Author(s): Wang, Jinxia; Wang, Yizhen; Liao, Meiling; Zou, Yefeng; Lei, Yi; Zhu, Yuxi

Title: Conditioned generalisation in generalised anxiety disorder : the role of concurrent perceptual and conceptual cues

Year: 2021

Version: Accepted version (Final draft)

Please cite the original version:

Wang, J., Wang, Y., Liao, M., Zou, Y., Lei, Y., & Zhu, Y. (2021). Conditioned generalisation in generalised anxiety disorder : the role of concurrent perceptual and conceptual cues. Cognition and Emotion, 35(8), 1516-1526. https://doi.org/10.1080/02699931.2021.1982677

Conditioned Generalisation in Generalised Anxiety Disorder: The Role of Concurrent Perceptual and Conceptual Cues

Jinxia Wang [a,b #], Yizhen Wang [a,c #], Meiling Liao [d], Yefeng Zou[e], & Yi Lei [a*], Yuxi Zhu [f]

[a] Institute of Brain and Psychological Sciences, Sichuan Normal University, Chengdu 610066, China

[b] Faculty of Education and Psychology, University of Jyväskylä, Jyväskylä, Finland

[c] School of Psychology, Shenzhen University, Shenzhen 518060, China

[d] Fujian Medical University, Fuzhou, 350100, China

[e] Fuzhou Neuropsychiatric Hospital Affiliated to Fujian Medical University, Fuzhou, 350000, China

[f] School of Management, Shenzhen Polytechnic, Shenzhen 518060, China

[#] Co-first author

*Corresponding author. Institute of Brain and Psychological Sciences, Sichuan Normal University, Chengdu 610066, China.

E-mail addresses: leiyi821@vip.sina.com(Y. Lei)

Abstract

Previous research in extinction indicates no difference in US expectancies for aversive and non-aversive unconditioned stimuli (USs). In this study, we bridged these topics by examining how concurrent perceptual and conceptual cues influence conditioned generalisation of generalised anxiety disorder (GAD) patients by using non-aversive USs. The study included two consecutive phases: acquisition and generalisation. In the acquisition phase, we used blue and purple images as the perceptually conditioned stimuli, images of animals and household items as the conceptually conditioned stimuli, and non-aversive images as unconditioned stimuli (US). In the generalisation phase, we used images containing both conceptual and perceptual cues (e.g., blue animals) as the generalisation stimuli. Participants rated the US expectancy for all images. We found that compared with the control group, the patients exhibited generalisation in response to stimuli that included conditional conceptual cues. These results reveal novel evidence of generalisation in GAD and may have implications for considering the concept-based information in extinction treatment.

Keywords: general anxiety disorder, generalisation, conceptual cue, perceptual cue

Introduction

A significant portion of the population is affected by anxiety disorders, including generalised anxiety disorder (GAD), social anxiety disorder (SAD), panic disorder, specific phobias, and separation anxiety (American Psychiatric Association, 2013). According to large population-based surveys in 2015, up to 33.7% of the population in the United States experiences having an anxiety disorder within their lifetime (Bandelow & Michaelis, 2015). In addition to the direct effects in individuals, anxiety disorders can lead to other mood disorders such as depression (Meier et al., 2015). Furthermore, treating anxiety disorders is expensive and arduous as the recurrence rate is high (Bandelow, Michaelis, & Wedekind, 2017). A defining feature of many anxiety disorders is the overgeneralisation of fear (e.g., Lissek et al., 2010; Lissek, 2012; Lissek et al., 2014), which refers to the spread of fear responses from fear-eliciting stimuli to items that only resemble fear-eliciting stimuli (e.g., Grant & Schiller, 1953; Lissek et al., 2010; Lissek et al., 2014).

As we know, moderate generalisation can benefit human beings to adjust to the variable environment (Öhman, 2009). It is important to learn how to apply previously acquired information about a stimulus to other novel stimuli that are similar to the original stimulus (Gentner, 2003). Associative learning can be used to broadly refer to the formation of associations in memory between stimuli, contexts, outcomes, and behaviours (e.g., Pavlovian, operant learning) (Treanor, Rosenberg, & Craske, 2021). Stimulus generalisation in associative learning refers to the extent of applying a new stimulus to a previously learned stimulus. For example, in Pavlovian conditioning, if a given conditioned stimulus (CS+; e.g., a tone) is paired with an unconditioned stimulus (US; e.g., electrical shock), the presentation of CS+ will elicit a conditioned response (Wheeler, Amundson, & Miller, 2006). A stimulus that is always presented alone (CS−) predicts the absence of an aversive US. Generalisation research is founded on the classic Pavlovian conditioning paradigm (Pavlov, 1927). A typical generalisation paradigm consists of two phases: acquisition and generalisation (e.g., Struyf, Zaman, Hermans, & Vervliet, 2017; Vervliet, Kindt, Vansteenwegen, & Hermans, 2010; Zaman, Ceulemans, Hermans, & Beckers, 2019). In the generalisation phase, individuals are presented with the CS+, the CS−, and generalisation stimuli (GSs)—stimuli that systematically vary in similarity to the CS+ (e.g., circles of different sizes when the CS was a circle). However, the disadvantage of preliminary research of generalisation is solely focusing on fear and using electrical shocks as the US. It makes the participants highly nervous, especially patients with anxiety disorders, and increases the difficulty of manipulation (Spix, Lommen, & Boddez, 2021). Additionally, existing research has identified that US expectancies for aversive and non-aversive USs convincingly show that there are no differences in this measure as a function of US aversiveness (e.g., Spix et al., 2021; Meulders, Boddez, Vansteenwegen, & Baeyens, 2013). Spix et al. (2021) estimated that the individual extinction used three geometrical shapes (triangle, square, and circle) as CS. Shock and a neutral picture served as the aversive US and the non-aversive US, respectively. Their findings showed considerable overlap in the extinction performance for aversive and non-aversive US conditioning. Therefore, we examined whether generalisation will occur with non-aversive US images.

