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Common and separable behavioral and neural mechanisms underlie the generalization of fear and disgust

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Abstract

Generalization represents the transfer of a conditioned responses to stimuli that resemble the conditioned stimulus (CS). Previous studies on generalization of defensive avoidance responses have primarily focused on fear and have neglected disgust generalization, which represents a key pathological mechanism in some anxiety disorders. In the present study we examined common and distinct mechanisms of fear and disgust generalization by means of a fear or disgust multi-CS conditioning and generalization paradigm with concomitant event-related potential (ERPs) acquisition in n = 62 subjects. We demonstrate that compared to fear, disgust-relevant generalized stimuli (GS) elicited larger expectancy ratings and longer reaction times (RTs) reflecting stronger ratings of 'risk'. On the electrophysiological level, increased P2 amplitudes were found in response to conditioned CS+ versus CS− across both domains, possibly reflecting higher motivational and attentional salience of aversive conditioned stimuli per se. Contingent negative variation (CNV) amplitude was significantly larger for disgust-CS+ than disgust-CS−, showing stronger preparation of the disgust US. Additionally, we found that the contingent negative variation (CNV) fear generalization gradient, and CNV amplitude were increased with similarity to CS+. In contrast the CNV to disgust-GS did not differ and did not reflect disgust generalization. Together this may indicate that the CNV represents a highly fear-specific index for generalization learning. This study provides the first neurobiological evidence for common and distinct generalization learning in fear versus disgust suggesting that dysregulations in separable defensive avoidance mechanisms may underly different anxiety disorder subtypes.

Keywords: Multi-conditioned stimulus conditioning; fear; disgust; event-related potentials; defensive responses

1. Introduction

Appropriate fear generalization represents an evolutionarily adaptive defensive mechanism allowing organisms to respond immediately to and avoid future potential dangers (Arnaudova et al., 2017). However, fine-grained balance between generalization and discrimination is vital for the organism to distinguish between safety threat signals in order to facilitate adaptive behavior in an ever changing environment (Sangha et al., 2020). The vast majority of previous studies on the underlying defensive and learning mechanisms have employed classical Pavlovian fear conditioning paradigms, during which repeated pairing with an aversive stimulus (Unconditioned Stimulus: US), renders an initially neutral stimulus (Conditioned Stimulus: CS+) or similar stimuli (Generalized Stimulus: GS) that resemble the original CS, as a trigger for the fear response (Conditioned Response: CR) (Yau & McNally, 2018).

The Pavlovian fear conditioning paradigm has been widely employed to examine mechanistic dysregulations in anxiety-related disorders, characterized by over-generalization, impaired extinction, and excessive avoidance (Duits et al., 2015; Pittig et al., 2018). Specifically, while no discrimination difference (CS+ minus CS−) was observed doing conditioning, anxiety patients exhibited stronger expression of fear to the CS− (safety signal; predicting the absence of an aversive US), which may reflect an over generalization to a safety cue or deficient fear inhibition to the safety signal (Lissek et al., 2013; Jovanovic et al., 2010). Anxious individuals have shown decreased ventromedial prefrontal cortex engagement during both, conditioning and extinction recall indicating dysregulated safety and fear learning (Marin et al., 2017). Furthermore, patients with generalized anxiety disorders exhibit a shallower generalization gradient suggesting that an overgeneralization of fear to safe stimuli may contribute to the development and maintenance of pathological anxiety (Lissek et al., 2014).

While a large body of research has investigated the important role of fear in anxiety disorders, accumulating evidence suggests that disgust-related mechanisms may also contribute to psychopathological dysregulations (e.g., Armstrong & Olatunji, 2017; Cisler et al., 2009; Ludvik et al., 2015). Both, fear and disgust represent adaptive defensive-avoidance mechanisms which have evolved to avoid potential threats in terms of predators or contaminations, respectively (Woody & Teachman, 2000). Individuals with high disgust proneness are more susceptible to developing dysregulated avoidance responses in terms of contamination-associated obsessive-compulsive disorder (OCD), blood-injection-injury phobia, and small animal phobias (e.g., Bhikram et al., 2017; Cougle et al., 2016; Hirai et al., 2018; Olatunji et al., 2017). Woody et al. (2005) moreover demonstrated that disgust plays an important role in avoidance symptoms in spider phobias such that individuals with high fear experienced both, stronger anxiety and disgust as compared to individuals with low fear. Although OCD and post-traumatic stress disorders (PTSD) were removed from anxiety disorder category in the DSM-5, both conditions are closely linked to exaggerated fear and disgust reactivity (McGuire et al., 2016). In parallel to studies examining dysregulations in fear learning, Pavlovian disgust conditioning models have been successfully applied to determine disgust-associated pathomechanisms in contamination-based OCD (Stein et al., 2001) as well as PTSD (Badour et al., 2013). Furthermore, accumulating evidence suggests a direct association between symptoms of contamination-based OCD and disgust sensitivity (Olatunji et al., 2010), and – in contrast to fear – acquired disgust responses are highly resistant to extinction as indexed by subjective experience as well as behavioral indices (Mason, & Richardson, 2010).

