, p = .132	0.07, p = .794	0.38, p = .539	0.001, p = .972
Time x STAI T	-	-	-	F(1, 199.36) = 0.001, p = .977	F(1, 200.82) = 0.004, p = .947	F(1, 262.37) = 0.10, p = .748	F(1, 214.01) = 0.01, p = .908	F(1, 225.84) = 0.03, p = .856	F(1, 255.93) = 0.32, p = .573
Stim x Time x IUS	-	-	-	F(1, 199.36) = 0.002, p = .964	F(1, 200.82) = 0.21, p = .647	F(1, 262.37) = 0.28, p = .595	F(1, 214.01) = 0.02, p = .883	F(1, 225.84) = 0.05, p = .821	F(1, 255.93) = 0.26, p = .611
Stim x Time x STAI T	-	-	-	F(1, 199.36) = 0.08, p = .784	F(1, 200.82) = 0.002, p = .963	F(1, 262.37) = 0.08, p = .772	F(1, 214.01) = 0.11, p = .744	F(1, 225.84) = 0.03, p = .858	F(1, 255.93) = 0.35, p = .556

Note. ACQ, EXT, and RET refer to the experimental phases acquisition, extinction, and extinction retention respectively. Additionally, Anx, Exp, and SCR refer to anxiety ratings, stimulus expectancy ratings, and SCR magnitudes respectively. Further, Stim and Time refer to CS vs CS- effects and early vs. late extinction/retention effects respectively.

*Denotes statistical significance.

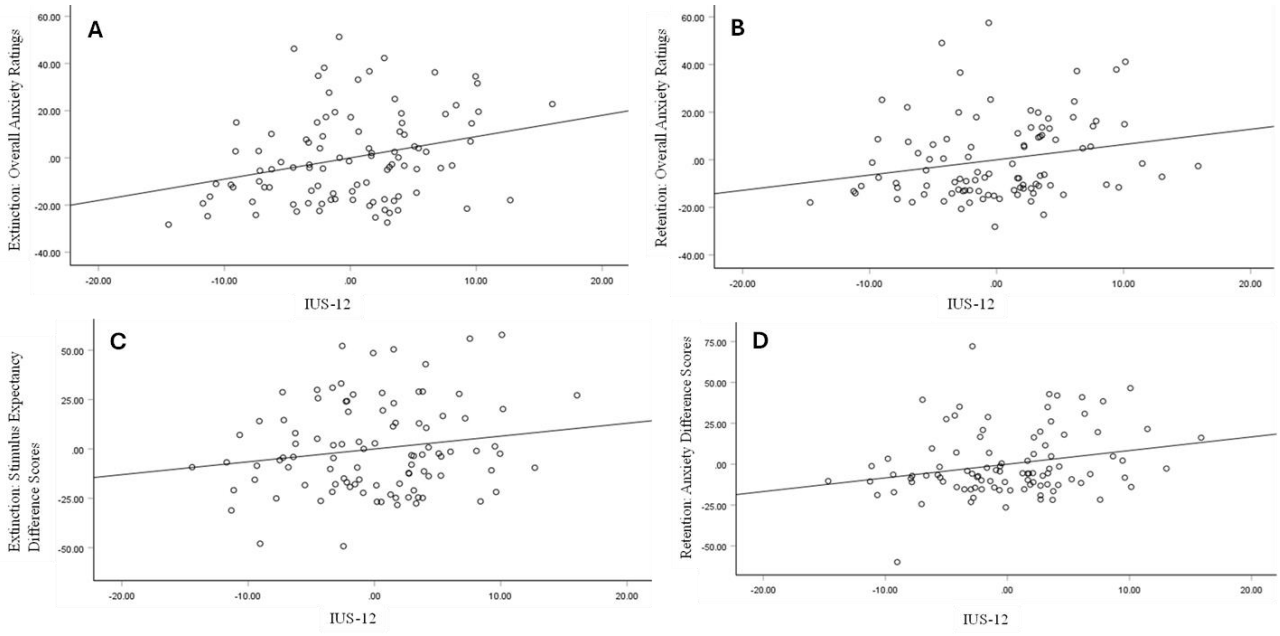
Bolded **IU effects** indicate retained significance within the subsequent set of MLMs i.e., whilst controlling for all symptom measures.

IU Follow-Up Analyses

Partial regression plots (Figure 3) demonstrate the direction of the IU-related main effects and interactions that emerged within the MLM analyses. These demonstrate that IU is associated with increased anxiety ratings within extinction (plot A) and retention (plot B). Additionally, IU is associated with heightened stimulus expectancy ratings in relation to the CS+, but not the CS-, within extinction (plot C). Similarly, IU is associated with higher anxiety ratings in relation to the CS+, but not the CS-, within retention (plot D).

Figure 3

Set of partial regression plots outlining the association of IUS-12 scores with various dependent variables whilst controlling for trait anxiety and all disorder-specific measures.



Note. Overall scores represent mean ratings across the entire trial i.e., CS+ and CS-. Difference scores calculated by subtracting CS- scores from CS+ scores across entire associated experimental phase. Regression lines for plots A, B, C, and D were associated with .079, .049, .029, and .059 R^2 scores respectively.

Exploratory Correlations

Exploratory parametric correlations were carried out to analyse the relationship between trait/disorder-specific measures with separate mean CS+ and CS- scores, CS+/CS- difference scores, and overall scores associated with each dependent variables per conditioning phase.

CS+/CS- Difference Score Correlations

Correlational analyses (Figure 4) revealed a lack of significant correlations between any of the questionnaire measures and CS+/CS- anxiety difference scores (CS+ anxiety ratings – CS- anxiety ratings) within the acquisition phase. Further, only the OCI-R was significantly, and negatively, correlated with stimulus expectancy difference scores within acquisition (OCI: $r(96) = -.29$, $p = .004$). Yet, there were not any significant correlations between questionnaire measures and SCR magnitude difference scores in acquisition.

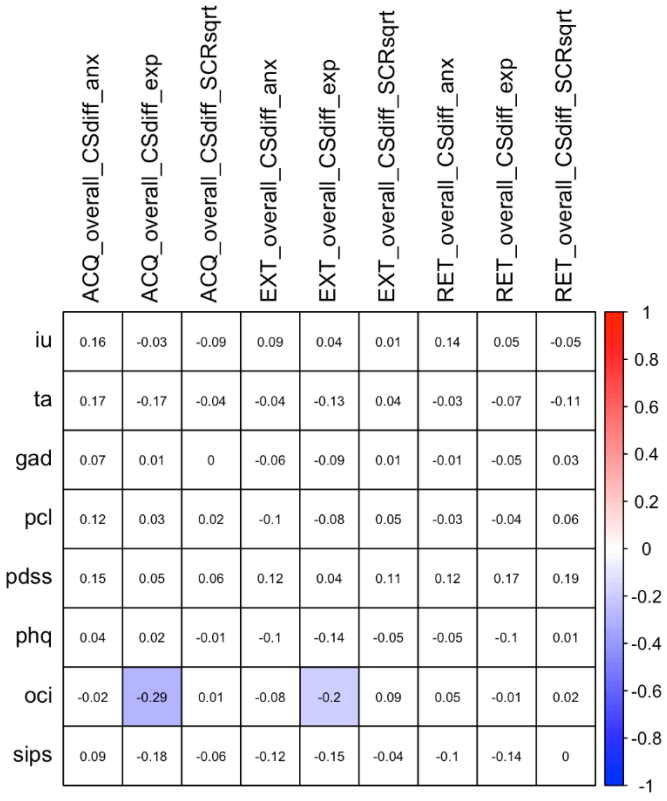
Next, correlational analyses (Figure 4) revealed a lack of significant correlations between any of the questionnaire measures and anxiety difference scores within the extinction phase. Mirroring the acquisition phase, only the OCI-R was significantly, and negatively, correlated with stimulus expectancy difference scores within extinction (OCI: $r(96) = -.20$, p

= .050). Again, mirroring the acquisition phase, none of the questionnaire measures were significantly correlated with SCR magnitude difference scores in extinction.