To date, numerous studies have investigated generalisation using perceptual and conceptual cues (for reviews, see Lonsdorf et al., 2017; e.g., Lissek et al., 2008; Dunsmoor & Murphy, 2015). Perceptual generalisation studies involve generalising across perceptual similarities, typically visual stimuli such as shapes (e.g., Meulders et al., 2012), colours (e.g., Vervliet et al., 2010; Lee et al., 2019), human faces (e.g., Dunsmoor, Mitroff, & LaBar, 2009), or context (e.g., Andreatta et al. 2020). Researchers have also demonstrated perceptual generalisation using auditory, tactile, and olfactory stimuli (Lonsdorf et al., 2017; e.g., Resnik, Sobel, & Paz, 2011; Wesson & Wilson, 2010). These studies have consistently shown that the perceptual similarity between GSs and the CS+ strongly influences fear generalisation; the more similar they are, the stronger the generalised fear response (e.g., Lissek et al., 2008; Lissek et al., 2010; Lissek et al., 2014). In addition, studies indicate that compared with healthy individuals, patients with anxiety disorders show an intensified perceptual generalisation of fear (e.g., Kaczkurkin et al., 2017; Lissek et al., 2010; Lissek et al., 2014; Morey et al., 2015). For example, Lissek et al. (2014) discovered that relative to their healthy peers, patients with GAD tended to overgeneralise the conditioned fear, as evidenced by a flatter generalised gradient across the GSs. In addition to perceptual similarities, generalisation can also be built through conceptual associations between GSs and the CS+. In real-life settings, people who have experienced fearful traumatic events are afraid of certain conditional objects/contexts. These objects/contexts often share little perceptual similarity with the initial CS+ but are conceptually closely associated with it (Dunsmoor, White, & LaBar, 2011). For example, a person who has a phobia of dogs may fear not only dogs but also cats, or even dog-associated objects (e.g., dog collar), people (e.g., veterinarian), or places (e.g., parks). Conceptual generalisation studies also rely on visual stimuli such as images of animals and tools (Dunsmoor, Martin, & LaBar, 2012) or words (Dunsmoor et al., 2011; Dunsmoor & Murphy, 2014). Previous studies have shown that in addition to perceptual similarity, fear can generalise through conceptual closeness. For example, Dunsmoor and colleagues (2012) showed that unconditional objects also induce fear responses when they belong to the same conceptual category as conditional objects. In their study, they used an electrical shock as the US and two superordinate categories (e.g., animals & tools) of basic−level exemplars (e.g., dog & hammer) as the CS+ and CS−, respectively. The results showed that the participants expected an electrical shock more after seeing the objects in the fearful category (i.e., the category containing conditional objects).

As mentioned above, evidence supports the idea that both perceptual similarity and conceptual closeness promote fear generalisation. However, only a few studies have examined the combined effect of perceptual and conceptual cues on fear generalisation (Bennett et al., 2015; Peperkorn, Alpers, & Mühlberger, 2014). Peperkorn et al. (2014) used a matching-to-sample (MTS) task, including sounds, nonsense words, and animal-like objects, to investigate whether learned fear could generalise to threat-relevant stimuli within the same category due to similar perceptual or conceptual features. They ascertained that both conceptual and perceptual variants related to the aversive stimulus category could heighten fear. However, to the best of our knowledge, no research has studied the relationship between anxiety disorders and conceptual generalisation, nor generalisation based on simultaneously incorporated conceptual and perceptual cues. Addressing these questions is valuable for expanding our knowledge of generalisation and specifically in finding ways to differentiate between anxiety disorders and healthy individuals. Indeed, more detailed knowledge might lead to better treatments for anxiety disorders. For example, decreasing generalisation along perceptual lines might not be enough if anxiety disorders are also rooted in generalisation in response to conceptual cues. Understanding the relationship between anxiety disorders and generalisation to conceptual cues or co-occurring perceptual and conceptual cues will expectantly provide suggestions for developing more effective means to treat anxiety disorders.

The current study

In this study, we used non-aversive USs to investigate the effect of concurrent perceptual and conceptual cues on generalisation and how GAD can affect generalisation based on these different co-occurring types of cues. We used two colours—blue and purple—as perceptual cues (P+; P−) and two object categories—animals and household items—as conceptual cues (C+; C−). In the acquisition phase, participants learned to differentiate unconditional cues (CS−: P− and C−) from conditional cues (CS+: P+ and C+). However, in the generalisation phase, the four cues were combined to generate four types of new stimuli (P+C+, P+C−, P−C+, and P−C−). Acquisition and generalisation were measured using the US-expectancy ratings. US-expectancy is a verbal measure that indicates the extent to which participants expect the US to occur. It is the most commonly used subjective measure in human fear-conditioning paradigms (Lonsdorf et al., 2017; Boddez et al., 2013). We hypothesised that (a) after the acquisition, US-expectancy ratings would be higher for CS+ than CS−; and (b) during the generalisation test, the difference in US-expectancy ratings between GS+ cues (conditional GS: P+C+, P+C−, and P−C+) and GS− cues (unconditional GS: P−C−) would be higher in patients with GAD than in healthy controls; and (c) conditioned generalisation to perceptually and conceptually conditional cues (C+P+) would be greater in patients with GAD than in controls.

Methods

Participants

Sixty-three Chinese participants voluntarily participated in our experiment. Thirty-two were patients with GAD, and the others were healthy individuals. All the participants were right-handed with normal or corrected-to-normal visual acuity and no colour-blindness. They filled out written consent forms and were asked to complete a demographic questionnaire before the experiment. The tasks, measures, and procedures were approved by the Medicine Ethics Committee of Shenzhen University, and all participants were treated in accordance with the declaration of Helsinki.

The patients with GAD were recruited from two hospitals and two medical centres in a southeast city of China. They were recruited only if they met all the following criteria: 1) diagnosed with GAD by psychiatrists who referred to the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5); 2) scored over seven on the Hamilton Rating Scale for Anxiety (HAMA); 3) aged between 15 and 55 years; 3) did not have major depression disorder (MDD), severe physical illnesses, such as schizophrenia, bipolar disorder, brain organic diseases, or epilepsy; and 4) no history of substance abuse. The healthy control group was recruited from communities, medical centres, and universities. They reported no history of mental illnesses, and they matched the patients in age, gender, and educational level. Education level was categorised as primary or junior high school, senior middle school, or university and above.

