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FACULTEIT PSYCHOLOGIE EN
PEDAGOGISCHE WETENSCHAPPEN

Centrum voor Leerpsychologie en Experimentele Psychopathologie

FEAR IS IN THE EYE OF THE BEHOLDER

Fear generalization: A perceptual phenomenon?

Masterproef aangeboden tot het verkrijgen
van de graad van Master of Science in de
psychologie
Door
Cara Verwimp

promotor: Bram Vervliet
copromotor: Tom Beckers
m.m.v: Jonas Zaman

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Nederlandse samenvatting

Hoewel vrees vaak als negatief wordt gezien, heeft deze emotie ook adaptieve functies. Vrees zorgt er bijvoorbeeld voor dat we gepast reageren op bedreigende situaties. Het wordt pas problematisch wanneer ook niet-bedreigende situaties of stimuli vrees uitlokken en de vrees begint te interfereren met het dagelijkse leven. Het fenomeen waarbij vreesresponsen ook uitgelokt worden door andere, gelijkende stimuli, noemen we angstgeneralisatie. Verschillende studies suggereren dat generalisatie van vrees mee bijdraagt tot het ontstaan en in stand houden van angststoornissen.

Angstgeneralisatie wordt vaak onderzocht met een Pavloviaans conditioneringsparadigma waarbij een neutrale stimulus (CS, bv. cirkel) gepaard gaat met een aversieve stimulus (US, bv. elektrische prikkel) en op zijn beurt dus een vreesrespons uitlokt (UR, bv. vrees). Wanneer deze vreesresponsen grafisch weergeven worden op een bepaalde stimulusdimensie (bv. op basis van objectgrootte), zien we dat de sterktes van deze conditioneringsresponsen vaak toenemen naarmate de perceptuele gelijkenis met de vreesinducerende stimulus (CS) groter wordt. Dit resulteert in een typisch symmetrische generalisatiecurve, waarbij de hoogste vreesrespons plaatsvindt ter hoogte van de initiële vreesinducerende stimulus (CS) en de vreesresponsen afnemen naarmate de fysieke afstand groter wordt. Recent onderzoek toonde echter aan dat dezelfde leerprocessen (nl. associatief leren) ook een sterke invloed hebben op perceptuele processen.

De invloed van perceptie op vreesresponsen werd in deze masterproef nagegaan aan de hand van een vreesconditioneringsparadigma waarbij cirkels van verschillende groottes dienden als geconditioneerde stimuli (CS), waarvan één gepaard ging met een elektrische prikkel (US). Gedurende vier generalisatieblokken werden participanten blootgesteld aan zeven cirkels met verschillende groottes (GS) en moesten ze aangeven of de gepresenteerde cirkel de initiële vreesinducerende stimulus (CS) was of een nieuwe cirkel (GS). Bij elke trial moesten ze ook aangeven in welke mate ze een elektrische prikkel verwachtten. De verwachting van de elektrische prikkel diende als subjectieve vreesmeting, de oogknipperreflex en de huidgeleiding als objectieve metingen.

In onze studie vonden we dat nieuwe cirkels (GS) vaak fout gepercipieerd werden als de initiële vreesinducerende stimulus (CS) en dat deze misperceptie ervoor zorgde dat vrees gegeneraliseerd werd naar andere stimuli (GS). Bijgevolg werd de typische generalisatiegradiënt verbreed. De gevonden effecten lijken in een niet-klinische populatie niet samen te hangen met de mate van ‘trait anxiety’ (angstdispositie), gemeten door de STAI-T.

Abstract

The ability to discriminate among stimuli and its potential role in a context of fear generalization has received little attention in the past decades. The current experiment investigated whether perceptual discrimination influences fear generalization. Forty-three healthy students participated in a fear conditioning paradigm, including a perceptual categorization task. Different sized circles served as conditioned stimuli (CS), of which one was co-terminated with an electrocutaneous stimulus (US). During four generalization blocks, participants were exposed to seven different sized circles (generalization stimuli or GS) in a random order, including the CS. Participants had to categorize the presented stimulus either as novel or as CS after which US-expectancy ratings, skin conductance and startle responses were recorded as fear responses. Repeated measures ANOVA and mixed models were conducted to investigate the role of perception upon generalization gradients. We found that generalization stimuli were often misperceived as the CS and that this misperception of a GS as CS strongly boosted fear responses. Consequently, this misperception led to broader gradients. This study provides some strong evidence for the role of perception in fear generalization but still needs further elaboration on both clinical and neuropsychological level as these new insights could ameliorate future therapies.

Keywords: fear conditioning, fear generalization, perception, trait anxiety

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Writing this thesis was challenging but extremely inspiring. I would like to thank the persons who contributed to the process of writing.

Jonas Zaman, daily supervisor. Thank you for the constructive feedback, suggestions and a lot of patience.

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My parents, for their support, trust and patience throughout my study and for giving me the opportunity to achieve a bachelor's and master's degree at KU Leuven.

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Karolien Van Gool, fellow student. Thank you for the help when I was stuck with something.

Last but not least, I would like to thank everyone who participated this study.

Approach and personal contribution

During the first contact, Jonas Zaman, daily supervisor, explained their expectations and the experimental design and suggested some relevant literature. I started preparing the experiment by making a sample of recruiting posters and working out a standardized script for the experiment. I did not contribute in the devise of the experimental design, as it was already developed by Jonas Zaman. In November 2016, I practiced the experiment with a volunteer, supervised by Jonas Zaman. Then I started looking for participants by distributing recruitment posters and through the Experiment Management System participant tool of the KU Leuven. I ended my first master's year by writing introduction, method and analyzing the first data. My daily supervisor provided me with the dataset in SPSS and helped me when I struggled with statistical analyses. During the second year, combining writing and my internship was very exhausting. First, I tried to write in the weekends. As soon as my internship ended, I could focus more on developing a deeper understanding of fear generalization. I think there was a good harmony between personal contribution and suggestions. After all, the experience of conducting this experiment and reporting on this interesting topic was of great added value to my studies.

In agreement with my daily supervisor it was decided that this thesis would be written in the form of an article. The content would be suitable for a journal such as Behaviour Research and Therapy, of which the main goal is to achieve better understanding of mechanisms that contribute to psychopathology and treatment, based on experimental studies in both healthy and clinical individuals.

Table of Contents

Table of figures

1 Introduction

Fear is often described as negative, despite its adaptive function (Blanchard, Blanchard, Griebel, & Nutt, 2008). When exposed to danger, fear prepares organisms to respond optimally to threatening situations, for example, through a fight or flight response. However, from the moment fear starts to interfere with a person's daily functioning, it becomes dysfunctional (American Psychiatric Association, 2013). Often acquired fears do not remain specific but spread towards a range of stimuli or events that resemble the initial fear-evoking stimulus, a process called fear generalization (e.g., becoming afraid of doctors in white coats after a painful dental injection by a dentist in a white coat).