Lastly, correlational analyses (Figure 4) revealed a lack of significant correlations between any of the questionnaire measures and anxiety, stimulus expectancy, and SCR magnitude difference scores within the extinction retention phase.

Figure 4

A correlation plot outlining correlations between trait/symptom measures and Mean Stimulus Difference Scores (CS+ - CS-) per Dependent Variable, per Conditioning Phase.



Note. ACQ, EXT, and RET refer to acquisition, extinction and retention phases respectively. CSdiff refer to mean stimulus difference (CS+ - CS-) scores for each dependent variable across its associated conditioning phase. Anx, exp, and SCRsqrt refer to anxiety ratings, stimulus expectancy scores, and square-root transformed SCR magnitudes respectively. Pearson correlation coefficient scores (r) represented within individual cells.

CS+ and CS-, Trait and Symptom measure Correlations

Correlational analyses (Figure 5) revealed that IU, TA, GAD-7, and the PDSS-SR were significantly and positively correlated with anxiety ratings in response to the CS+ within the acquisition phase (IU: $r(96) = .30$, $p = .003$; TA: $r(96) = .28$, $p = .005$; GAD: $r(96) = .21$,

p = .036; PDSS-SR: r(96) = .23, p = .026). Further, questionnaires were not significantly correlated with anxiety ratings in response to the CS- within the acquisition phase. Further, questionnaires were not significantly correlated with stimulus expectancy ratings in response to the CS+ within acquisition. Yet, TA, SIPS, and OCI-R were significantly and positively correlated with stimulus expectancy ratings in response to the CS- within acquisition (TA: r(96) = .28, p = .005; SIPS: r(96) = .22, p = .030; OCI-R: r(96) = .31, p = .002). Lastly, questionnaire scores were not significantly correlated with SCR magnitudes in response to either the CS+ or CS- within acquisition.

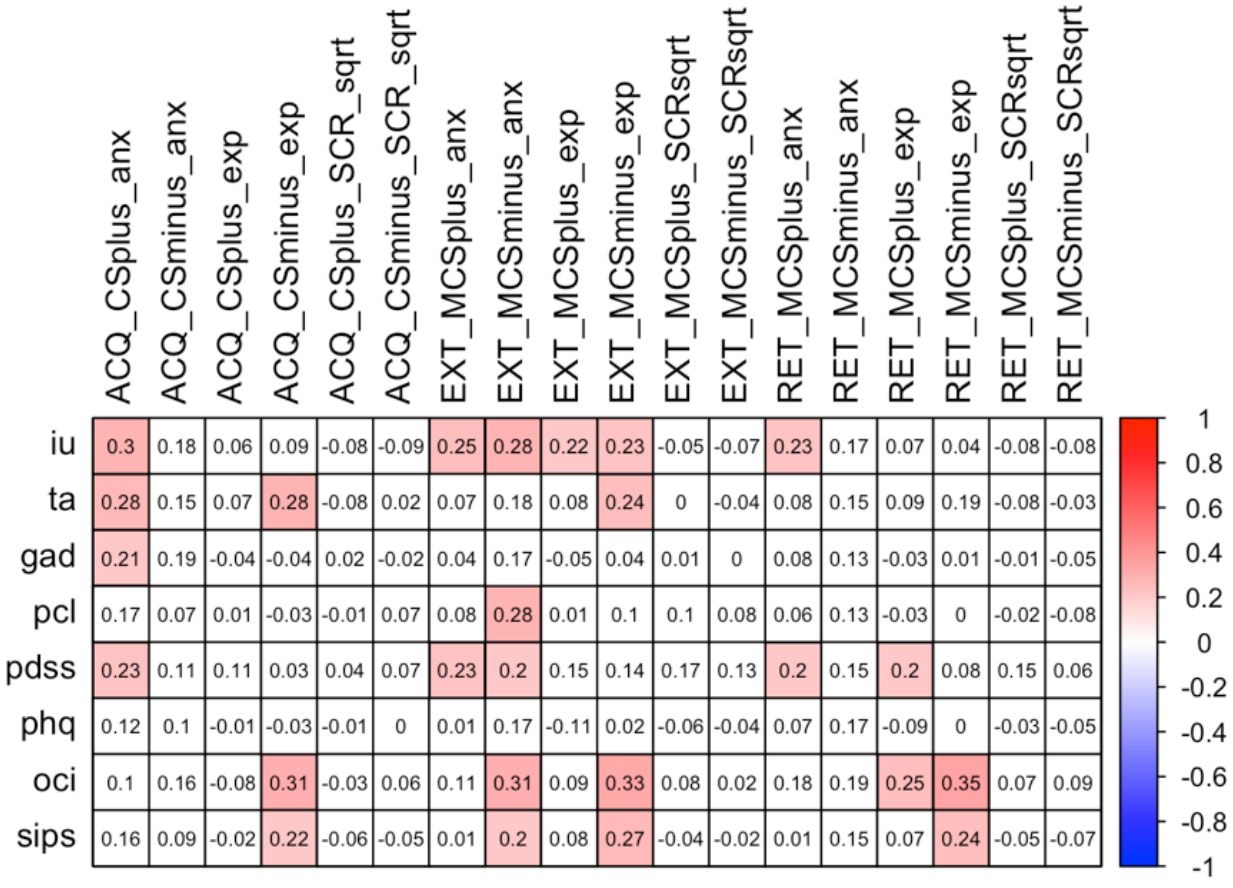
Next, correlational analyses (Figure 5) revealed that IU and the PDSS-SR were significantly and positively correlated with anxiety ratings in response to the CS+ within the extinction phase (IU: r(96) = .25, p = .015; PDSS-SR: r(96) = .23, p = .026). Whereas, IU, SIPS, PDSS-SR, OCI-R, and PCL-5 were significantly and positively correlated with anxiety ratings in response to the CS- within extinction (IU: r(96) = .28, p = .005; SIPS: r(96) = .20, p = .048; PDSS-SR: r(96) = .20, p = .047; OCI-R: r(96) = .31, p = .002; PCL: r(96) = .28, p = .005). Only IU was significantly and positively correlated with stimulus expectancy scores in response to the CS+ within extinction (IU: r(96) = .22, p = .026). Whereas, IU, TA, SIPS, and the OCI-R were significantly and positively correlated to stimulus expectancy ratings in response to the CS- within extinction (IU: r(96) = .23, p = .026; TA: r(96) = .24, p = .016; SIPS: r(96) = .27, p = .008; OCI: r(96) = .33, p = <.001). Lastly, questionnaire scores were not significantly correlated with SCR magnitudes associated with either the CS+ or CS- within extinction.