We excluded five participants (three patients and two healthy individuals) because they failed to follow our instructions during the experiment. The final sample was 58 participants, including 29 patients with GAD and 29 healthy individuals (aged 17–55 years; mean age: 32.26 ± 10.39 years). A previous study reported that the estimated age of onset (AOO) for GAD is 34.9 years. Additionally, the AOO differs greatly depending on anxiety disorder subtypes, and another study reported GAD onset to be in young adulthood (Lijster et al., 2017). Thus, we limited the participants' age to between 15 and 55 years. An independent-samples t-test on showed that the two groups did not differ in age ($t(56) = 0.41$, p =.68, Cohen's $d = 0.11$). A Chi-square analysis on education level also showed no difference between the groups ($\chi^2(2, N=58) = 0.348$, p = .84. Table 1 displays sample characteristics for each group.

Stimulus materials

Unconditioned stimuli

One hundred and fifteen undergraduate students (51 men; mean age: 21.92 ± 1.43 years) were asked to complete a free-association task and provide as many fear-inducing nouns as possible (e.g., snake). We picked the most frequent items as the head-word, then from three categories (animals, scenes, and objects) the participants were asked to choose images combined with the headword, 30 images respectively (public resources like Baidu, Souhu). Then, we recruited 84 participants (45 women; age range: 18–25 years) that were recruited to rate the valence, arousal, and fear levels of the pictures on a 9-point scale. Finally, 81 fear-evoking images were chosen. The mean ratings were as follows: Fear, 4.80 ± 1.06; valence, 3.57 ± 0.16; and arousal, 6.16 ± 0.58. Subsequently, we selected 20 images of moderately fearful[1] (5.82 ± 0.80), valence rating (3.10 ± 0.50) and

[1] In this experiment, we intentionally used moderately (instead of highly) fearful images as US to limit their negative impact on the patients with GAD. This might have led to a

arousal rating (6.80 ± 0.42) to represent the US. These images were rated on 9-point scales (fear: 1 = *not fearful at all*, 9 = *very fearful*; valence: 1 = *low pleasure*, 9 = *high pleasure*; arousal: 1 = *very calm*, 9 = *very excited*).

Conditioned stimuli

We used two types of conditioned stimuli: perceptual and conceptual. The stimuli for perceptual acquisition were 30 meaningless cloud-like shapes, of which half were blue, and the other half were purple. For each participant, one of the two colours was the P+, and the other was the P−. The stimuli for conceptual acquisition were 30 black line drawings, of which half were animals (e.g., a dog) and the other half were household items (e.g., a kettle). Assignment of colours to the P+ and P− and assignment of categories to the C+ and C− were partially counterbalanced across participants; 'animals' and 'blue' served as the CS+ for 32 participants, and 'furniture' and 'purple' were the CS+ for the other 26 participants. In a pilot study, 45 university students rated the valence and arousal levels of the conceptual CS on a 9-point scale (1 = *extremely unpleasant/calming*, 9 = *extremely pleasant/exciting*). The average valence and arousal ratings for the animal (valence: M = 5.21 ± 0.46; arousal: M = 5.12 ± 0.20) and household item (M = 5.38 ± 0.27; M = 5.13 ± 0.18) images were both neutral (near 5), and neither valence ($t(28) = 1.28$, $p = .21$) nor arousal ($t(28) = 0.22$, $p = .83$) differed between categories.

Generalised stimuli

Four types of stimuli served as GS: C+P+, C+P−, C−P+, and C−P−. The set of generalised stimuli were thus 40 coloured line drawings; 10 blue animals, 10 purple animals, 10 blue household items, and 10 purple household items. In addition, GS items are different from those in the acquisition phase. For example, when the P+ stimuli were blue, and the C+ stimuli were animals in the acquisition phase, the P+C+ stimuli in the generalisation phase were blue animals. Similar to black conceptual CS, the coloured GS

weakened effectiveness of US. See the detailed discussion regarding the use of images in the Discussion.

were rated as neutral in valence and arousal (animals: $M = 5.26 \pm 0.60$; $M = 5.14 \pm 0.23$, respectively; household items: $M = 5.34$, $SD = 0.26$; $M = 5.07 \pm 0.17$), and neither differed between the groups (valence: $t(38) = 0.57$, $p = .57$; arousal: $t(38) = 1.22$, $p = .23$).

Procedure

Importantly, throughout the experiment, the contingencies between the CS/GS and the US were not provided; the participants were simply instructed to learn the association between the images they were shown.

Stimulus presentation

We programmed the experiment with E-prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). All the stimuli were presented on a white background. A fixation (+) was presented at the centre of a screen for 800–1200 ms at the beginning of each trial. Then the CS or GS was presented, and the participants rated the US-based on a five-alternative forced-choice scale (1 = no likely at all, 5 = very likely) that appeared beneath the images. The instructions were: “Please rate the likelihood that you will be shown an unpleasant image.” The participants were asked to provide the ratings as soon as possible according to their immediate feelings. Choices were made using a computer keyboard. When the choice was made, the CS disappeared, and the US (or a blank screen) was then presented 1000 ms after the CSs offset. All the stimuli were presented in a pseudorandomised order. The inter-trial interval (ITI) was 1200–1500 ms (see Figure 1).

Experimental paradigm. The experiment consisted of two phases: acquisition and generalisation. The participants had a break between the phases. The acquisition phase consisted of 60 trials, 15 each for the P+, P−, C+, and C−. The reinforcement rate for the P+ and C+ was 80%. The P− and C− were always followed by a blank screen and thus were never associated with the US. The generalisation phase comprised 40 trials, 10 for each type of GS (C+P+, C+P−, C−P+, and C−P−). No GS was paired with the US during this phase, but we never informed participants of this.

Statistical analyses

Statistical analyses were performed using IBM SPSS 22 (IBM Corporation, Armonk, NY, USA). Before analysis, acquisition trials were divided into four blocks consisting of 15 trials of each type (P+; P−; C+; C−), and generalisation trials were divided into four blocks, including 10 trials of each type (P+C+; P+C−; P−C+; P−C−). Behavioural data during acquisition were analysed within a 2 (Group: GAD, healthy control) × 2 (CS Type: CS+, CS−) × 2 (Cue type: Perceptual, Conceptual) × 4 (Block: 1, 2, 3, & 4) repeated measures ANOVA. Responses from the generalisation phase were analysed with a 2 (Group: GAD, healthy control) × 2 (Perceptual type: P+, P−) × 2 (Conceptual type: C+, C−) × 4 (Block: 5, 6, 7, & 8) repeated measures ANOVA.