There has been a renewed interest in fear generalization the last decades, as overgeneralization of fear has been proposed as mechanism in the pathophysiology of anxiety disorders (Dunsmoor & Paz, 2015; Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2015; Lissek, 2012; Vervliet, Kindt, Vansteenwegen, & Hermans, 2010a). As such, insight into mechanisms underlying fear generalization could have profound clinical implications for therapy, as it might lead to better or novel treatment. Overgeneralization has been observed in generalized anxiety disorder (GAD) and panic disorder (PD) patients compared to healthy controls (Lissek et al., 2009, 2014) whereas other studies failed to find overgeneralization in GAD patients (Greenberg, Carlson, Cha, Hajcak, & Mujica-Parodi, 2013; Tinoco-González et al., 2015). The predominant paradigm to investigate fear generalization within an experimental context has been Pavlovian Conditioning (Pavlov, 1927). During a fear conditioning protocol, a neutral stimulus (Conditioned Stimulus (CS), e.g., circle) starts to elicit a response (Unconditioned Response (UR), e.g., fear) after it has been paired with an aversive stimulus (Unconditioned Stimulus (US), e.g., electrocutaneous stimulus). Pavlov (1927) noted that, in addition to the CS, stimuli which shared physical features with the original CS (called generalization stimuli or GS), elicited a CR as well. Hovland (1937), one of the pioneers of fear generalization research in humans, used a paradigm where one tone was contingently paired with an electric shock. In the generalization phase, four tones were presented and skin conductance responses were measured as an index of fear. Tones that were perceptually similar to the CS also elicited fear responses with increasing response strength as the CS-GS similarity increased, resulting in a logarithmic curve. This logarithmic curve, widely known as generalization gradient, had a peak in response strength at the location of the reinforced CS and gradually diminished as the CS-GS similarity decreased. Beside this CS, a range of GSs was created which differentiated on a perceptual dimension (e.g., size). Fear responding to these

stimuli was a function of the physical resemblance between the CS and the GSs. Such gradients have been reliably found in both humans and animals along diverse stimulus dimensions such as sound frequency and light spectra (Ghirlanda & Enquist, 2003). In the work of Lissek et al. (2010, 2014), a differential conditioning was adopted (which is frequently used in generalization research), where one CS served as a danger cue (frequently paired with the US, e.g., electrocutaneous stimulus (CS+)) while another CS served as a safety cue (never paired with the US (CS-)).

Frequently used measurements as index of fear learning are the fear-potentiated startle reflex (FPS, enhanced eye blink startle reflex induced by fear) (Grillon & Davis, 1997; Lissek et al., 2008) and the skin conductance response (SCR) (Hovland, 1937; Vervliet, Vansteenwegen, & Eelen, 2004). US-expectancy ratings are often used as a subjective index of fear learning (Meulders, Vandael, & Vlaeyen, 2017; Struyf, Zaman, Hermans, & Vervliet, 2017). Based on these measurements, generalization gradients can be obtained, which are defined by the steepness of the gradient (Lissek et al., 2009, 2010). These slopes quantify the effect between groups (e.g., anxiety patients versus healthy controls) and experimental manipulations. Less decrement in conditioned responding as the physical CS-GS similarity decreases indicates overgeneralization. This means, the steeper the slope, the less fear generalization occurred (Lissek et al., 2010). In generalized anxiety disorder and panic disorder patients, a wider generalization gradient (i.e., less decrement in fear responses as the physical similarity from GS differentiated from the CS) compared to healthy persons was observed (Lissek et al., 2014; but also see Tinoco-González et al., 2015). In those studies, fear responses were plotted across a physical stimulus dimension and as such the authors implicitly assume that stimuli can be discriminated perfectly with a one-on-one relationship between perception and physical properties. However, recent studies question this assumption as they demonstrated that different types of conditioning (e.g., aversive, positive) profoundly impaired the ability to discriminate between conditioned and new (generalization) stimuli in anxiety patients compared to healthy controls (Laufer, Israeli, & Paz, 2016). Moreover, conditioning has been demonstrated to directly affect the ability to discriminate between stimuli (Laufer & Paz, 2012; Laufer et al., 2016; Resnik, Sobel, & Paz, 2011; Schechtman, Laufer, & Paz, 2010), suggesting the potential importance of perception in fear generalization. As a study of Laufer and Paz (2012) found that the CS was not even consistently identified as the initial trained stimulus during a generalization phase, the perfect discrimination between stimuli can be questioned. However, currently no work has congruently assessed perception and behavior in a context of fear generalization to disentangle the role of perception from other mechanisms. For example,

similar gradients could be obtained when fear responses were not determined by physical similarity, but driven by the probability to perceive a certain stimulus as CS where only CS-percepts elicit fear responses (Struyf et al., 2017). The probability to misperceive a stimulus as CS also seems to be a function of the physical resemblance between the CS and the GSs, as this probability decreased when the physical CS-GS similarity decreased (Laufer & Paz, 2012).

Hence, inferences should be made cautiously as different underlying mechanisms may result in similar gradients. Various mechanisms have been proposed to explain differences in behavior between patients and controls. For example, Hartley and Phelps (2012) found that anxiety patients are more likely to interpret an ambiguous stimulus as threatening (i.e., better-safe-than-sorry) and consequently behave overly anxious in new situations to avoid potential risks. Alternative to these cognitive explanations, Laufer, Israeli and Paz (2016) demonstrated that the conditioning-induced inability to discriminate GSs from the initial fear-evoking stimulus was stronger in anxiety patients, compared to healthy controls. As such, impaired discrimination acuity is a plausible mechanism behind the observed overgeneralization in anxiety disorders. Therefore, differences in generalization gradients could be the result of a cognitive bias, a byproduct of reduced perceptual acuity or a combination of both (Struyf, Zaman, Vervliet, & Van Diest, 2015). Given that the same pathological behavior could be maintained by different mechanisms, it is crucial to identify these mechanisms because different mechanisms may require different therapeutic interventions. For example, patients with a cognitive bias may benefit from a cognitive behavior therapy, patients with a reduced perceptual acuity from perceptual discrimination training (Struyf et al., 2015).

Recent research tried to fill in this lacuna by scrutinizing the effect of perception on conditioned fear responses. Struyf et al. (2017) added a categorization task during generalization phase whereby subjects had to categorize the stimulus as CS or as novel after differential conditioning, with the intention to identify the contribution of misperceptions (i.e., GS misperceived as CS) on the generalization of fear. In a differential conditioning paradigm, one circle (CS+) co-terminated with an aversive IAPS picture (US) in 75% of the acquisition trials whereas another circle was never paired with the US (CS-). During the generalization phase, only one stimulus was presented (either the CS+, CS- or a GS). Participants had to indicate a US-expectancy rating and whether this stimulus was the CS+, CS- or another stimulus (GS). The authors observed that, during generalization phase, GSs close to the CS were frequently incorrectly perceived as the CS and elicited equal fear levels as the actual CS. These preliminary findings demonstrate essential support for the perceptual account for overgeneralization but need further elaboration as the described experiment contained certain

limitations. First, although most generalization research presents the same stimulus repeatedly, the previous experiment consisted of only one trial. Second, only US-expectancy was measured as an index of fear. Physiological measures should be added as an additional, more objective index of arousal. Furthermore, the size of the CSs was not counterbalanced.