Lastly, correlational analyses (Figure 5) revealed that IU and the PDSS-SR were significantly and positively correlated with anxiety ratings in response to the CS+ within the extinction retention phase (IU: r(95) = .23, p = .022; PDSS-SR: r(95) = .20, p = .045). Whereas, and unlike within extinction, there no questionnaire scores that significantly correlated with anxiety ratings in response to the CS- within retention. Furthermore, the

PDSS-SR and OCI-R were significantly and positively correlated with stimulus expectancy scores in relation to the CS+ within retention (PDSS-SR: $r(95) = .20$, $p = .047$; OCI-R: $r(95) = .25$, $p = .013$). Whereas, the SIPS and OCI-R were significantly and positively correlated with stimulus expectancy scores in response to the CS- within retention (SIPS: $r(95) = .24$, $p = .017$; OCI-R: $r(95) = .35$, $p = <.001$). In line with previous phases, questionnaire scores were not significantly correlated with SCR magnitudes associated with either the CS+ or CS- within retention.

Figure 5

A correlation plot outlining correlations between trait/symptom measures and Sample Mean Scores per Stimulus Type, per Dependent Variable, per Conditioning Phase.



Note. ACQ, EXT, and RET refer to acquisition, extinction and retention phases respectively. MCSplus and MCSminus refer to mean scores composed of CS+ and CS- minus scores across both early and late extinction and retention phases. Anx, exp, and SCRsqrt refer to anxiety ratings, stimulus expectancy scores, and square-

root transformed SCR magnitudes respectively. Pearson correlation coefficient scores (r) represented within individual cells.

Overall Score Correlations

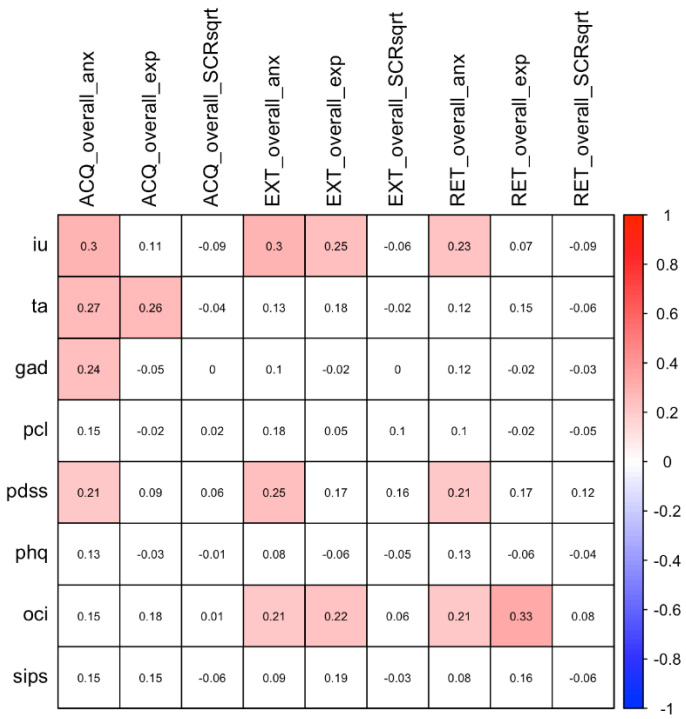
Correlational analyses (Figure 6) revealed that IU, TA, GAD, and PDSS-SR were significantly and positively correlated with overall anxiety ratings within the acquisition phase (IU: $r(96) = .30$, $p = .003$; TA: $r(96) = .27$, $p = .008$; GAD-7: $r(96) = .24$, $p = .017$; PDSS-SR: $r(96) = .21$, $p = .040$). Whereas, only TA was significantly and positively correlated with overall stimulus expectancy ratings within acquisition (TA: $r(96) = .26$, $p = .009$). Further, there were not any significant correlations between any of the questionnaire measures and overall SCR magnitudes within acquisition.

Next, correlational analyses (Figure 6) revealed that IU, PDSS-SR, and the OCI-R were significantly and positively correlated with overall anxiety ratings within the extinction phase (IU: $r(96) = .30$, $p = .003$; PDSS-SR: $r(96) = .25$, $p = .013$; OCI-R: $r(96) = .21$, $p = .037$). Interestingly, IU and the OCI-R were significantly and positively correlated with overall stimulus expectancy scores within extinction (IU: $r(96) = .25$, $p = .012$; OCI-R: $r(96) = .22$, $p = .026$). However, there were not any significant correlations between any of the questionnaire measures and overall SCR magnitude within extinction.

Lastly, correlational analyses (Figure 6) revealed that IU, PDSS-SR, and OCI-R scores significantly and positively correlated with overall anxiety ratings within the extinction retention phase (mirroring the extinction phase) (IU: $r(95) = .24$, $p = .021$; PDSS-SR: $r(96) = .21$, $p = .042$; OCI-R: $r(96) = .21$, $p = .040$). Interestingly, only OCI-R was significantly and positively correlated with overall stimulus expectancy scores within retention (OCI-R: $r(95) = .31$, $p = .001$). In line with prior phases, SCR magnitude difference scores did not significantly correlate with any of the questionnaire measures within retention.

Figure 6

A correlation matrix outlining correlations between trait/symptom measures and Overall Grand Mean Scores (CS+ and CS-) per Dependent Variable, per Conditioning Phase.



Note. ACQ, EXT, and RET refer to acquisition, extinction and retention phases respectively. Anx, exp, and SCRsqrt refer to anxiety ratings, stimulus expectancy scores, and square-root transformed SCR magnitudes respectively. Pearson correlation coefficient scores (r) represented within individual cells.

Discussion

The current study utilised a two-day threat conditioning paradigm to examine whether IU was specifically associated with individual differences in threat extinction learning and retention whilst controlling for either trait anxiety or disorder-specific symptoms. On balance, this study failed to replicate the well-established association between high IU and dampened threat extinction learning (Morriss et al., 2021a; Morriss et al., 2021b). More specifically, IU was not associated with differential responding in relation to anxiety ratings or SCR magnitudes during threat extinction whilst controlling for trait anxiety. However, high IU was specifically associated with heightened stimulus expectancy ratings to the CS+, vs. the CS-, within extinction whilst controlling for both trait anxiety and disorder-specific symptoms separately. Further, IU was not associated with differential responding to stimulus expectancy

ratings or SCR magnitudes during extinction retention whilst controlling for trait anxiety. Yet, high IU was specifically associated with heightened anxiety ratings in response to the CS+, vs the CS-, within extinction retention whilst controlling for both trait anxiety and disorder specific symptoms separately. Hence, based on the results of this study, it would appear that IU is not consistently, or specifically, associated with poorer extinction learning and retention, although this varies on the basis of the extinction index used and the extinction phase.

Within acquisition successful threat conditioning was achieved, with participants demonstrating heightened responding to the CS+, vs the CS-, for anxiety ratings, expectancy ratings, and SCR magnitudes. Yet, heightened conditioned responding to the CS+, vs the CS-, continued throughout the extinction phase for all three measures, suggesting a lack of extinction within the sample. However, stimulus-time interactions observed in the extinction phase revealed larger stimulus difference scores (CS+ - CS-) within the earlier half, as opposed to the latter half, of extinction for both anxiety and stimulus expectancy ratings therefore demonstrating a trend towards extinction for these measures. However, this trend was not observed for SCR magnitudes. Mirroring the extinction phase, continued heightened responding to the CS+, vs the CS-, was observed throughout the retention phase for all three measures further demonstrating a lack of extinction, statistically. In line with predictions, a 'return of fear' effect (Lonsdorf et al., 2017) was demonstrated via a slight increase in stimulus expectancy ratings and SCR magnitudes in response to the CS+ in early retention vs late extinction. Similarly, stimulus-time interactions revealed larger stimulus difference scores within the earlier half, vs the latter half, of retention for both anxiety and stimulus expectancy ratings, again demonstrating a trend towards extinction retention for these measures. Mirroring the extinction phase, this trend was not observed for SCR magnitudes within retention. In summary, the sample did not fully extinguish their aversion to the CS+ within this study hence failing to demonstrate a typical threat extinction pattern, particularly in relation to SCR magnitudes where extinction trends were non-existent statistically, and weak visually.