In testing our *a priori* hypotheses, a Bonferroni correction was applied when making multiple comparisons. The Greenhouse-Geisser (1959) correction was applied for repeated-measures ANOVAs when the sphericity assumption was not met. The effect size indication η^2 is reported for significant ANOVA effects. Furthermore, the alpha threshold for statistical significance was 0.05.

Results

Acquisition

Analysis of the results revealed significant main effects of CS Type ($F(1,56) = 19.909$, $p < .001$, $\eta^2 = .262$), Cue Type ($F(1,56) = 7.806$, $p = .007$, $\eta^2 = .122$), and Block ($F(2.307,13.207) = 11.828$, $p < .001$, $\eta^2 = .174$), resulting from higher US expectancy ratings for the CS+ ($M_{CS+} = 2.829$, $SD_{CS+} = .112$) than for the CS− ($M_{CS-} = 2.375$, $SD_{CS-} = .117$), higher US expectancy ratings to the Perceptual cue ($M_P = 2.77$, $SD_P = .124$) versus the Conceptual cue ($M_C = 2.434$, $SD_C = .115$), and lower US expectancy ratings regarding the Block1 ($M_{B1} = 2.33$, $SD_{B1} = .108$) compared to the Block2($M_{B2} = 2.56$, $SD_{B2} = .121$), 3($M_{B3} = 2.815$, $SD_{B3} = .119$), and 4($M_{B4} = 2.702$, $SD_{B4} = .114$). Additionally, a CS Type × Block interaction ($F(2.6,145.621) = 9.318$, $p < .001$, $\eta^2 = .143$), revealed that US-expectancy evaluations of CS+ and CS− did not differ during Block1, $F(1,56) = .613$, $p = .437$, $\eta^2 = .011$, but the US-expectancy evaluations of CS+

were evaluated as higher than the CS− during all other blocks, $F(1,56) > 10.689$, $p < .002$, $\eta^2 > .16$. The remaining omnibus effects did not reach significance, $F < 2.66$, $p > .103$, $\eta^2 < .045$.

Generalisation

Analysis of the results revealed a significant main effect of Conceptual Cue ($F(1,56) = 10.602$, $p = .002$, $\eta^2 = .159$) and Block ($F(2.342,131.133) = 4.217$, $p = .007$, $\eta^2 = .07$), resulting from higher US expectancy ratings for the C+ ($M_{C+} = 2.271$, $SD_{C+} = .138$) than for the C− ($M_{C-} = 1.866$, $SD_{C-} = .122$), and higher US expectancy ratings regarding the Block5 ($M_{B5} = 2.23$, $SD_{B5} = .122$) compared to the Block7($M_{B7} = 1.988$, $SD_{B7} = .116$). Furthermore, Group × Conceptual Cue ($F(1,56) = 7.884$, $p = .007$, $\eta^2 = .123$) interactions were significant, indicating that patients with GAD reported higher US expectancy ratings for stimuli with C+ cues than for stimuli with C− cues ($F(1,56) = 18.386$, $p < .001$, $\eta^2 = .247$, see Figure 2). The remaining omnibus effects did not reach significance, $F < 2.039$, $p > .125$, $\eta^2 < .035$.

Discussion

In the current study, we used non-aversive USs to investigate the influence of simultaneous perceptual and conceptual cues on generalisation and examined whether patients with GAD exhibited enhanced generalisation. We discerned that acquisition itself did not differ between the two groups. However, patients with GAD tended to generalise conceptual cues: Although the two groups of participants perceived the stimuli with unconditional conceptual cues (C−), the patients made higher US-expectancy ratings for conceptual cues (C+) than the healthy controls.

One of the most important findings is that the patients with GAD exhibited elevated generalisation for stimuli containing conditional conceptual cues. This is consistent with a previous study that found that conditioned fear might be stimuli with conceptual similarities to the CS (e.g., Dunsmoor et al., 2011; Vervoort et al., 2014). Research has shown that compared with healthy people, patients with anxiety disorders show an intensified perceptual generalisation of fear (e.g., Lissek et al., 2010; Lissek et al., 2014). To our knowledge, our research is the first to examine how patients with GAD and healthy people might differ in generalisation based on concurrent perceptual and conceptual cues. Our findings increase our knowledge of the relationship between generalisation and anxiety disorders by showing that patients with GAD exhibit generalisation not only for perceptual cues, but also for conceptual cues. One could speculate that the differences in generalisation between the two groups are due to differences in how the groups responded to the acquisition process. However, we argue against this speculation because we found no group difference in US-expectancy ratings during the acquisition phase.

Our findings also suggest that conceptual cues outweigh the colour cues for generalisation, as shown by patients with GAD. Specifically, when presented with a stimulus with both colour and category information (e.g., a blue animal), the patients depended principally on the category information to predict the occurrence of the US. Category information has an edge over colours when processing the object. Indeed, in our study, category information is predominantly informative, while colours are unnecessary for a person to understand the meaning of the stimulus. When the patients rely mostly on category information to process the images, they might depend accordingly on category cues to rate the US-expectancy level. This results in generalising the pictures with conditional conceptual cues but not to the pictures with conditional perceptual cues. It is consistent with a previous research that established that avoidance is generalised more into category stimuli than to the perceptual variants (Bennett et al., 2015). In this study, the healthy participants exhibited stunted generalisation, as evidenced by consistently low US expectancy ratings for all four types of GS. This observation contrasts with previous findings showing that both perceptual and conceptual cues can trigger generalisation in healthy participants (Bennett et al., 2015). Furthermore, the US never appeared in the generalisation phase. Thus, the US expectancy ratings tended to decrease over time. The US expectancy for both groups indicated extinction. Zbozinek and Craske (2018) evaluated the effects of multiple extinction stimuli on inhibitory learning. Participants were randomised to Extinction_CS+ (presentations of the original conditional stimulus), Extinction_Singular (presentations of a GS), or Extinction_Variety (presentation of GSs). The results revealed that extinction with a variety of GSs reduced the fear of those GSs.