The purpose of this study was to further investigate the role of perception upon generalization gradients in healthy individuals. To this end, a classical fear conditioning paradigm with circles of varying sizes as CS and GSs and a painful electrocutaneous stimulus as US was used, similar to Lissek et al. (2008). Skin conductance and startle responses served as objective measures of fear, US-expectancy as a subjective measure. The experiment started with an acquisition phase, in which a circle was repeatedly associated with pain (i.e., electrocutaneous stimulus). During four generalization blocks participants were exposed to novel, different sized stimuli which shared perceptual features with the conditioned stimulus. Both fear responses and perception were measured concurrently. The congruent assessment of perception and fear generalization enabled us to investigate the effect of perception upon generalization gradients. More precisely, fear responses elicited by a GS that was perceived as different from the CS could be separated from those where the same GS was misperceived as the CS. We hypothesized that perception of the stimulus determined the generalization gradient and the effect of physical features was limited. In other words, the misperception of the stimulus as the CS would lead to elevated and generalized fear responses. In addition, we expected that highly anxious subjects showed a broader generalization gradient compared to low anxious subjects, based on the State-Trait Anxiety Inventory (STAI).

2 Method

2.1 Participants

Forty-three students with an age range from 18 until 41 (M = 22.40, SD = 5.22, 28 women), participated in this study in exchange for 12 euro or 1 course credit. Exclusion criteria were pregnancy, serious medical diseases or wearing an electric medical device. Inclusion criteria were Dutch speaking and aged above 18. Participants signed up through the Experiment Management System participant tool of the KU Leuven. Three participants were excluded from analysis due to an uncompleted experiment or some technical problems (e.g., the computer did not register answers on the left side of the scale). As such, the final sample consisted of 14 men (M = 23.93, SD = 1.55) and 26 women (M = 21.08, SD = .64), with an age range from 18 until 37 (M = 22.08, SD = 4.46). The local Ethics Committee of the KU Leuven approved this study on 18/10/2016.

2.2 Stimuli and apparatus

Seven circles of varying diameters (from 7.37 to 11.94 cm, increasing in steps of 0.762 cm) were used as CS and GSs. Counting from the smallest, the fourth circle was used as CS. These stimuli were presented on a computer screen (Dell LCD monitor, type Pentium III) as white lines against a black background, controlled by Affect 4 software.

2.2.1 Electrocutaneous stimulus

An electrocutaneous stimulus, calibrated to pain tolerance, served as the US. Using the Ascending Methods of Limits, stimuli were presented in a staircase manner, starting with a very low stimulus. Stimulus intensity increased using small steps until participants rated the stimulus as painful and demanding some effort to tolerate. These stimuli were generated by an electrical stimulator (DS7A, Digitimer, Welwyn Garden City, England) through two reusable Ag/AgCL electrodes (8 mm), filled with K-Y gel, on the left wrist. The average intensity was 28.23 mA (*SD* = 14.21).

2.3 Procedure

Participants arrived in a small dimly lit room, equipped with a Dell desktop computer, camera and microphone. The researcher monitored participants in an adjacent room and had one-way visual contact. After oral instructions, the informed consent and the form with exclusion criteria were signed. Next, electrodes were attached. Once set, the researcher repeated the most important instructions, dimmed the lights and closed the door. The experiment consisted of a calibration, practice, acquisition and generalization phase.

2.3.1 Calibration

During the calibration phase, electrocutaneous stimuli of increasing intensity were presented until participants rated the stimulus as painful and demanding some effort to tolerate. Participants rated the stimuli on a scale from 0 to 10 (with 0 = no pain and 10 = unbearable pain). The highest tolerable stimulus was used during the experiment.

2.3.2 Practice

In order to familiarize participants with the trial structure and auditory startle probes, 10 practice trials were included. Instead of circles (used during acquisition and generalization),

rectangles were presented. In the middle of the screen a rectangle appeared as white lines against a black background. At the same time a scale appeared on the bottom of the screen where participants had to indicate whether the presented rectangle was same or different as a prior rectangle (presented before the practice task). After 3 seconds this scale disappeared and a visual analogue scale (VAS) appeared where participants had to rate their expectation of the US from 1 to 10, while the rectangle remained on screen. The position of the cursor was reset after each trial to the middle of the screen. Startle probes were presented every trial. No electrocutaneous stimuli were presented during this phase.

2.3.3 Acquisition

The acquisition phase comprised 16 trials where the CS appeared in the middle of the screen for 8 seconds. After 3 seconds a VAS appeared on the bottom of the screen for 5 seconds prompting participants to rate US-expectancy. When both the CS and VAS disappeared, the US was presented (in 50% of the trials). The position of the cursor was reset after each trial. The inter-trial interval (ITI) varied between 4 and 7 seconds. Startle probes could be presented between the 4^{th} - 7^{th} second after circle onset in 41% of the trials or during the ITI in 5% of the trials. Startle and startle free trials were alternating.

2.3.4 Generalization

During four generalization blocks, participants were exposed to seven different sized circles in a random order, including the CS. Each block comprised 22 CS trials and 24 GS trials (4 per GS) and started with 10 consecutive CS trials. Similar to the practice trials, a scale appeared on the bottom of the screen during the first 3 seconds on every trial where participants categorized the presented stimulus as the stimulus of the previous phase (i.e., CS) or as a novel stimulus (same vs. different). After 3 seconds this scale disappeared and a visual analogue scale (VAS) appeared for 5 seconds where participants rated US-expectancy. The CS remained partially reinforced (50%) to avoid extinction. No more than two consecutive trials with the same stimulus were presented and startle and startle free trials were alternating. Blocks were separated by three minute breaks during which participants filled in the questionnaires (STAI-T, STAI-S and demographic information).

2.4 Measures

2.4.1 US-expectancy

Participants indicated their expectation of the US by mouse-clicking on a rating scale ranging from 1 (“certainly no shock”) to 10 (“certainly shock”). After clicking, a red dot appeared on the corresponding position for that trial. During generalization phase, participants rated perceptual categorization with “same” or “different”. When participants did not answer or answered too late, a missing value was registered.

2.4.2 Orbicularis Oculi electromyographic

Orbicularis Oculi electromyographic (EMG) was measured by placing three disposable Kendall Arbo EMG elektrodes (H124SG, 30mm x 24mm), filled with a hydrogel, on the face of participants: one on the forehead and two under the left eyelid (according to Blumenthal et al., 2005). The recordings of the EMG signal varied between 90 Hz (low pass filter) and 500 Hz (high pass filter). Startle responses were recorded 500 milliseconds before the onset of the auditory probe (105 dB white noise delivered through headphones for a period of 50 ms) until 1000 milliseconds after. The raw EMG signal was recorded by a Coulborn isolated bioamplifier with a bandpass filter (LabLinc v75-04), rectified online and smoothed by a Coulborn multifunction integrator (LabLinc v76-23A), with a time constant of 20 ms. Participants with more than 50% startle responses coded as non-response were considered non-responders (11 participants) and were excluded from analysis.

2.4.3 Skin conductance

The galvanic skin responses were recorded using a Coulborn Instrument (model V71-23). This device applied a constant voltage of 0.5V across two disposable Biopac Systems EL507 Ag/AgCL electrodes (11 mm), filled with isotonic gel, attached at the hypothenar eminence of the left hand. The signal was digitized at 10 Hz and smoothed using 9 smoothing points. Skin responses were recorded 2 seconds before the stimulus onset until 8 seconds after. Participants with more than 50% skin responses coded as non-response were considered non-responders (26 participants) and were excluded from analysis.