Furthermore, the muted extinction effect on SCR magnitude was a particularly unexpected finding considering that many conditioning studies have achieved extinction of SCR magnitudes utilising similar experimental designs and trial lengths (For instance, Morriss et al., 2016). One possible explanation of this discrepancy relates to the effect of sample age on extinction learning, particularly with regards to indices that capture arousal such as SCR. For instance, it is well-established within conditioning research that adolescent humans and rodents exhibit muted or reduced extinction effects in comparison to same-species adults (Pattwell et al., 2012). This is likely due to a relative neurobiological immaturity in higher-order cortical structures, such as the ventromedial prefrontal cortex, producing a reduction in top-down regulation of fear-related subcortical structures, such as the amygdala, during extinction (Morriss et al., 2019b). Given that human neurobiological maturation occurs post-20 years of age (Semple et al., 2013) and that the current sample had a mean age of 23.13, it is likely that a large proportion of our participants were displaying continued conditioning during the extinction phase due to developmental effects. Indeed, previous conditioning research has failed to achieve extinction when experimenting on younger samples (Morriss et al., 2019b). In fact, conditioning studies often require twice the number of extinction trials when experimenting on adolescent rats in order to achieve extinction (Kim et al., 2011). Therefore, it is plausible that the current study failed to demonstrate extinction in SCR magnitudes due to the sample age. Further, with a higher number of extinction trials the expected extinction effect may have been observed.

The current study outlines an absence of specific associations between IU and heightened responding to the CS+ during both extinction and retention (poorer extinction learning) which is contrary to the wider literature. For instance, high IU has been specifically associated with poorer extinction learning by multiple studies utilizing multiple indices of extinction e.g., skin conductance, corrugator supercilii activity, pupil dilation, amygdala activity, and greater late positive potential whilst controlling for trait anxiety and worry (Morriss et al., 2021b). This association has been particularly reliably demonstrated in relation

to SCR (Morriss et al., 2021a). Hence, it is interesting that the current study failed to replicate this association with SCR. Although less is known about extinction retention, previous research has outlined that high IU is associated with heightened skin conductance responding to the CS+, vs the CS-, (Morris et al., 2021b) with an emphasis on the initial retention trials (Dunsmoor et al., 2015; Wake et al., 2021). Again, such results were not replicated here. One could argue that the current results suggest a null relationship between IU and threat extinction learning, particularly in relation to skin conductance. However, given the ubiquity and robustness of the IU-extinction learning association elsewhere in the literature, this is unlikely to be the case (Morriss et al., 2021a, 2021b). Instead, this lack of detection may have been caused by the significantly weakened extinction effect observed within the sample. Given that the sample continued to demonstrate conditioned responding to the CS+ throughout the conditioning task it is likely that this resulted in a lack of variance in sample-wide stimulus-difference scores (CS+ - CS-) which may have thwarted our ability to detect an effect. Indeed, previous research has failed to detect IU-extinction learning associations within samples that failed to achieve extinction (Morriss et al., 2024). For example, Morriss et al., (2024) found a similar lack of IU-extinction learning associations within a clinical sample of individuals with heightened IU and attributed this result to the limited variance in IU scores. Hence, it is likely that the IU-extinction learning association would have been detected in the current study if extinction were achieved. Indeed, it is well-known that limited measure variance is associated with a lack of power and an inflation of type 2 error risk (Simkovic & Trauble, 2019).

Interestingly, most trait and disorder-specific measures failed correlate with stimulus-difference scores within the post-hoc exploratory analyses. However, OCD symptoms correlated negatively with expectancy difference scores during both acquisition and extinction. This suggests that those high in OCD symptoms are more likely to expect the presentation of the aversive stimulus when presented with the CS- than those with less OCD symptoms. This result is somewhat at-odds with the finding outlined by Cooper and

Dunsmoor (2021) which revealed significantly heightened responding to the CS+ during acquisition in those with OCD, whereas the current data would suggest that CS+ and CS- responding is more similar in those with higher OCD symptoms. Further, multiple trait and symptom measures were positively correlated with the CS+ and CS- separately within different conditioning phases. Most notably, IUS-12, PDSS-SR, and the OCI-R frequently and positively correlated with individual conditioned stimuli across the conditioning procedure. However, these measures differed with regards to the specific aspects of conditioning with which they correlated most frequently, which may suggest different mechanistic associations. For instance, IU correlated quite frequently with conditioned responding during extinction, which seems to coalesce with research identifying IU as an extinction-relevant construct (Morriss et al., 2021b). Whereas the OCI-R correlated most frequently with stimulus expectancy ratings throughout conditioning. Further, the PDSS-SR correlated most frequently with CS+ anxiety ratings and overall anxiety ratings throughout the conditioning procedure. IU and the OCI-R on the other hand, correlated with both overall stimulus expectancy and anxiety ratings throughout conditioning. In sum, it may be useful to investigate both the PDSS-SR and OCI-R in relation to threat conditioning mechanisms more closely with the aim of elucidating the nature of these associations further. Relatedly, future research may wish to investigate whether discrete, transdiagnostic symptom clusters are associated with specific conditioning processes as opposed to focussing on disorder-specific associations.

Taken together, our exploratory analyses appear to simultaneously contradict and substantiate previous research in relation to anxiety-related disorders (Abend et al., 2020; Duits et al., 2015). Namely, symptom measures failed to correlate with stimulus-difference scores which may suggest that anxiety symptoms are not associated with perturbed or aberrant threat conditioning or extinction processes (Abend et al., 2020). Similarly, multiple symptom measures correlated positively with anxiety in response to the CS- during extinction, which opposes the notion that anxiety is characterised by heightened responding to the CS+ during

extinction as suggested by Duits et al. (2015). Further, the GAD-7, PDSS-SR, and OCI-R correlated positively with overall anxiety and expectancy ratings at different points throughout the conditioning process which may suggest that anxiety symptoms are associated with overall arousal levels, as suggested by Abend et al. (2020). However, it must be noted that the current study differs from previous research in important ways i.e., dimensional anxiety measures, non-clinical sample etc. which makes it difficult to draw direct comparisons. For instance, it could be the case that patient-control differences in acquisition and extinction are explained by differences in overall functioning, as opposed to specific symptomatology, hence explaining the discrepancy between these analyses and the results of Duits et al. (2015). Further, the difference in results between Abend et al. (2020) and Duits et al. (2015) may be due to differences in sample characteristics i.e., Duits et al. (2015) gathered data on patients with PTSD whereas Abend et al. (2020) did not. Similarly, Duits et al. (2015) had larger heterogeneity in terms of study methodology which could have accounted for the discrepancy. Further research is required to elucidate the role that anxiety-related disorders in general, and specific anxiety-related disorders, play in relation to human threat conditioning.

This study had some noteworthy limitations. As mentioned, the sample did not achieve extinction from a statistical standpoint which may have limited our ability to detect individual differences in extinction learning. Relatedly, the study sample was largely homogenous in terms of age and student-status. Future replications may wish to either increase the mean sample age or increase the number of extinction trials to improve the likelihood of achieving extinction and mitigate this limitation. Lastly, the current sample was not a clinical sample, hence caution must be made when interpreting the associations between conditioning processes and disorder-specific symptoms as high symptomatology as measured by the questionnaire measures is not equivalent, qualitatively speaking, to a diagnosed psychiatric disorder. Nonetheless, the current study is the first of its kind to investigate the association between IU and threat extinction whilst controlling for trait and disorder-specific measures.