In our study, the extinction of conceptual conditional GSs was more resistant in patients with GAD than in healthy controls. This was consistent with a previous study that found that, in contrast to control participants, PD patients exhibited larger skin conductance responses to CS+ stimuli during extinction, although there was no difference between the two groups during acquisition (Michael et al., 2007). Therefore, it might be necessary to pay more attention to concept-based information in the extinction treatment of patients with GAD.

We thought of two factors that might have led healthy participants to give similarly low US-expectancy ratings for all four types of GS. First, acquisition often used electro-tactile stimulation, noise, tones, or screams as the US (Glenn et al., 2012). In this study, we used non-aversive pictures in the US, which were probably weaker inducers of emotional responses than other kinds of US, such as electrical shock. Since patients with GAD may be more sensitive and more likely to suffer if the US is too strong, we selected non-aversive pictures as the US to protect them from undue stress. There are advantages to using picture–picture conditioning paradigms when investigating anxiety disorders (Klucken et al., 2009). For example, Schweckendiek and colleagues (2011) used images of spiders, aversive scenes, or household items as the US to study fear learning in patients with specific phobias. Trauma-specific pictures have also been used as the US in a study of PTSD (Wessa and Flor, 2007). However, using these images instead of a stronger fearful stimulus might have led to the fast extinction that we observed in the healthy participants. Generalisation is still likely to happen for healthy individuals when the US is more intense. Therefore, we suggest that the current findings should be verified in future studies to verify that the use other kinds of USs (e.g., electrical shock) can induce stronger responses.

The second factor that might have made it difficult to detect responses was the measure we used. There are some ways to measure response to the CS, containing autonomic arousal (skin conductance, heart rate, and pupillary dilation) and self-reports, which include associative learning (US-expectancies, learned the contingency between the US and CS) and evaluative learning (affective ratings, the perceived unpleasantness of the CS because of paired with the US) (Constantinou et al., 2021). We chose to use US-expectancy ratings, which are self-reports that index the degree of associative learning (the CS-US contingency). This is the most commonly used subjective measure in human conditioning paradigms (Lonsdorf et al., 2017). However, Lipp et al. (2020) found that evaluative and conditioning are not independent, and it is necessary to incorporate associative and evaluative learning measures (Constantinou et al., 2021). Furthermore, the lack of affective ratings before and after conditioning could make it difficult to distinguish associative and evaluative learning processes. Thus, additional measures such as CS valence, skin conductance responses (SCRs), affective ratings should be included in future studies to distinguish associative and evaluative learning.

Our study has several limitations, based on which we provide suggestions for future research. First, we used category information and colours rather than other kinds of cues. There are two distinct relationships between concepts: taxonomic and thematic. Taxonomically related objects share similar features, whereas thematically related objects co-occur in certain events or scenarios. Thus far, little is known about the roles of these two types of conceptual relationships in generalisation (for an exception, see e.g., Lei, Mei, Dai, & Peng). It is unknown whether the effect of conceptual and perceptual cues on generalisation found in this study can generalise to other types of conceptual and perceptual cues. Future research should examine this question by putting various conceptual and perceptual cues into comparisons. Another limitation is that we used blue and purple animals and furniture, which are fairly unrealistic objects. This flaw may decrease the ecological validity of our findings. Future research should use stimuli that are usual in real life. A third limitation is the age range, which was somewhat large from 15 to 55 years. In the generalisation phase, results indicated a difference between patients and healthy controls in the 15-35 age range. Thus, future studies should reduce the maximum age and focus on in-depth research in young people.

Conclusion

In this study, we used non-aversive USs to examine whether patients with GAD would differ from healthy people in the generalisation triggered by concurrent conceptual and perceptual cues. We found that compared with the healthy individuals, the patients showed that generalisation that was induced by category cues but not colour cues. This finding suggests that categories outweigh colours in influencing the formation of generalisation in patients with GAD. Therefore, this knowledge broadens our understanding of the relationship between anxiety disorders and generalisation.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (NSFC, Grant Numbers, 31871130), the Guangdong Key Project in "Development of new tools for diagnosis and treatment of Autism" (2018B030335001), Shenzhen Peacock Plan (KQTD2015033016104926).

Declaration of interest statement

The authors declare no conflict of interest.

References

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlingon, VA: American Psychiatric Publishing. 2013

Bandelow, B., & Michaelis, S. (2015). Epidemiology of anxiety disorders in the 21st century. *Dialogues in clinical neuroscience, 17*(3), 327–335.

Bandelow, B., Michaelis, S., & Wedekind, D. (2017). Treatment of anxiety disorders. *Dialogues in Clinical Neuroscience*, *19*(2), 93–107. Retrieved fromhttps://www.ncbi.nlm.nih.gov/pmc/articles/PMC5573566/.

Bennett, M., Vervoort, E., Boddez, Y., Hermans, D., & Baeyens, F. (2015). Perceptual and conceptual similarities facilitate the generalization of instructed fear. Journal of behavior therapy and experimental psychiatry, 48, 149–155. https://doi.org/10.1016/j.jbtep.2015.03.011

Boddez, Y., Baeyens, F., Luyten, L., Vansteenwegen, D., Hermans, D., & Beckers, T. (2013). Rating data are underrated: validity of US expectancy in human fear conditioning. Journal of behavior therapy and experimental psychiatry, 44(2), 201–206. https://doi.org/10.1016/j.jbtep.2012.08.003

Constantinou, E., Purves, K. L., McGregor, T., Lester, K. J., Barry, T. J., Treanor, M., Craske, M. G., & Eley, T. C. (2021). Measuring fear: Association among different measures of fear learning. Journal of behavior therapy and experimental psychiatry, 70, 101618. https://doi.org/10.1016/j.jbtep.2020.101618

Dunsmoor, J. E., Martin, A., & LaBar, K. S. (2012). Role of conceptual knowledge in learning and retention of conditioned fear. *Biological Psychology*, *89*(2), 300–305. https://doi.org/10.1016/j.biopsycho.2011.11.002.