2.4.4 Trait anxiety

Trait anxiety was measured via the Dutch version of the Spielberger State-Trait Anxiety Inventory (Van der Ploeg, Defares, & Spielberger, 2000), a self-report questionnaire which is

used to measure an individual's tendency to appraise situations as threatening (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). Two different questionnaires have been used, the "STAI-T" and the STAI-S". The STAI-T measured "trait-anxiety", the anxiety proneness, a relatively stable personality characteristic. The STAI-S measured "state-anxiety", an emotional state at a particular moment (e.g., during experiment). These questionnaires each consisted of 20 items, scored on a 4-point Likert scale ranging from "never" until "always". STAI-T scores ranged from 29 until 58 (M = 39.10, SD = 7.01), where higher scores indicated greater anxiety.

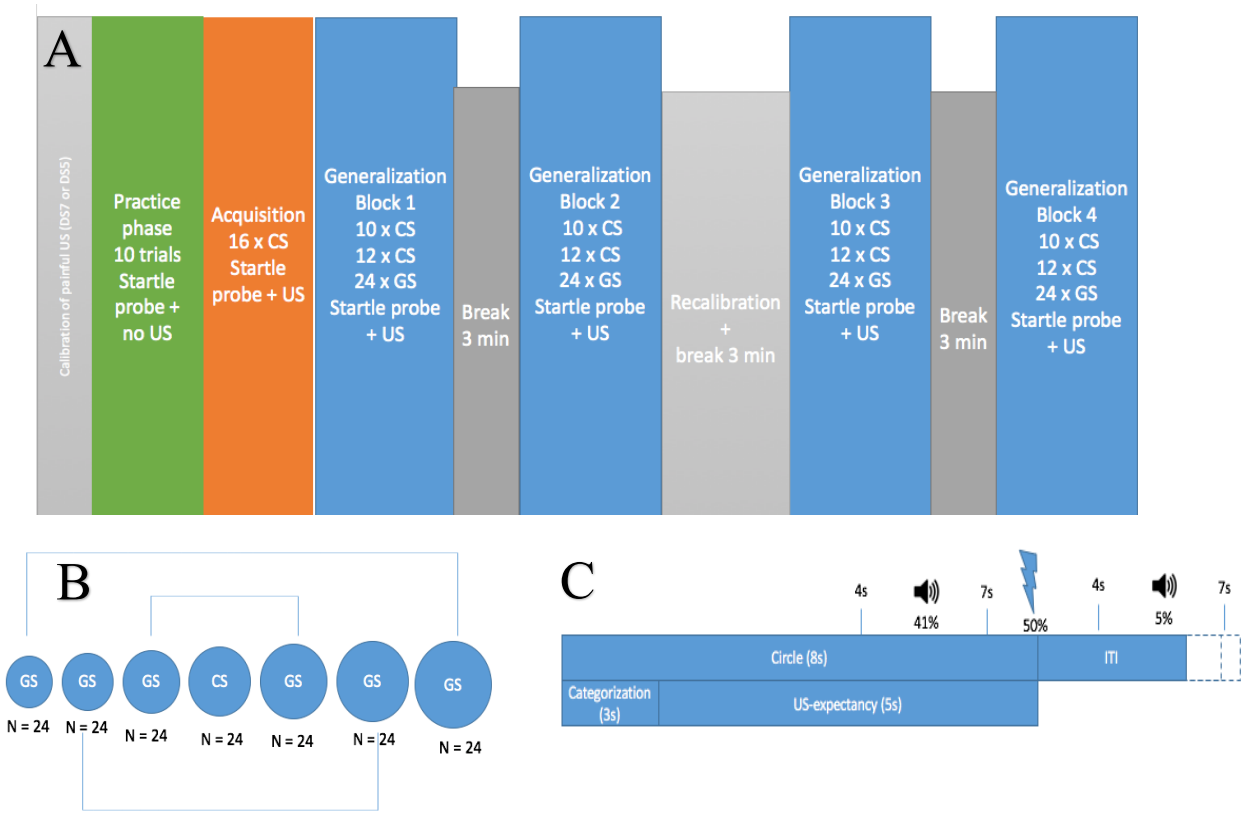

Fig. 1. (A) Overview of the experimental protocol. (B) Overview of the different stimuli including number of trials during generalization phase. (C) Overview of one trial structure. The circle was presented for 8 seconds. During generalization, participants had 3 seconds to categorize the stimulus as CS or as novel (GS). After 3 seconds this scale disappeared and a visual analogue scale (VAS) appeared where participants rated US-expectancy. The CS remained partially reinforced (50%) to avoid extinction.

2.5 Data analysis

A repeated measures analysis of variance (RM ANOVA) was used to analyze the probability that a certain stimulus was misperceived as the CS.

Behavioral data were analyzed with three mixed models. Model 1 only included a random intercept and Stimulus and Stimulus as main effects. Next, perception was added, resulting in a mixed model including Stimulus, Stimulus and Categorization as main effects and Categorization x Stimulus and Categorization x Stimulus^2 as interaction effects. Post-hoc tests were conducted to investigate whether the generalization stimuli were rated significantly different on US-expectancy compared to the CS. Furthermore, data were divided based on categorization (categorized as either CS or novel) to investigate the role of perception upon the gradient in each categorization category separately.

Since stimuli equally distanced from the CS (GS_4 and GS_{10}, GS_5 and GS_9, GS_6 and GS_8) elicited a comparable amount of skin and startle responses, symmetrical GSs were merged to ensure sufficient data for reliable estimates when accounting for perception (hereafter mentioned as Stimulus_merged). Startle and skin data were analyzed with similar models as US-expectancy. First, the base model included Stimulus_merged as main effect. Next, the same data were reanalyzed including perception, resulting in mixed model including Stimulus_merged and Categorization as main effects and Categorization x Stimulus_merged as interaction effect. Post-hoc tests were conducted to compare startle responses elicited by the several Stimulus_merged with startle responses elicited by the CS (either preceded by a CS-percept or a GS-percept) and to examine at which Stimulus_merged startle potentiation occurred, compared to baseline startle (ITI).

Exploratively, we reran all analyses, including STAI-T as covariate. Main effects and interaction effects with STAI-T were followed up.

An alpha of .05 was set for all statistical tests and adjusted Bonferroni correction was used for post-hoc testing. Greenhouser-Geisser corrections are reported when necessary. Data were analyzed using SPSS 24 software.

3 Results

3.1 Percentage categorized as CS+

Analyzing the probability to perceive a stimulus as CS revealed a gradient similar to the typical generalization gradient. Figure 2 shows that during stimulus generalization, the probability a stimulus was perceived as CS peaked at CS itself (M = .56) and decreased as the CS-GS dissimilarity increased, confirmed by a RM ANOVA analysis which showed a significant main effect of Stimulus ($F(6,234) = 9.94$, $p < .001$, $\eta^2_p = .20$, $\varepsilon = .39$) on the probability of perceiving a stimulus as CS. This means, when the physical CS-GS similarity decreased, the chance of misperception decreased. Across the group, the CS was correctly

identified in only half of the actual CS trials (56%). Next, categorization probabilities between CS and the different GSs were compared by post hoc pairwise comparisons. The GSs on the left side of the CS were almost equally identified as CS as the CS itself whereas $GS_{8,}$ GS_9 and GS_{10} were more often identified as a novel stimulus compared to the CS (*p*'s < .001). This yielded an asymmetrical gradient with a higher probability to misperceive the smaller circles (GS_4, GS_5, GS_6) as CS than the bigger circles (GS_8, GS_9, GS_{10}).