The associated findings should be of use to future researchers aiming to investigate threat conditioning processes in relation to either anxiety-related disorders, or IU, or both.

In sum, the current experiment showed an absence of specific associations between IU and poorer threat extinction learning as indexed by differential SCR magnitudes in both the extinction and extinction-retention phase whilst controlling for trait anxiety, failing to replicate previous findings. Specific IU associations with extinction learning, as indexed by differential responding, in relation to stimulus expectancy and anxiety ratings were mixed; IU was associated with differential stimulus expectancy and anxiety ratings within extinction and retention, respectively (whilst controlling for both trait anxiety and disorder-specific measures). Yet, IU was not specifically associated with these measures elsewhere within the conditioning procedure. In terms of general conditioning effects, successful threat conditioning to the CS+, vs the CS-, was observed during acquisition, however extinction of said conditioned responses was not achieved, statistically speaking, within either extinction or retention. However, an extinction trend was observed with stimulus-difference scores being significantly higher in early, vs. late, extinction and retention. The authors speculate whether this lack of extinction was partially responsible for the failure to replicate previous IU-extinction learning associations given the presumed lack of variance in stimulus-difference scores. Overall, the study represents a valuable attempt to investigate the specificity of IU associations with threat conditioning processes whilst controlling for disorder-specific symptoms. Additionally, the study provides valuable exploratory correlational data that can be used to steer future research between trait/disorder-specific constructs and threat conditioning processes.

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Chapter 3

Title: Threat Acquisition and Extinction Differences between Patients with Panic Disorder or Specific Phobia and Non-Clinical Control Participants: A Systematic Review.

Journal Specification: The journal 'Neuroscience and Bio-Behavioural Reviews' was chosen to guide the writing and formatting of this paper. The journal specifies a maximum abstract word count of 250 words. It does not specify a particular formatting or referencing style. Similarly, it does not specify a maximum overall word count.

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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, multiple systematic reviews have been 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 threat acquisition, extinction, and extinction retention processes in relation to PD and SP separately. This resulted in the inclusion of 14 PD studies and 7 SP studies. Across the PD sample, 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 the SP sample, 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 critiqued and compared to the wider literature. Implications, limitations, and directions for future research are discussed.

Keywords: Panic Disorder, Specific Phobia, Threat Conditioning, Threat Acquisition, Threat Extinction, Extinction Retention.

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, thereafter, signalling guaranteed or potential threat i.e., 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., safety stimulus. The function of the CS− is to differentiate conditioned responding to conditioned threat and safety stimuli (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 hours). 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/anxiety disorders (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 fear or disgust responses akin to patient responses 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 (ET) are explicitly based on classical conditioning and extinction principles (Boschen et al., 2009; Foa & McLean, 2016; Rachman, 2015). Yet, despite the concrete finding that ET's 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 for 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). Such 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., 2024). For instance, Duits et al., (2015) carried out a meta-analysis on studies comparing patients with ADs with 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, variation was found in relation to specific anxiety disorders. For instance, said analyses revealed differences between PTSD patients and anxiety disorders/obsessive-compulsive disorder (OCD) patients (patient group consisting of those diagnosed with an AD 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 AD/OCD group (Kausche et al., 2025). Similarly, multiple individual studies have found similar patient-control differences in conditioning indices per specific anxiety disorders (Lissek et al., 2010; Otto et al., 2014; Rabinak et al., 2017). Hence, it would appear that individual anxiety disorders may possess their own unique associations with threat acquisition, extinction learning, and threat 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 anxiety-related disorders: 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 patient-control differences in conditioned or differential responding during both acquisition and extinction. Therefore, demonstrating high inter-diagnostic variation in patient-control differences in relation to 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 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 patient-control 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 rate/instruction type used. For clarity, this review defines both PD and SP in accordance with the most recent diagnostic and statistical manual (DSM-V-TR; American Psychiatric Association (APA), 2022). Namely, that

PD is characterised by recurrent panic attacks and persistent concern/worry, or maladaptive behaviour change, 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). However, it is worth noting that each individual study will likely have slightly altered definitions of these diagnoses as pertaining to the time and country in which the research was carried out. 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 'No' and 'Predictable' conditions and CS- and CS+ stimuli respectively. Even though threat conditioning (Lonsdorf et al., 2017) and NPU procedures (Schmitz & Grillon, 2012) have remained largely disparate within academia, the authors recognise the overwhelming similarity in the designs and implications associated with both procedures. 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.

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 (WoS) 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:

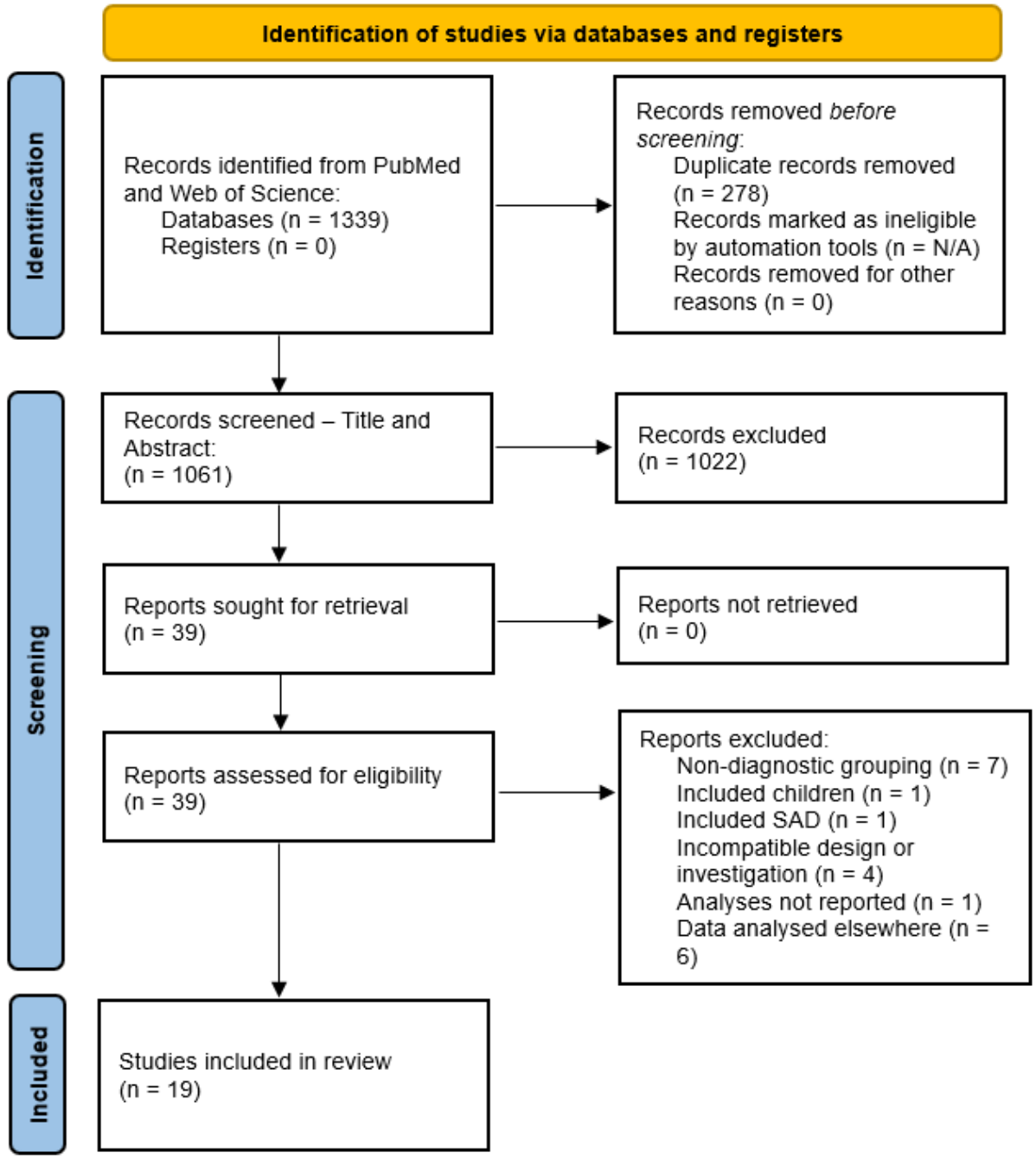
- Population: Adult humans (18+ years) that meet diagnostic criteria for either panic disorder or specific phobia via standardised clinical interview.
- Intervention/exposure: Classical threat conditioning task or unpredictable threat paradigm task with a discernible CS+ and CS-.
- Comparator/control: 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 Figure 7 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 3). 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 EPHPP tool (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 (see Appendix A). 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 their being a sole rater, inter-rater agreement was not assessed. Each study was rated as strong, moderate, or weak in quality (see Table 3).