Further evidence for distinct yet also interacting mechanisms underlying fear and disgust learning comes is provided by developmental studies reporting that children experienced increased disgust after vicarious fear learning by presenting novel animals (CSs) with adult faces expressing fear (USs) as well as increased fear experience after vicarious disgust learning (Askew et al., 2014). Klucken et al. (2012) investigated the neural basis of fear- and disgust-conditioning and demonstrated that both aversive learning mechanisms involved common neural circuits encompassing the occipital cortex, the nucleus accumbens, the orbitofrontal cortex, and the dorsal anterior cingulate cortex, with higher disgust sensitivity being associated with increased insula activation. However, common and distinct generalization gradients and underlying differentiable electrophysiological responses during fear- and disgust-generalization have not been systematically examined.

An increasing number of recent studies examined the temporal dynamics of fear conditioning by means of electrophysiological approaches such as event-related potentials and demonstrated that early attention components, including P2 and P3, showed enhanced amplitude in response to CS+ compared to CS− (Junghöfer et al., 2015; Junghöfer et al., 2017; Sperl et al, 2021). Further, studies focusing on the late positive potential (LPP) component suggest a sustained attention to CS+ probably representing the newly acquired fear (Pavlov & Kotchoubey, 2019; Ventura-Bort et al., 2016). Krusemark and Li (2011), employed visual fear and disgusting stimuli of natural objects in a visual search paradigm with concomitant event-related potential (P1) acquisition, contrasting the effects of the two defensive responses on early neural indices of sensory perception and attention. The results showed that, compared to neutral stimuli, fear images elicited a larger P1 (96 ms) amplitude whereas disgust images evoked an attenuated P1 amplitude, demonstrating an opposite pattern of early sensory discrimination. Despite these initial findings on differential early perceptual discrimination the common and separable ERP-responses underlying generalization may further allow to determine the process-specific contribution of neurobiological separable fear and disgust mechanisms to segregate separable psychopathological markers for fear and disgust-related anxiety disorders.

Against this background the present study aimed to determine common and distinct behavioral and neural signatures of fear and disgust generalization during associative learning. Particularly, to ensure a sufficient signal-to-noise ratio, we adopted the MultiCS conditioning learning paradigm. In MultiCS conditioning, many similar stimuli were paired with the aversive US (CSs-US association), whereas the same number of similar CS was presented alone (CSs-no US association) (Rehbein et al., 2018). MultiCS conditioning paradigms use a series of similar and complex stimuli to comprise an affective category, making the associative learning process more complex and avoiding rapid extinction in the generalization test (Steinberg et al., 2012; Steinberg et al., 2013). To avoid carry over effects, habituation and expectations in the experimental design participants were divided into two groups in this study, with one group completing the fear generalization paradigm, and the other group completing the disgust learning paradigm. Thus, we analyzed the acquisition and the generalization phase of these two aversive conditioning processes. We hypothesized that the US expectancy of CS+/GS+ would be significantly higher than that of CS−/GS−. Based on the different evolutionary functions of disgust (avoidance of contamination from a class of stimuli) and fear (anticipation of physical attack e.g. in a highly specific context) (e.g. Curtis, de Barra., & Aunger, 2011) we expected enhanced generalization for the conditioned disgusting-CS+ as compared to the fearful-CS+. On the ERP activation level, we hypothesized that (1) fear-conditioned and disgust-conditioned CS+ and GS+ would evoke an early attentional bias reflected by P2; (2) LPP amplitude would be modulated by both stimuli types reflecting that both stimuli types capture strong sustained attention possible suggesting threat monitoring; and (3) differential electrophysiological modulation of disgust-relevant CS/GS versus the fear-related CS/GS, in particular larger LPP amplitudes response to conditioned disgust-CS+ than to fear-CS+ given that previous studies reported a larger attentional bias for disgusting than fear stimuli (Charash & McKay, 2002; Carretié et al., 2011) and stronger interference by disgusting stimuli (Cisler et al., 2009; van Hooff et al., 2013).