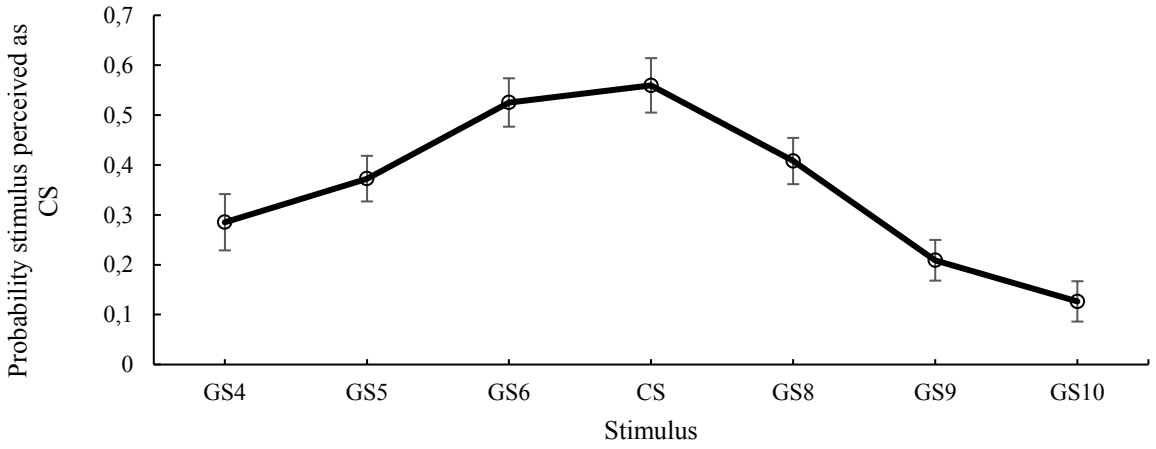

Fig. 2. Categorization probabilities plotted on a physical dimension, including the CS. Note the error bars represent standard errors. CS = conditioned stimulus, GS = generalization stimulus.

3.2 US-expectancy

Figure 3 shows the expected bell shape gradient, indicated by main effects of Stimulus ($F(1,439.28) = 49.86$, $p < .001$) and Stimulus ($F(1,439.23) = 48.95$, $p < .001$). Post-hoc testing revealed that, except GS_6, all other generalization stimuli were rated significant lower on US-expectancy compared to the CS (*p*'s < .001). Next, we reran the same model, including Categorization as predictor and its interaction with Stimulus and Stimulus to investigate the role of perception upon the gradient. We found again main effects of Stimulus ($F(1,436.40) = 37.50$, $p < .001$) and Stimulus ($F(1,436.47) = 32.64$, $p < .001$). The (mis)perception of a stimulus as CS led to higher US-expectancy ratings compared to perception as GS (main effect of Categorization: $F(1,437.36) = 6.90$, $p = .009$). There was a significant Categorization x Stimulus^2 interaction effect ($F(1,436.74) = 4.84$, $p = .03$) but no Categorization x Stimulus ($F(1,436.87) = 2.05$, $p = .15$) interaction effect. Next, data were reanalyzed separately for each perceptual category (categorized as either the CS or GS). Preceded by a CS-percept, we found a linear ($F(1,173.25) = 4.61$, $p = .03$) but no exponential effect ($F(1,173.09) = 1.70$, $p = .20$) of

Stimulus on US-expectancy. When the stimulus was categorized as GS, we found a typical exponential generalization pattern (linear effect: $F(1,225.37) = 70.87$, $p < .001$, exponential effect: $F(1,225.34) = 79.67$, $p < .001$).

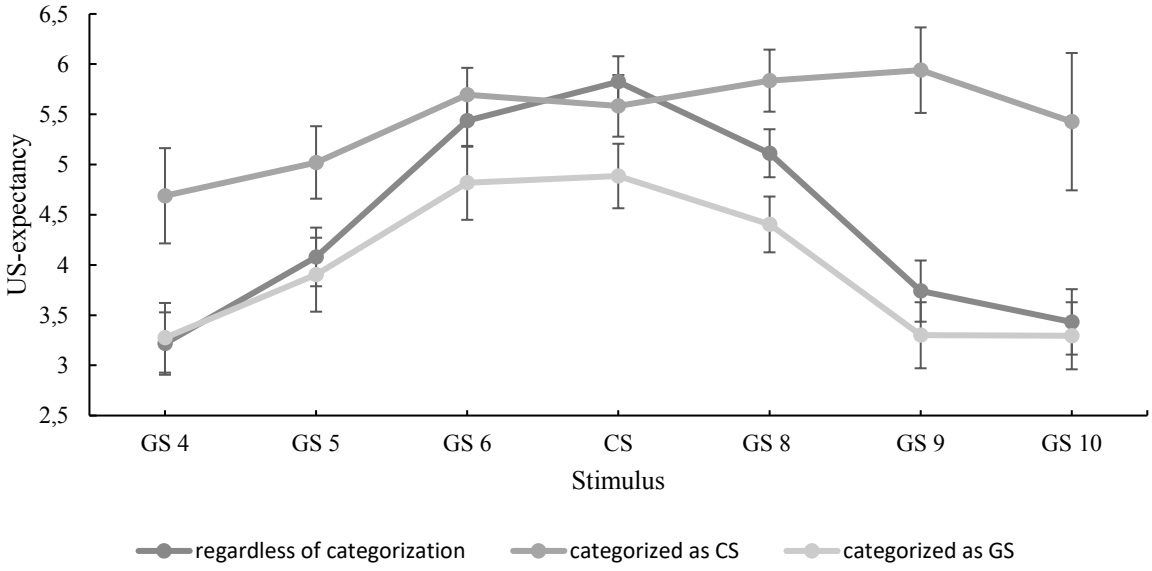

Fig. 3. Mean US-expectancies for all stimuli, (in)dependent of stimulus categorization. Note the error bars represent standard errors. CS = conditioned stimulus, GS = generalization stimulus.

3.3 Orbicularis Oculi

The first mixed model analysis revealed a main effect of Stimulus_merged ($F(1,175) = 25.31$, $p < .001$). This means that the startle was significantly determined by the presented Stimulus_merged, as graphically displayed in Figure 4. The same model including Categorization as a predictor and its interaction with Stimulus_merged revealed again a main effect of Stimulus_merged ($F(1,173) = 17.93$, $p < .001$. In addition, the (mis)perception of a stimulus as CS led to higher startle responses compared to perception as GS (main effect of Categorization: $F(1,173) = 8.83$, $p = .003$). There was no significant Categorization x Stimulus_merged interaction effect ($F(1,173) = 2.53$, $p = .11$).

Post-hoc testing revealed that, when the stimulus was perceived as CS, startle responses elicited the same amount of fear in all Stimulus_merged (p's ≥ .22). When the stimulus was perceived as GS, all generalization stimuli, except GS_6_GS_8, elicited significant lower startle responses compared to the CS (p's ≤ .002). Next, fear potentiated startle responses during ITI were compared to startle responses during the generalization blocks. Except startle responses

elicited by GS_4_GS_{10} merged, all startle responses during generalization were significantly higher than startle responses during ITI (p's ≤ .002).