Dunsmoor, J. E., Mitroff, S. R., & LaBar, K. S. (2009). Generalization of conditioned fear along a dimension of increasing fear intensity. *Learning & Memory*, *16*(7), 460–469. https://doi.org/10.1101/lm.1431609.

Dunsmoor, J. E., & Murphy, G. L. (2014). Stimulus typicality determines how broadly fear is generalized. *Psychological Science*, *25*(9), 1816–1821. https://doi.org/10.1177/0956797614535401.

Dunsmoor, J. E., & Murphy, G. L. (2015). Categories, concepts, and conditioning: How humans generalize fear. *Trends in Cognitive Sciences*, *19*(2), 73–77. https://doi.org/10.1016/j.tics.2014.12.003.

Dunsmoor, J. E., & Paz, R. (2015). Fear generalization and anxiety: Behavioral and neural mechanisms. *Biological Psychiatry*, *78*(5), 336–343. https://doi.org/10.1016/j.biopsych.2015.04.010.

Dunsmoor, J. E., White, A. J., & LaBar, K. S. (2011). Conceptual similarity promotes generalization of higher order fear learning. *Learning & Memory*, *18*(3), 156–160. https://doi.org/10.1101/lm.2016411.

Dymond, S., Dunsmoor, J. E., Vervliet, B., Roche, B., & Hermans, D. (2015). Fear generalization in humans: Systematic review and implications for anxiety disorder research. *Behavior Therapy*, *46*(5), 561–582. https://doi.org/10.1016/j.beth.2014.10.001.

Glenn, C.R., Klein, D.N., Lissek, S., Britton, J.C., Pine, D.S., Hajcak, G., 2012. The development of fear learning and generalization in 8–13 year-olds. Dev.Psychobiol. 54, 675–684, http://dx.doi.org/10.1002/dev.20616.

Grant, D. A., & Schiller, J. J. (1953). Generalization of the conditioned galvanic skin response to visual stimuli. *Journal of Experimental Psychology*, *46*(5), 309–313. https://doi.org/10.1037/h0056698.

Janssens, T., Martens, F., Storms, N., & Van den Bergh, O. (2015). Generalization of respiratory symptom triggers. *Behavior Therapy*, *46*(5), 689–698. https://doi.org/10.1016/j.beth.2015.05.003.

Kaczkurkin, A. N., Burton, P. C., Chazin, S. M., Manbeck, A. B., Espensen-Sturges, T., Cooper, S. E., Sponheim, S. R., & Lissek, S. (2017). Neural Substrates of Overgeneralized Conditioned Fear in PTSD. *The American journal of psychiatry, 174*(2), 125–134. https://doi.org/10.1176/appi.ajp.2016.15121549

Klucken, T., Kagerer, S., Schweckendiek, J., Tabbert, K., Vaitl, D., & Stark, R. (2009). Neural, electrodermal and behavioral response patterns in contingency aware and unaware subjects during a picture-picture conditioning paradigm. Neuroscience, 158(2), 721–731. https://doi.org/10.1016

Koban, L., Kusko, D., & Wager, T. D. (2018). Generalization of learned pain modulation depends on explicit learning. *Acta psychologica, 184*, 75–84. https://doi.org/10.1016/j.actpsy.2017.09.009

Lee, J. C., Lovibond, P. F., Hayes, B. K., & Navarro, D. J. (2019). Negative evidence and inductive reasoning in generalization of associative learning. *Journal of experimental psychology. General, 148*(2), 289–303. https://doi.org/10.1037/xge0000496

Lei, Y., Mei, Y., Dai, Y., & Peng, W. (2019). Taxonomic relations evoke more fear than thematic relations after fear conditioning: An EEG study. *Neurobiology of learning and memory*, *107099*. https://doi.org/10.1016/j.ijpsycho.2018.11.002.

Lei, Y., Wang, J., Dou, H., Qiu, Y., & Li, H. (2019). Influence of typicality in category-based fear generalization: Diverging evidence from the P2 and N400 effect. *International journal of psychophysiology, 135*, 12–20. https://doi.org/10.1016/j.ijpsycho.2018.11.002

Lipp, O. V., Luck, C. C., & Muir, A. C. (2020). Evaluative conditioning affects the subsequent acquisition of differential fear conditioning as indexed by electrodermal responding and stimulus evaluations. Psychophysiology, 57(3), e13505. https://doi.org/10.1111/psyp.13505

Lissek, S., Biggs, A. L., Rabin, S. J., Cornwell, B. R., Alvarez, R. P., Pine, D. S., & Grillon, C. (2008). Generalization of conditioned fear-potentiated startle in humans: Experimental validation and clinical relevance. *Behaviour Research and Therapy*, *46*(5), 678–687. https://doi.org/10.1016/j.brat.2008.02.005.

Lissek, S., Rabin, S., Heller, R. E., Lukenbaugh, D., Geraci, M., Pine, D. S., & Grillon, C. (2010). Overgeneralization of conditioned fear as a pathogenic marker of panic disorder. The American journal of psychiatry, 167(1), 47–55. https://doi.org/10.1176/appi.ajp.2009.09030410

Lissek S. (2012). Toward an account of clinical anxiety predicated on basic, neurally mapped mechanisms of Pavlovian fear-learning: the case for conditioned overgeneralization. Depression and anxiety, 29(4), 257–263. https://doi.org/10.1002/da.21922

Lissek, S., Kaczkurkin, A. N., Rabin, S., Geraci, M., Pine, D. S., & Grillon, C. (2014). Generalized anxiety disorder is associated with overgeneralization of classically conditioned fear. *Biological Psychiatry*, *75*(11), 909–915. https://doi.org/10.1016/j.biopsych.2013.07.025.