Figure 7

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.

Results

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 collected for screening (Figure 7). 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 3 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 minute) 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 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 (both studies analysed the same participants focussing on different conditioning measures). 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.

Table 3

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	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:	Aversive Images	100%	Instructed	ACQ 1 ACQ 2[b]	Ratings: EXP	Strong

					2 CS+ 1 CS- ACQ 2: 1 CS+ 1 CS-					
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 subscale of MDSQ)	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	Strong

										Ratings: VAL, ARO	
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
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.

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

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 3 for more details).

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 3 for more details).

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 3 for more details).

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 3 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).

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.

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 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 adequately to our review question.

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 categories: US expectancy ratings, distress ratings (anxiety, fear, disgust, negative mood, symptoms), valence ratings, arousal ratings, FPS, SCR, fMRI, and miscellany. The following section details the key results tables per disorder followed by a narrative description of the key results per study as informed by the results table. Results not included in the key results tables (Tables 4 and 5) are also outlined in text where necessary. For ease, fMRI results have been bullet pointed and arranged alphabetically whilst outlining subcortical structures first and cortical structures subsequently.

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 included studies (Table 4).

Table 4

Overview of Key Results in Relation to the Included Panic Disorder Studies.

Study	Conditioning Phase	Measure	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
		- Insula	-	-	PD>CON
		- ACC	-	-	PD>CON
		- (l/m)PFC	-	-	PD>CON

		- 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 ROIs:			
	Overall	- Amygdala	-	-	ns
	Early	- Amygdala	-	-	ns
		Whole brain	-	-	*In text*
	EXT	VAL	CON>PD	CON>PD	ns[b]
		ARO	PD>CON	PD>CON	ns[b]
		fMRI			
	Overall	- Amygdala	-	-	ns
Marin et al. (2020)	ACQ	SCR	ns	ns	-
		fMRI			
		- Amygdala	-	-	ns
		- HiPPC	-	-	ns
		- Insula	-	-	ns
		- dACC	-	-	ns
		- vmPFC	-	-	ns
	EXT	SCR	CON>PD	CON>PD	
		fMRI			
	Early and Late	- Amygdala	-	-	ns
		- HiPPC	-	-	ns
		- Insula	-	-	ns
		- dACC	-	-	ns
		- vmPFC	-	-	ns
	RET	SCR	ns	ns	-
		fMRI			
		- Amygdala	-	-	ns
		- HiPPC	-	-	ns
		- Insula	-	-	ns
		- dACC	-	-	ns
		- 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	-
		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
		- P300	-	-	ns
Tinoco-Gonzalez et al. (study 1, 2015)	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.

Threat Acquisition.

US Expectancy Ratings. During threat acquisition, one (Lissek et al., 2010) out of three analyses found evidence of heightened expectancy ratings to the CS+ in patients compared to controls (De Kleine et al., 2023; Lissek et al., 2010). Similarly, evidence of heightened expectancy to the CS- in controls compared to patients was found in one (Lissek et al., 2010) out of three of these analyses. Only one of these studies investigated patient-control differences in discrimination and reported evidence of 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 found evidence of 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 studies found evidence of lowered valence ratings (heightened dislike) to the CS- in patients compared to controls. Only one of these studies 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 i.e., evidence of increased discrimination in controls. 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 found evidence of 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 studies found evidence of 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, again providing evidence for increased discrimination in controls.

Distress Ratings. During threat acquisition, four (Benke et al., 2023; Brinkmann et al., 2017; Klahn et al., 2017) out of seven analyses found evidence of heightened distress ratings towards the CS+ in patients compared to controls, whereas one (Lissek et al., 2010) found evidence of 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 evidence of 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). Two of these studies investigated discrimination differences and one (Lissek et al., 2010) found evidence of heightened CS+/CS- discrimination scores in distress ratings in controls compared to patients.

FPS. During threat acquisition, one (Benke et al., 2023) out of four analyses found evidence of heightened FPS towards the CS+ in patients compared to controls (Benke et al., 2023; Lissek 2009; Lissek 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 2009) out of four analyses found evidence of heightened FPS towards the CS- in patients compared to controls (Lissek 2009; Lissek 2010; Shankman 2013). Of the two studies that investigated discrimination, one (Lissek 2009) found evidence of heightened discrimination in controls compared to patients, and the other (Shankman et al 2013) found evidence of 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 evidence of 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 studies investigated SCRs towards the CS- and similarly found evidence of null group differences between patients and controls. Similar to valence ratings, Schwarzmeier et al. (2019) found evidence of 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.

fMRI. 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" (1s 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 and 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 (amoung 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).

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

evidence of null group differences. Said ERPs were not investigated by another study within the final sample.

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 evidence of 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 studies found evidence of 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 observe 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 evidence of 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 studies found evidence of null patient-control differences in arousal ratings towards the CS-. Further, Lueken et al. (2014) was the only study to investigate discrimination and found evidence of null patient-control differences in CS+/CS- discrimination in relation to arousal ratings.

Distress Ratings. During extinction, two out of two analyses found evidence of null 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 studies found evidence of 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 evidence of a null 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 evidence of null group differences in FPS responses towards the CS+, CS-, or in CS+/CS- discrimination scores.

SCR. During extinction, one (Michael et al., 2007) out of three analyses found evidence of increased SCRs towards the CS+ in patients compared to controls, whereas one (Marin et al., 2020) of these studies also found evidence of 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 evidence of 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.

fMRI. 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).

Extinction Retention.

Valence Ratings. Only Schwarzmeier et al. (2019) investigated group differences in valence ratings during extinction retention. This study found evidence of 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 evidence of 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 studies found evidence of null 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.

fMRI. 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 insula cortex 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).

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 5).

Table 5

Overview of Key Results in Relation to the Included Specific Phobia Studies.