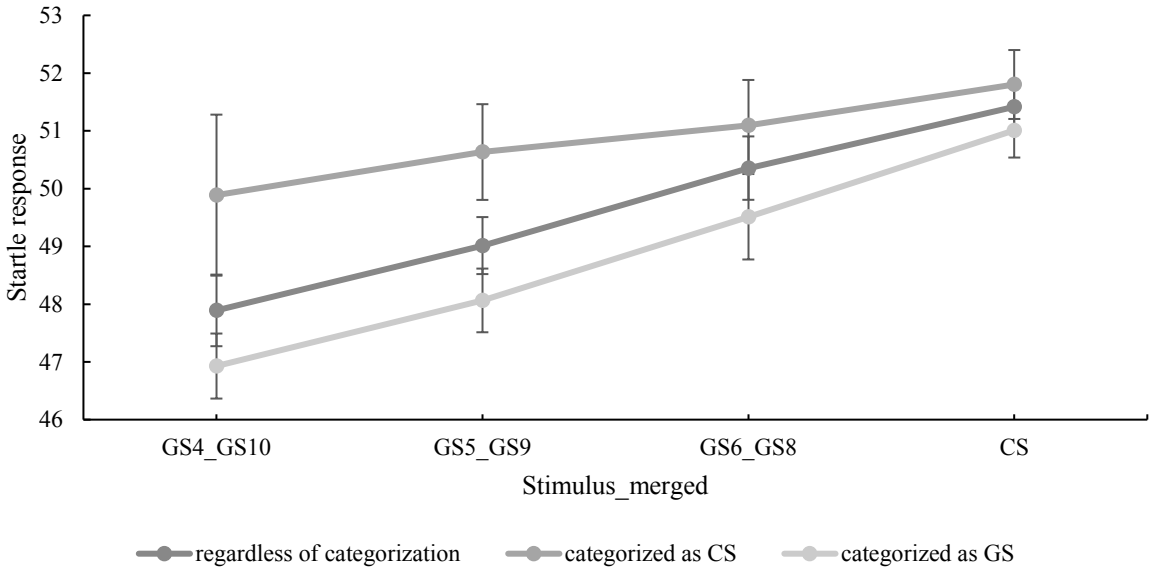

Fig. 4. Mean startle responses, (in)dependent of stimulus categorization. Note that symmetrical stimuli are merged into one category. Note the error bars represent standard errors. GS = generalization stimulus, CS = conditioned stimulus.

3.4 Skin conductance response

Analysis of skin conductance responses (see Figure 5) revealed the following results. The first mixed model analysis showed no main effect of Stimulus_merged (F(1,92.12) = 2.48, p = .12). Reanalyzing the same data including Categorization as predictor revealed no significant main effect of Stimulus_merged (F(1,90.13) = 2.07, p = .15) or Categorization (F(1,90.26) = .90, p = .35). Furthermore, no significant Categorization x Stimulus_merged interaction effect was found (F(1,90.25) = .13, p = .73).

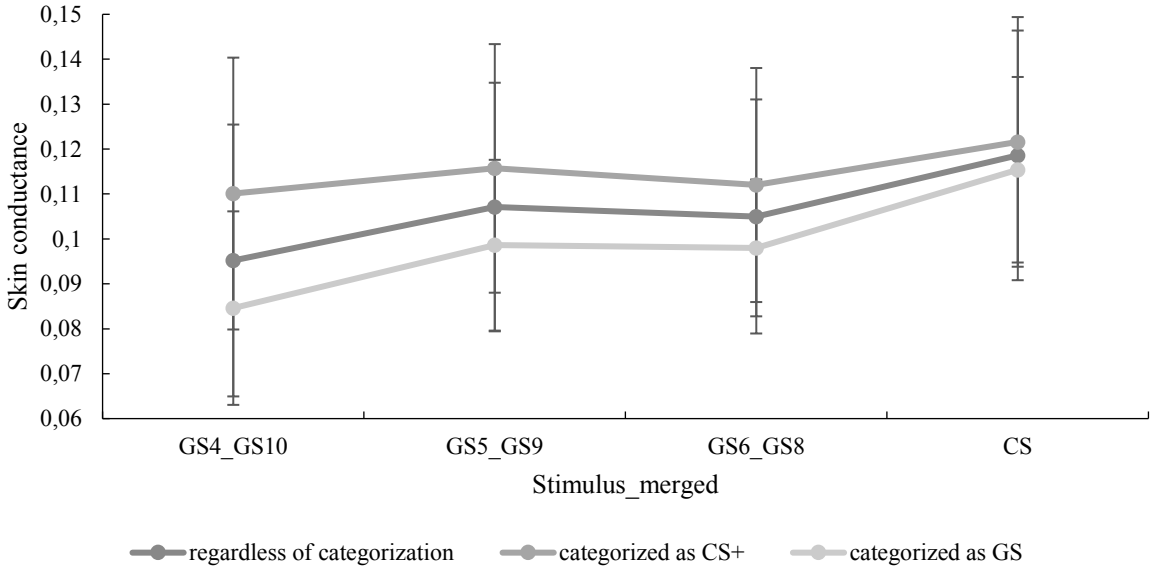

Fig. 5. Mean skin conductance responses, (in)dependent of stimulus categorization. Note that symmetrical stimuli are merged into one category. Note the error bars represent standard errors. GS = generalization stimulus, CS = conditioned stimulus.

3.5 STAI and generalization gradients

All previous analyses were repeated with STAI-T as an additional covariate. The probability to misperceive a GS as CS was not significantly different between high and low trait anxiety participants ($F(6,228) = 1.99$, $p = .07$, $\eta^2_p = .05$). Reanalyzing US-expectancy revealed no main effect of STAI-T ($F(1,243.90) = .01$, $p = .95$). However, a significant interaction effect with categorization was found ($F(1,434.71) = 25.33$, $p < .001$). Reanalyzing startle data also revealed no main effect of STAI-T ($F(1,170) = .05$, $p = .83$) and no interaction effect with Categorization ($F(1,170) = .50$, $p = .48$) and Stimulus_merged ($F(1,170) = .23$, $p = .63$). Analyzing skin conductance revealed no main effect of STAI-T ($F(1,20.11) = .15$, $p = .70$). Neither an interaction effect between STAI-T and Stimulus_merged ($F(1,88.09) = 2.47$, $p = .12$), nor an interaction effect between STAI-T and Categorization was found ($F(1,88.07) = .06$, $p = .81$).

4 Discussion

For almost a century, researchers have been attempting to identify mechanisms underlying the generalization of fear. Recent work suggests that the well-known generalization gradient could be obtained by plotting the probability of incorrect CS-percepts against a stimulus continuum based on physical similarity (including GSs and CS). This resulted in a curve that strongly resembled the typical generalization gradient. The purpose of this study was to

investigate the role of perception upon generalization gradients in healthy individuals within a classical fear conditioning paradigm. To this end, a categorization task was incorporated in a generalization protocol. We found (I) the typical bell shape gradient, (II) that generalization stimuli were often misperceived as the CS and (III) that the misperception of a GS as CS strongly boosted fear responses.

Similar to previous work (Lissek et al., 2010; Struyf et al., 2017), we found the typical bell-shape pattern. Fear responses peaked at presentation of the CS and decreased as more the physical distance between CS and GS increased. Such gradients have been reliably found in both humans and animals along diverse stimulus dimensions such as sound frequency and light spectra (Ghirlanda & Enquist, 2003). However, some studies failed to find a comparable symmetrical gradient. Often, these studies used a differential paradigm, including both CS+ and CS- (never co-terminated with US), resulting in an asymmetrical gradient (Ghirlanda & Enquist, 2003; Struyf et al., 2017). According to associative learning, GSs on the side of the CS+ away from the CS-, evoked heightened fear responses than GSs within the CS-/CS+ spectrum, better known as area-shift (Ghirlanda & Enquist, 2003; Hanson, 1959). In addition, the peak response was no longer located at the CS+ but at the GS adjacent to the CS+ (Hanson, 1959). Alternatively, a study of Holt et al (2014) revealed that generalization did not occur above discrimination thresholds (i.e., can be clearly discriminated from the CS+). As a consequence, not finding a comparable gradient could be attributable to the use of stimuli which are clearly distinguishable from the CS+, resulting in less generalization.