Lissek, S., & van Meurs, B. (2015). Learning models of PTSD: Theoretical accounts and psychobiological evidence. International journal of psychophysiology: official journal of the International Organization of Psychophysiology, 98(3 Pt 2), 594–605. https://doi.org/10.1016/j.ijpsycho.2014.11.006

Lonsdorf, T. B., Menz, M. M., Andreatta, M., Fullana, M. A., Golkar, A., Haaker, J., Heitland, I., Hermann, A., Kuhn, M., Kruse, O., Meir Drexler, S., Meulders, A., Nees, F., Pittig, A., Richter, J., Römer, S., Shiban, Y., Schmitz, A., Straube, B., Vervliet, B., … Merz, C. J. (2017). Don't fear 'fear conditioning': Methodological considerations for the design and analysis of studies on human fear acquisition, extinction, and return of fear. Neuroscience and biobehavioral reviews, 77, 247–285. https://doi.org/10.1016/j.neubiorev.2017.02.026

Luck, C. C., & Lipp, O. V. (2020). Measuring unconditional stimulus expectancy during evaluative conditioning strengthens explicit conditional stimulus valence. Cognition & emotion, 34(6), 1210–1225. https://doi.org/10.1080/02699931.2020.1736007

Maren, S., Phan, K. L., & Liberzon, I. (2013). The contextual brain: implications for fear conditioning, extinction and psychopathology. Nature reviews. Neuroscience, 14(6), 417–428. https://doi.org/10.1038/nrn3492.

Meier, S. M., Petersen, L., Mattheisen, M., Mors, O., Mortensen, P. B., & Laursen, T. M. (2015). Secondary depression in severe anxiety disorders: A population-based cohort study in Denmark. *The Lancet Psychiatry*, *2*(6), 515–523. https://doi.org/10.1016/S2215-0366(15)00092-9.

Meulders, A., Boddez, Y., Vansteenwegen, D., & Baeyens, F. (2013). Unpredictability and context conditioning: does the nature of the US matter?. The Spanish journal of psychology, 16, E46. https://doi.org/10.1017/sjp.2013.32

Meulders, A., Vandael, K., & Vlaeyen, J. W. (2017). Generalization of Pain-Related Fear Based on Conceptual Knowledge. *Behavior therapy, 48*(3), 295–310. https://doi.org/10.1016/j.beth.2016.11.014

Meulders, A., Vervliet, B., Fonteyne, R., Baeyens, F., Hermans, D., & Vansteenwegen, D. (2012). Preexposure to (un)predictable shock modulates discriminative fear learning between cue and context: An investigation of the interaction between fear and anxiety. *International Journal of Psychophysiology*, *84*(2), 180–187. https://doi.org/10.1016/j.ijpsycho.2012.02.004.

Morey, R. A., Dunsmoor, J. E., Haswell, C. C., Brown, V. M., Vora, A., Weiner, J., … LaBar, K. S. (2015). Fear learning circuitry is biased toward generalization of fear associations in posttraumatic stress disorder. *Translational Psychiatry*, *5*(12), e700–e700. https://doi.org/10.1038/tp.2015.196.

Öhman, A. (2009). Of snakes and faces: An evolutionary perspective on the psychology of fear. *Scandinavian Journal of Psychology*, *50*(6), 543–552. https://doi.org/10.1111/j.1467-9450.2009.00784.x.

Park, D., Lee, H. J., & Lee, S. H. (2018). Generalization of Conscious Fear Is Positively Correlated with Anxiety, but Not with Depression. *Experimental neurobiology, 27*(1), 34–44. https://doi.org/10.5607/en.2018.27.1.34

Pavlov, I. P. (1927). *Conditioned Reflexes*. London: Oxford University Press.

Peperkorn, H. M., Alpers, G. W., & Mühlberger, A. (2014). Triggers of fear: perceptual cues versus conceptual information in spider phobia. Journal of clinical psychology, 70(7), 704–714. https://doi.org/10.1002/jclp.22057

Resnik, J., Sobel, N., & Paz, R. (2011). Auditory aversive learning increases discrimination thresholds. *Nature Neuroscience*, *14*(6), 791–796. https://doi.org/10.1038/nn.2802.

Schweckendiek, J., Klucken, T., Merz, C. J., Tabbert, K., Walter, B., Ambach, W., Vaitl, D., & Stark, R. (2011). Weaving the (neuronal) web: fear learning in spider phobia. NeuroImage, 54(1), 681–688. https://doi.org/10.1016/j.neuroimage.2010.07.049

Sevenster, D., Haesen, K., Vervliet, B., Kindt, M., & D'Hooge, R. (2017). Prevention and treatment strategies for contextual overgeneralization. Scientific reports, 7(1), 16967. https://doi.org/10.1038/s41598-017-16893-2

Spix, M., Lommen, M., & Boddez, Y. (2021). Deleting "fear" from "fear extinction": Estimating the individual extinction rate via non-aversive conditioning. Behaviour research and therapy, 142, 103869. https://doi.org/10.1016/j.brat.2021.103869

Struyf, D., Zaman, J., Hermans, D., & Vervliet, B. (2017). Gradients of fear: How perception influences fear generalization. *Behaviour research and therapy, 93*, 116–122. https://doi.org/10.1016/j.brat.2017.04.001

Tinoco-González, D., Fullana, M. A., Torrents-Rodas, D., Bonillo, A., Vervliet, B., Blasco, M. J., … Torrubia, R. (2015). Conditioned fear acquisition and generalization in generalized anxiety disorder. *Behavior Therapy*, *46*(5), 627–639. https://doi.org/10.1016/j.beth.2014.12.004.

Urcelay, G.P., Miller, R.R., 2014. The functions of contexts in associative learning. Behav. Processes 104, 2–12, http://dx.doi.org/10.1016/j.beproc.2014.02.008.

Vervliet, B., Kindt, M., Vansteenwegen, D., & Hermans, D. (2010). Fear generalization in humans: Impact of verbal instructions. *Behaviour Research and Therapy*, *48*(1), 38–43. https://doi.org/10.1016/j.brat.2009.09.005.