Study	Conditioning Phase	Measure	SP vs. CON		
			CS+	CS-	CS Diff
Gorka et al. (2017)	ACQ	FPS	-	-	ns
Klahn et al. (2017)	ACQ	Discomfort (MDSQ)	ns	ns	-
Li & Graham (2016)	ACQ	EXP	ns	ns	-
		VAL	CON>SP	CON>SP	-
		SCR	ns	NR	-
	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
		- HiPPC	-	-	ns
		- Insula	-	-	ns
		- dACC	-	-	ns
		- vmPFC	-	-	ns
	EXT	SCR	CON>SP	CON>SP	-
		fMRI			
	Early and Late	- Amygdala	-	-	ns
		- HiPPC	-	-	ns
		- Insula	-	-	ns
		- dACC	-	-	ns
		- vmPFC	-	-	ns
	RET	SCR	ns	ns	-
		fMRI			
		- Amygdala	-	-	ns
		- HiPPC	-	-	ns
		- Insula	-	-	ns
		- dACC	-	-	ns
		- vmPFC	-	-	CON>SP
Schienle et al. (2005)	ACQ	VAL		ns	-
		- Fear CS+	ns		-
		- Disgust CS+	ns		-
Schweckendiek et al. (2011)	ACQ	Fear		-	
		- F-rel CS+	-		SP>CON
		- F-irrel CS+	-		NR

		Disgust		-	
		- F-rel CS+	-		SP>CON
		- F-irrel CS+	-		NR
		ARO		-	
		- F-rel CS+	-		SP>CON
		- F-irrel CS+	-		NR
		VAL		-	
		- F-rel CS+	-		SP>CON
		- F-irrel CS+	-		NR
		SCR		-	
		- F-rel CS+	-		SP>CON
		- F-irrel CS+	-		NR
		fMRI			
		F-rel CS+ ROIs			
	Early	- blAmygdala	-	-	ns
	Early	- ACC	-	-	ns
	Early	- mPFC	-	-	SP>CON
	Early	- blOFC	-	-	ns
	Early	- bl Thalamus	-	-	ns
	Early	- bl Insula	-	-	SP>CON
	Late	- All ROIs	-	-	ns
		F-irrel CS+			
	Early	- All ROIs	-	-	ns
	Late	- All ROIs	-	-	ns
		Whole brain	-	-	*In Text*
Siminski et al. (2021)	ACQ	fMRI			
		- BNST	-	-	ns
		- 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.

Threat Acquisition.

US Expectancy Ratings. Only Li and Graham (2016) studied patient-control differences in expectancy ratings. They found evidence of null group differences in expectancy ratings towards both the CS+ and CS-. Differences in CS+/CS- discrimination were not investigated.

Valence Ratings. During threat acquisition, one (Li & Graham, 2016) out of three analyses found evidence of 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 evidence of lowered valence ratings towards the CS- in patients vs. controls. Only one study investigated CS+/CS- discrimination, finding evidence of heightened discrimination in patients vs. control subjects in relation to CS+ paired with fear-relevant stimuli (Schweckendiek et al., 2011).

Arousal Ratings. Only Schweckendiek et al., (2011) studied patient-control differences in arousal ratings during acquisition and found evidence of heightened CS+/CS- discrimination in patients vs. controls in response to CS+ paired with fear-relevant stimuli.

Distress Ratings. Only Klahn et al. (2017) studied patient-control differences in distress (discomfort) ratings towards the CS+ and CS- during acquisition and found evidence of null group differences. Further, only Schweckendiek et al. (2011) studied CS+/CS- discrimination in relation to distress ratings and found that two out of two analyses showed evidence of 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 evidence of null differences 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, two out of two analyses found evidence of null patient-control differences in SCRs to the CS+ (Li & Graham, 2016; Marin et al., 2020). Further, only (Marin et al., 2020) analysed and reported patient-control differences in SCRs to the CS- and found evidence of null group differences. Lastly, only Schweckendiek et al. (2011) studied group differences in SCR CS+/CS- discrimination, finding evidence of

heightened CS+/CS- discrimination SCR scores in patients vs. controls in response to fear-relevant CS+ stimuli (fear-irrelevant CS+/CS- discrimination not reported).

fMRI. 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.

Threat Extinction.

US Expectancy Ratings. Only Li and Graham (2016) studied patient-control differences in expectancy ratings during extinction. They found evidence of heightened 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 evidence of 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 evidence of heightened SCRs towards the CS+ in control subjects vs. patients (Li & Graham, 2016; Marin et al., 2020). These same studies found that two out of two analyses found evidence of null group differences in SCRs towards the CS- within extinction. CS+/CS- discrimination differences in SCR were not investigated by any study.

fMRI. 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).

Extinction Retention.

US Expectancy Ratings. Only Li and Graham (2016) studied patient-control differences in expectancy ratings during extinction retention. They found evidence of null 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 evidence of 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 evidence of null group differences between patients and controls 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.

fMRI. 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).

Discussion

This systematic review aimed to elucidate the presence and/or 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 results of this review will first be summarised for panic disorder and specific phobia separately, before contrasting these sets of results with one another and the wider literature.

Panic Disorder

Results show compelling evidence for reduced CS+/CS- discrimination during acquisition in panic patients with the majority of subjective outcomes demonstrating effects in this direction i.e., expectancy, valence, and arousal ratings across the included studies. Further, there is mixed evidence for heightened CS+ responding in panic patients in relation to subjective outcomes as evidenced by a roughly equal proportion of the included analyses demonstrating and not demonstrating this effect. Interestingly, this result materialised in relation to arousal and distress ratings more so than expectancy and valence ratings. The previous results were only demonstrated in relation to subjective ratings as physiological

outcome measures i.e., SCR and FPS generally showed an overall lack, or inconsistent pattern, of patient-control differences in relation to CS+ responding, CS- responding, and CS+/CS- discrimination during acquisition. Further, subjective measures showed weak evidence for heightened CS- responding in patients with the majority of analyses finding no group differences, however evidence for this effect was stronger regarding distress ratings, specifically, with the majority of studies showing heightened distress ratings towards the CS- in panic patients. During extinction, results show weak evidence for heightened CS+ and CS- responding in patients and a lack of patient-control differences in CS+/CS- discrimination across subjective measures. Similarly, results show a lack, or inconsistent pattern, of patient-control differences in CS+ responding, CS- responding, and CS+/CS- discrimination across physiological measures during extinction. Further, results show a lack of patient-control differences in CS+ responding, CS- responding, and CS+/CS- discrimination during extinction retention across both subjective and physiological outcome measures with all studies showing null group differences. 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, heightened CS+ responding, and a tendency towards heightened distress towards the CS-. This suggests that panic patients possess heightened threat acquisition alongside a tendency to transfer threat associations from the CS+ to the CS- during acquisition, yet these effects only seem to materialize at the subjective level.

Further, neuroimaging studies (collating both ROI and whole-brain analyses) provide mixed support for panic-control alterations in the activation of amygdala, insula cortex, ACC, PFC, and BNST regions during threat conditioning. Specifically, half of the relevant studies showed heightened differential neural activation in the amygdala and ACC regions in patients during acquisition. Results in relation to the PFC during acquisition were more varied with most studies finding heightened differential neural activation within the PFC as a whole, or within specific regions of the PFC e.g., superior frontal gyrus, in patients vs. controls,

whereas another study found heightened differential activation in controls in different PFC areas e.g., middle frontal gyrus. Additionally, one study found heightened differential neural activation in the BNST in patients. On the contrary, support for alterations in differential neural activation during extinction was sparse with only one study finding increased differential activation in the superior frontal gyrus (PFC) in controls among other less relevant effects. Similarly, effects within extinction retention were also sparse, however heightened differential neural activation was demonstrated in the insula cortex in patients vs. controls by a single study, and within prefrontal regions (inferior frontal operculum and gyrus) by another single study. Whilst, heightened differential activation was demonstrated in the vmPFC in controls during retention. 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.