Vervliet, Kindt, Vansteenwegen and Hermans (2010b) found that verbal instructions influenced fear generalization by focusing attention to a specific stimulus. In their study participants were, prior to conditioning, informed which information was relevant (either the shape or the color) for the particular task. Generalization was strongest towards the stimulus that shared the feature instructed by the researcher (shape in the SHAPE group and color in the COLOR group). In analogue, we expected that including a perception task would implicitly focus attention to physical similarities and consequently would influence the gradient, since better attention could lead to better discrimination. The observation of similar gradients as previous studies (Lissek et al., 2010; Struyf et al., 2017) suggests that the mere introduction of categorization task seems to have a limited impact on behavioral responses. Nevertheless, future studies should include a control group without the categorization task to quantify the effect of the task on behavioral responses.

In line with Laufer and Paz (2012), we also found a curve that strongly resembled the typical bell shape generalization gradient for the probability distribution of a perceptual

response. This means, this gradient peaked at CS and gradually declined as physical distance between the CS and the GS decreased. The probability to misperceive a stimulus as CS seems to be a function of physical CS-GS similarity as this probability decreased when the similarity decreased. Participants were surprisingly bad in identifying the stimuli as only half of the actual CS trials were correctly identified (56%), contrary to a study of Struyf et al. (2017), where both the CS+ and the CS- stimuli were almost always correctly identified (CS+: 100%, CS-: 95%). In the study of Struyf et al. (2017), the generalization test occurred immediately after differential conditioning, which means, representation of the CS was less likely modified by memory processes. In another study (Laufer & Paz, 2012), subjects had to indicate whether the presented tone was the CS-tone or not during a similar perceptual categorization task. In this study, the CS was correctly identified in 70% of the trials. The reduction of accuracy, compared to Struyf et al. (2017), could be due to the larger amount of trials, as more trials increase the difficulty to correctly identify the CS. However, the CS was still more correctly identified compared to our study. A potential explanation is that the rewards and visual feedback in the study of Laufer and Paz (2012) improved participants' ability to correctly identify the CS as it could serve as a motivating factor for better performance. Nevertheless, as previous studies revealed that the CS was not consistently identified as the initial trained stimulus during generalization phase, the perfect discrimination between stimuli can be questioned, suggesting the potential role of perception in fear generalization.

It is interesting to note that the highest probability of incorrect CS-percepts was found for the same GS where also behavioral differences between healthy controls and clinical samples have been reported (Lissek et al., 2014). This suggests that inferences should be made cautiously, as different mechanisms may result in comparable gradients.

Furthermore, the aim of this study was to investigate the role of perceptual alterations in a context of fear generalization. We hypothesized that a perceptual failure to discriminate between the CS and the GS might broaden the gradient. In line, we found different generalization gradients when accounting for perception. When the stimulus was perceived as CS, a linear but no exponential effect of Stimulus was found. More precisely, the misperception of a stimulus as CS led to generalized higher fear responses, irrespective of the presented stimulus. As a consequence, misperception of a stimulus as CS led to a broadened gradient. The gradient observed for stimuli that were perceived as novel, peaked at the CS and gradually declined as the physical similarity between the presented stimulus and the initial fear-evoking stimulus decreased. This suggests that differences in gradients could be driven by an (in)ability to discriminate.

In line with previous research (Lissek et al., 2010; Torrents-Rodas et al., 2013) we found similar gradients for both psychophysiological and self-reported measures. This is, a downward gradient as the presented stimulus differentiated from the conditioned danger cue. Startle responses were significantly determined by the presented stimulus. Moreover, startle responses increased when the stimulus was identified as CS. This means that perception of a stimulus as CS strongly boosted both psychophysiological and behavioral fear responses. In addition, we found a significant startle potentiation compared to ITI startle responses in both categorization categories.

Although skin conductance responses are frequently used to operationalize fear (Hovland, 1937; Vervliet et al., 2004), we could not find the same significant effects for skin conductance. Possibly this could be explained by the short inter-trial-intervals. As changes in skin conductance develop and decrease slowly, the 4-7 seconds inter-trial intervals used in this experiment could possibly not permit an entire recovery in baseline level resistance before eliciting another response. As a result, responses between two consecutive stimuli should be separated properly by applying long ITIs (see Dawson, Schell, & Filion, 2007). Furthermore, numerous studies (Dawson & Biferno, 1973; Dawson, Catania, Schell, & Grings, 1979) revealed that skin conductance responses reflect the cognitive level of contingency learning. In practice, this implies that only participants who were able to identify the correct CS-US contingencies showed significant skin conductance learning (see Hamm & Weike, 2005). Given that participants in this study were surprisingly bad in identifying the stimuli, it is plausible that some participants did not recall the correct CS-US contingency and consequently did not reveal significant skin conductance learning. Alternatively, skin conductance is very sensitive to habituation (Frith & Allen, 1983). Repeated exposures of a neutral stimulus could lead to decreased attention and consequently lead to decrement in skin response, called habituation (Hay & Sokolov, 1966). The failure to find the typical generalization gradient might be attributed to this decreased skin response. Finally, Dunsmoor, Kroes, Braren and Phelps (2017) demonstrated that fear generalization is dependent of threat intensity. For ethical reasons, the shock intensity was calibrated to a level that participants rated as painful but tolerable. Possibly, participants opted for a less painful, comfortable intensity. As a consequence, the intensity of the electrical stimulation might not be sufficient to elicit a significant potentiation and in addition, generalization in all participants.

Based on previous report describing that high trait anxiety could lead to generalized anxiety disorder (Rapee, 1991) and anxiety patients are more susceptible for conditioning-induced inability to discriminate GSs from the initial fear-evoking stimulus (Laufer et al., 2016), we

expected to find that high trait anxiety participants would misperceive more stimuli as CS and consequently had a wider gradient, compared to low trait anxiety participants, as more CS-percepts would lead to more fear responses. However, we could not find a significant effect of trait anxiety on neither the probability of CS-percepts nor the behavioral and fear responses. This is in line with more recent observations of Struyf et al. (2017) that high anxious patients showed similar gradients as low anxious patients, to stimuli perceived as novel. Possibly, such differences could only be found in patients with clinical levels of anxiety, whereas only participants with non-clinical levels of anxiety participated the current study.

As illustrated, various mechanisms have been proposed to explain differences in behavior between patients and controls. Differences in fear generalization could be the result of a cognitive bias (i.e., better-safe-than-sorry), a memory bias or an impairment in discrimination acuity. These alternatives do not have to be mutually exclusive. For instance, this latter alternative, perceptual discrimination, does not have to be a binary decision task (either perceive it right or perceive it wrong) but might be influenced by a memory bias. Performance to discriminate tend to decrease as the time interval between the initial fear evoking stimulus and the new stimulus increases, since the representation of the fear evoking stimulus could be modified by memory processes. During generalization, GSs are compared to a retrieved representation of the CS. As a consequence, the chance to perceive the new stimulus as initial fear evoking stimulus is a function of the new representation of the stimulus.