Vervoort, E., Vervliet, B., Bennett, M., & Baeyens, F. (2014). Generalization of human fear acquisition and extinction within a novel arbitrary stimulus category. PloS one, 9(5), e96569. https://doi.org/10.1371/journal.pone.0096569

Wessa, M., & Flor, H. (2007). Failure of extinction of fear responses in posttraumatic stress disorder: evidence from second-order conditioning. The American journal of psychiatry, 164(11), 1684–1692. https://doi.org/10.1176/appi.ajp.2007.07030525

Wesson, D. W., & Wilson, D. A. (2010). Smelling sounds: olfactory-auditory sensory convergence in the olfactory tubercle. The Journal of neuroscience: the official journal of the Society for Neuroscience, 30(8), 3013–3021. https://doi.org/10.1523/JNEUROSCI.6003-09.2010

Yehuda, R., Hoge, C. W., McFarlane, A. C., Vermetten, E., Lanius, R. A., Nievergelt, C. M., Hobfoll, S. E., Koenen, K. C., Neylan, T. C., & Hyman, S. E. (2015). Post-traumatic stress disorder. *Nature reviews. Disease primers, 1*, 15057. https://doi.org/10.1038/nrdp.2015.57

Zaman, J., Ceulemans, E., Hermans, D., & Beckers, T. (2019). Direct and indirect effects of perception on generalization gradients. *Behaviour Research and Therapy*, *114*, 44–50. https://doi.org/10.1016/j.brat.2019.01.006.

Zbozinek, T. D., & Craske, M. G. (2018). Pavlovian extinction of fear with the original conditional stimulus, a generalization stimulus, or multiple generalization stimuli. Behaviour research and therapy, 107, 64–75. https://doi.org/10.1016/j.brat.2018.05.009

Table 1. Demographics and clinical characteristics across patients and control samples

	GAD Patients (*n* = 29)		Healthy Control (*n* = 29)		Significance[a]
Variable	Mean	SD	Mean	SD	
Age (years)	32.83	11.26	31.69	9.60	*p* = .68
	N	%	N	%	Significance[a]
Male Gender	15	52%	15	52%	*p* = 1.00
Educational levels					
Primary or junior high school	5	17%	6	21%	
Senior middle school	10	35%	8	27%	*p* = .84
University or above	14	48%	15	52%	

[a]Two−tailed *p* values reflecting the significance of group differences derived from independent samples *t*−tests for all variables except gender which was assessed using the chi−square statistic.

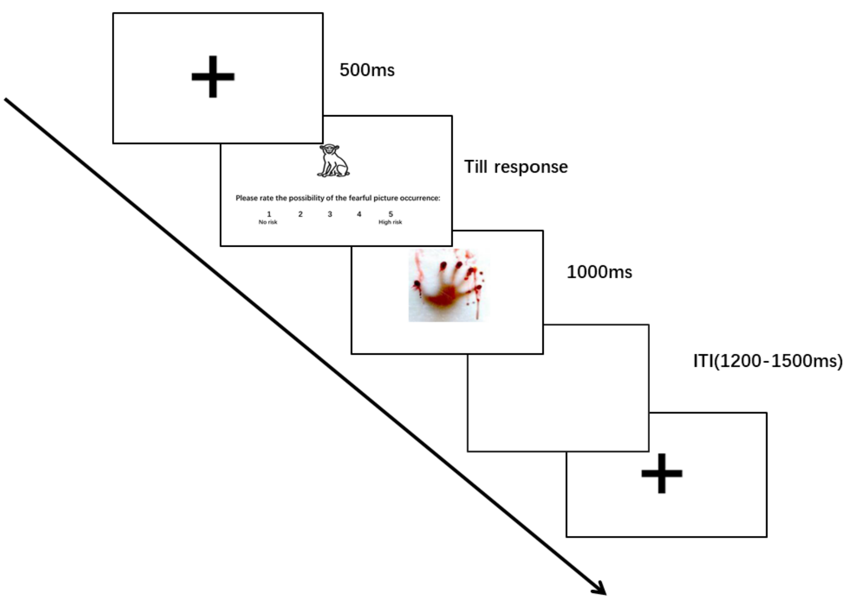

Figure 1. Example of a trial. A fixation (+) was presented at the centre of a screen for 800–1200 ms at the beginning of each trial. Then, the CS or GS was presented, and the

participants rated the likelihood that a fearful picture would be shown next. Ratings were made on a five-alternative forced-choice scale (1 = no likelihood, 5 = high likelihood) using a computer keyboard, and the participants were asked to do them as soon as possible according to their immediate feelings. Then US (or a blank screen) was presented 1000 ms after CS offset. All the stimuli were presented in a fully randomised order. The inter-trial interval (ITI) was 1200-1500 ms.

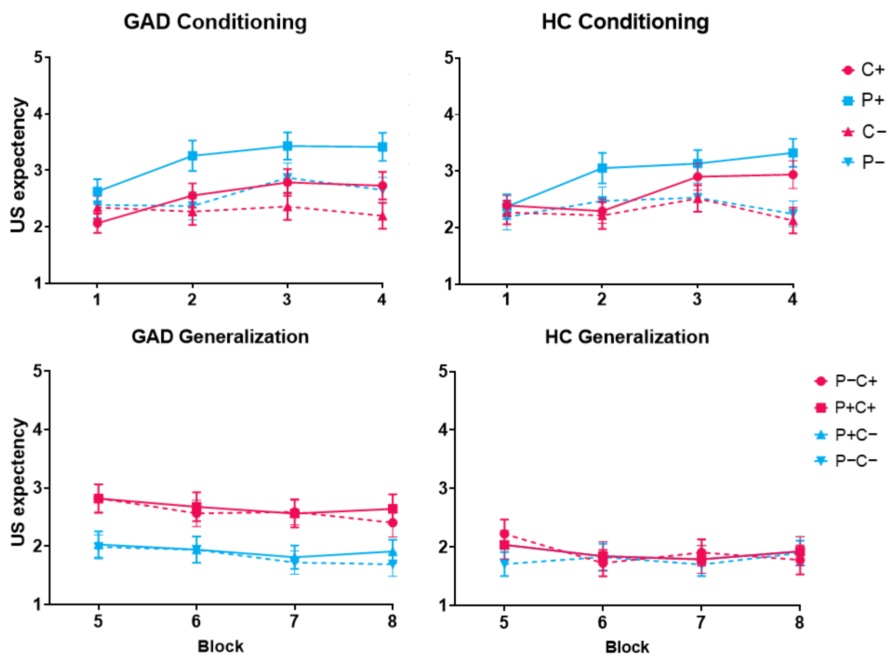

Figure 2. Average US-Expectancy ratings in acquisition trials, which were divided into blocks consisting of 15 trials of each type (P+; P−; C+; C−). Generalisation trials were divided into blocks consisting of 10 trials of each type (P+C+; P+C−; P− C+; P−C−). Error bars represent standard errors.