Specific Phobia

Results show mixed evidence for heightened CS+/CS- discrimination in phobic patients during acquisition via the use of physiological outcome measures with patients displaying equal levels of stimulus discrimination in relation to FPS but heightened discrimination in relation to SCR (in response to fear-relevant CS+ stimuli). However, evidence for heightened discrimination across subjective measures is strongly supported with all available analyses showing heightened CS+/CS- discrimination in phobic patients during acquisition, albeit from a single study. Further, there is compelling evidence for a lack of patient-control differences in CS+ and CS- responding across subjective measures i.e., expectancy, valence, and distress ratings and physiological measures i.e., SCR and FPS during acquisition with the majority, or all, relevant analyses demonstrating null group effects. Alternatively, within extinction, there

is mixed evidence for heightened CS+ responding in controls as indexed via SCR, yet all available analyses found a lack of group differences in CS- responding as indexed via SCR. Further, the evidence regarding patient-control differences in CS- responding as indexed via subjective measures is mixed with lowered patient valence ratings but null group differences in relation to expectancy ratings. Alternatively, evidence for heightened CS+ responding in phobic patients across subjective measures during extinction is strong with all relevant analyses showing this effect i.e., expectancy and valence (lowered) ratings, albeit from one single study. Within extinction retention, results demonstrate compelling evidence for a lack of patient-control differences in CS+ and CS- responding across physiological measures with all relevant analyses demonstrating null effects. Alternatively, there is mixed evidence for heightened patient responding to the CS+ and CS- during retention across subjective measures with half of relevant analyses demonstrating this effect i.e., null differences in relation to expectancy ratings yet lowered valence ratings for phobic patients. CS+/CS- discrimination differences were not investigated during either extinction or retention. 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 muted extinction learning during extinction. Again, patient-control differences seem most detectable in relation to subjective, as opposed to physiological, outcome measures generally.

Further, neuroimaging studies (collating both ROI and whole-brain analyses) provide mixed support for phobic-control alterations in the differential activation of the insula cortex and PFC regions during threat conditioning. Specifically, most analyses found a lack of patient-control differences in differential neural responding in the insula cortex during acquisition, however one study found heightened differential activity in this region specifically in relation to fear-relevant CS+ stimuli during early acquisition. Further, this

previous effect was mirrored in the mPFC with one study finding heightened differential neural responding in this area specifically in relation to fear-relevant CS+ stimuli within early acquisition. There were no differences in differential neural activation found during extinction by any study. Whereas a single study found heightened differential neural activation in the vmPFC in controls vs. patients during extinction retention. 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.

Critique and Contextualisation of Results

In general, the conditioning findings in relation to PD and SP tend to both corroborate and contradict the findings associated with general, and specific, anxiety-related disorders. Firstly, Kausche et al. (2024) found heightened AD patient responding (all anxiety disorders 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, which found strong evidence of lowered CS+/CS- discrimination in PD patients coupled with a lack of group differences in CS- responding, disregarding distress ratings, during acquisition. Additionally, this review found a lack of group 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. (2024). On the other hand, our findings demonstrated mixed evidence of heightened patient CS+ responding in acquisition, heightened distress towards CS- in acquisition, and a lack of group differences in CS+/CS- discrimination in extinction which matches the findings of Kausche et al. (2024). 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 anxiety-related disorders.

Regarding SP, this review finds both distinguishing and corroborating effects in relation to the conditioning signatures associated with general, and specific, anxiety-related disorders. Firstly, the finding that SP patients possess heightened CS+/CS- discrimination in comparison to controls directly contradicts the entire corpus of prior research 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 the fear-relevant CS+ (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 also (Ney et al., 2022). Further, in light of this review, SP patients were characterised by heightened CS+ responding during extinction which coalesces with the effects found for both anxiety disorders 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). Overall, the results of this review, in relation to both PD and SP, seem to highlight the large degree of inter-diagnostic variability within anxiety disorders 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 i.e., poorer threat acquisition. Further, even though there was mixed evidence for heightened CS+ responding, but not

heightened generic CS- responding, in panic patients vs. controls during acquisition, panic patients did seem to report heightened distress towards both the CS+ and CS- during acquisition. Taken together, this suggests that those with PD may erroneously transfer threat associations from the CS+ and CS- (Duits et al., 2015) which implies that those with PD may struggle to discriminate between threat and safety cues within ecological learning contexts e.g., new situations. Further, this may partially explain how 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. Further, 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 the clinical recommendations in relation to exposure therapy that emphasize 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 multitude of stimuli e.g., physical sensations 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; 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). 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. Clinically, these results suggest that exposure therapy should focus specifically on the phobic stimulus (due to muted extinction and retention). Further, prolonged exposure

protocols with a heavy emphasis on follow-up assessment and top-up exposure work may be required. 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 CS 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 anxiety-related disorders, 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 anxiety disorders 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. 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., 202). 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. Upon further inspection, it was observed that this study utilised facial stimuli and verbal insults as the US; one could argue that this is a fear-relevant US stimulus specific to SAD patients, 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, CS type is a known moderator of patient-control differences in anxiety disorders (Kausche et al., 2025), and the PD studies in this review that utilised more generic USs 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 USs 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 & Ohman, 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 gaps to produce a more comprehensive corpus of knowledge in this area. 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 a meta-analysis, therefore both published and future studies should share all of their 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.

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 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 these results and conclusions 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 retention 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 specifically 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 anxiety disorders in general. This review has highlighted current gaps in the literature and made recommendations for future research to improve our understanding of this topic.

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Appendix A – Modified EPHPP Tool

Included Items:

1. **A) SELECTION BIAS**

(Q1) Are the individuals selected to participate in the study likely to be representative of the target population?

2. Very likely
3. Somewhat likely
4. Not likely
5. Can't tell

(Q2) What percentage of selected individuals agreed to participate?

1. 80 – 100% agreement
2. 60 – 79% agreement
3. less than 60% agreement
4. Not applicable
5. Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

B) STUDY DESIGN

Indicate the study design

1. Randomized controlled trial
2. Controlled clinical trial
3. Cohort analytic (two group pre + post)
4. Case-control
5. Cohort (one group pre + post (before and after))
6. Interrupted time series
7. Other specify _____

8. Can't tell

Was the study described as randomized? If NO, go to Component C.

No Yes

If Yes, was the method of randomization described? (See dictionary)

No Yes

If Yes, was the method appropriate? (See dictionary)

No Yes

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

E) DATA COLLECTION METHODS

(Q1) Were data collection tools shown to be valid?

1. Yes
2. No
3. Can't tell

(Q2) Were data collection tools shown to be reliable?

1. Yes
2. No
3. Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

F) WITHDRAWALS AND DROP-OUTS

(Q1) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?

1. Yes
2. No

3. Can't tell
4. Not Applicable (i.e. one time surveys or interviews)

(Q2) Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).

1. 80 -100%
2. 60 – 79%
3. less than 60%
4. Can't tell
5. Not Applicable (i.e. Retrospective case-control)

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

H) ANALYSES

(Q2) Indicate the unit of analysis (circle one)

community organization/institution practice/office individual

(Q3) Are the statistical methods appropriate for the study design?

1. Yes
2. No
3. Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

Follow the following link for more information on excluded items and overall scoring procedure: https://www.ephpp.ca/qadictionary.html