Although the current study indicated the importance of perception in fear generalization, there are several limitations. First, since this study served as an initial assessment in order to investigate the role of perception in fear generalization, it only included a small sample of healthy students. Inferences between healthy controls and patients cannot be made. To quantify the account of perception in anxiety patients, further studies should include clinical participants. Second, only an electrocutaneous stimulus was used as US. It might be interesting to investigate whether other types of stimulation, both appetitive and aversive, lead to the same amount of generalization, with a comparable influence of perception. Finally, a replication of the current study with longer time intervals for measuring skin conductance to assure a complete decline to baseline level and a control group to quantify the effect of the categorization task on behavioral responses will be interesting.

Despite the demonstrated impact of perception, physical features seem to maintain a major role in fear generalization. However, real-world fear learning often occurs to complex stimuli that cannot be represented at a physical dimension. Instead of physical similarity, real-world

fear learning is based on an associative or semantic network. Fear generalization within this context remains unclear.

In sum, this study demonstrates that misperception of new stimuli as the CS tend to broaden generalization gradients. However, perception is underestimated in current therapies. Different mechanisms might require different therapeutic interventions so it is crucial to understand the underlying mechanism of this spreading of fear. As this study is innovating, further research is required at both clinical and neuropsychological level of fear generalization, since it could ameliorate future therapies.

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Appendix

Appendix 1: Exclusion criteria

Beste proefpersoon,

Met toestemming van de Commissie Medische Ethiek van de UZ KU Leuvenzijn er bepaalde uitsluitingscriteria voor dit onderzoek vastgesteld.

Dit zijn namelijk de volgende:

1. **Jonger** zijn dan **18 jaar**.
2. De **Nederlandse taal** niet perfect beheersen;
3. Een **psychiatrische** stoornis;
4. **Hart- en cardiovasculaire** problemen of ademhalingsstoornissen;
5. Een **neurologische ziekte** (bijvoorbeeld epilepsie);
6. Andere **ernstige medische aandoeningen**;
7. Acute of Chronische **pijn;**
8. U door uw arts gevraagd bent om **stressvolle situaties te vermijden**;
9. Een recreationele druggebruiker zijn;
10. Het dragen van een **elektronisch implantaat** (pace-maker of andere medisch-elektrische toestellen);
11. **Zwangerschap;**
12. **Gehoorproblemen** hebben;
13. Je bent herstellende van ernstig trauma of operatie;

Indien tenminste één van de bovenstaande criteria op u van toepassing is, gelieve dit aan te duiden door het passende vakje ("JA") aan te kruisen. Ook indien het om condities gaat die momenteel medisch onder controle zijn (bv. door het nemen van medicatie voor een hartziekte), vragen we u om "JA" aan te kruisen. U dient niet aan te duiden welk(e) van de bovenstaande uitsluitingscriteria op u van toepassing is/zijn. Indien geen van de bovenstaande criteria op u van toepassing is, gelieve "NEEN" aan te kruisen.

☐ JA, één of meer van de bovenstaande uitsluitingscriteria is op mij van toepassing ☐ NEEN, géén van de bovenstaande uitsluitingscriteria is op mij van toepassing

Plaats en Datum Naam en Handtekening
Leuven, ____/_____/_____ _____

Appendix 2: Informed consent

Geïnformeerde toestemming G- 2016 10 641 ***10/10/2016 (Versie 1.2)***

Titel van het onderzoek: **Angst is voor iedereen anders.**

Naam + contactgegevens onderzoeker:
Jonas Zaman
e-mail: jonas.zaman@kuleuven.be
tel: Onderzoeksgroep gezondheidspsychologie Tiensestraat 102 – bus 3726, 3000 Leuven Lokaal 02.89
Tel: +32 16 37 31 97

Doel en methodologie van het onderzoek:
Tijdens deze studie zal u gedurende één laboratoriumsessie gevraagd worden een leertaak uit te voeren waarbij een aantal visuele stimuli, alsook pijnlijke elektrische prikkels aangeboden worden. Daarnaast zal u gevraagd worden enkele vragenlijsten in te vullen. De elektrische prikkels zullen worden toegediend aan de hand van elektroden die worden bevestigd op de huid aan uw niet-dominante arm. U mag zelf de intensiteit van deze prikkels bepalen. De bedoeling is dat de intensiteit als pijnlijk maar tolereerbaar worden ervaren. Als proefpersoon is het uw taak om de verscheidene visuele stimuli zo goed mogelijk te onderscheiden.

Er zijn geen risico's verbonden aan deelname aan dit onderzoek. Alle procedures zijn geheel veilig en leiden niet tot schade. Het experiment zal ongeveer 1 uur duren. Voor deelname aan dit onderzoek ontvangt u een financiële vergoeding van 8 euro, die u via een overschrijving op uw bankrekening ontvangt, of indien u dit wenst 1 leerkrediet. Door deel te nemen aan dit onderzoek, kan u nuttige en interessante ervaring opdoen in verband met onderzoek in de gezondheidspsychologie. Bovendien kunnen de resultaten op termijn een bijdrage leveren aan de ontwikkeling van meer efficiënte en doelgerichte interventies voor gezondheidspsychologische problemen.

Duur van het experiment: Ongeveer 1 uur

➢ Ik begrijp wat van mij verwacht wordt tijdens dit onderzoek.

➢ Ik weet dat ik zal deelnemen aan volgende proeven of testen: - Een leertaak waarbij een aantal visuele stimuli, alsook korte pijnlijke elektrische prikkels aangeboden worden

➢ Ik weet dat er risico's of ongemakken kunnen verbonden zijn aan mijn deelname: - Korte pijnlijke elektrische prikkels

➢ Ikzelf of anderen kunnen baat bij dit onderzoek hebben op volgende wijze:
- Een financiële vergoeding van 8 euro, die u via een overschrijving op uw bankrekening ontvangt, of indien u dit wenst 1 leerkrediet

➢ Ik begrijp dat mijn deelname aan deze studie vrijwillig is. Ik heb het recht om mijn deelname op elk moment stop te zetten. Daarvoor hoef ik geen reden te geven en ik weet dat daaruit geen nadeel voor mij mag ontstaan.

➢ De resultaten van dit onderzoek kunnen gebruikt worden voor wetenschappelijke doeleinden en mogen gepubliceerd worden. Mijn naam wordt daarbij niet gepubliceerd, anonimiteit en de vertrouwelijkheid van de gegevens is in elk stadium van het onderzoek gewaarborgd.

➢ Ik wil graag op de hoogte gehouden worden van de resultaten van dit onderzoek. De onderzoeker mag mij hiervoor contacteren op het volgende e-mailadres:
.....

➢ Voor vragen weet ik dat ik na mijn deelname terecht kan bij: *Jonas Zaman*
e-mail: jonas.zaman@kuleuven.be
tel: Onderzoeksgroep gezondheidspsychologie

Tiensestraat 102 – bus 3726, 3000 Leuven Lokaal 02.09
Tel: +32 16 37 31 97

Appendix 3: Demographic information

Geslacht: M / V

Leeftijd: .....

Is dit de eerste keer dat u aan dergelijk onderzoek deelneemt?
.....

Welke richting studeer je?
.....