2. Materials and Methods

2.1 Participants

A priori sample size calculation (G*Power) indicated that 52 participants in total would be sufficient to achieve a medium effect size of 0.20, an alpha level of 0.05, and a 1-beta level of 0.80 (Erfelder, Faul, & Buchner, 1996; Faul et al., 2007; Hendrikx et al., 2021). We recruited 62 healthy college participants (27 women; $M_{age} = 20.87$; $SD_{age} = 2.51$) who were randomly assigned to either fear- or disgust-associative learning (n = 31 per group; $Age_{fear} = 21.07 \pm 2.92$; $Age_{disgust} = 20.68 \pm 2.09$). Five participants (three in fear group: $N_{fear} = 28$ and two in disgust group: $N_{disgust} = 29$) were excluded from the final data analysis because they rated the US expectancy of the CS− larger than that of the CS+. All participants had normal or corrected vision and had no history of psychiatric or neurological diseases (according to self-report). All subjects had a BDI score < 13 and STAI < 50 which is in the normal range and thus indirectly confirm the absence of mood, anxiety disoders. Participants provided written informed consent and received monetary compensation. The research was approved by the Medicine Ethics Committee of Shenzhen University and the experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration.

2.2 Stimuli

2.2.1 CS and GS

The generalized stimuli used in this study were a modified version of those used in a previous study to maximize signal to noise ratio (Lissek et al., 2008). The conditioned and generalized stimuli were a series of shapes including a circle, triangle, square, and parallelogram, and each shape was presented in a separate block. Specifically, each shape was designed with 10 stimuli, continuously increasing in size (5.08–14.22 cm in diameter, 20% increments) (Figure 1). The assignment of CS+ was counter-balanced between blocks. For two of the four blocks, the smallest stimuli (5.08 cm) served as CS+ paired with the US (75% reinforcement), and the largest stimuli served as CS− (14.22 cm). In the remaining two blocks, the largest stimuli were used as CS+, and the smallest stimuli were used as CS−. The remaining stimuli in the middle served as GS.

Figure 1. The conditioned stimuli (CS) and generalized stimuli (GS) used in the present study, adapted from the procedures of Lissek et al. (2008). The database included four different shapes, each with 10 stimuli continuously increasing in size. The smallest and the largest stimuli served as CS+ and CS−, respectively, and the CS+ and CS− were counterbalanced across participants. The remaining stimuli served as GS.

2.2.2 US

The USs were chosen from the Threat Picture System, including 36 different fear-evoking pictures (e.g., a spider) and 36 different disgust-evoking pictures (e.g., vomit). The arousal of the fear-eliciting set ($M = 6.16$; $SD = .58$) was significantly higher than that of the disgust-related set ($M = 5.54$; $SD =0.47$, $t(80) = 7.329$, $p < .001$, Cohen's d = 1.17). Importantly, the ratings of fear in the fear set ($M = 4.80$; $SD = 1.06$) were larger than those in the disgust set ($M = 3.32$; $SD = .86$; $t(80) = 12.715$, $p < .001$, Cohen's d = .87), and the ratings of disgust in the disgust category ($M = 5.84$; $SD = 1.21$) were higher than those for the fear category ($M = 4.05$; $SD = .97$; $t(83) = 22.737$, $p < .001$, Cohen's d = 2.40). The Threat Picture System has been validated in previous studies (Wang, J. et al., 2021).

2.3 Procedure

The stimuli were presented via E-Prime (version 3.0) in a pseudo-randomized order with a gray background. The experimental procedure consisted of four blocks and each block included two parts, i.e. the acquisition and the generalization phase (Figure 2). Earlier studies showed that providing explicit information about the CS-US contingency to the participants before the formal experiment led to stronger fear conditioning (Duits et al., 2017). However, to provide a more ecologically valid learning we did not provide explicit instructions and, participants were required to learn the threat association.

Each of the four CS/GS types was presented in a separate block (10 stimuli per block) and four blocks (circle, triangle, square, and parallelogram) were displayed in a randomized order. During the acquisition phase, two pictures (those of the smallest and the largest size) were employed as as conditioned stimuli, one paired with fear US or disgust US (CS+) with a 75% reinforcement schedule (9/12), and the other used as a safety cue (CS−) presented with a blank picture. Each block included 12 repetitions of each CS (48 trials in total). In the generalization test phase, each of the eight generalized stimuli, varying in size, were displayed six times (24 trials in total). Furthermore, we divided all generalized stimuli into four groups: every two neighboring intermediaries were averaged to form a level of similarity with CS+ (e.g., [Ring 2 + Ring 3] / 2 = GS1) (Lissek et al., 2008). Thus, the test phase included four types of GS: GS1; GS2; GS3, and GS4; each condition including 48 trials. To prevent extinction, the CS+ and CS− were presented six times in each block, and the CS+ was followed by the US with a 50% reinforcement rate (Dunsmoor & Murphy, 2014).

In both phases, a central fixation cross was presented for 300–500 ms first followed by a blank screen (300–500 ms) on each trial. The CS/GS was subsequently displayed, and the duration of each CS/GS was 3000 ms. Participants were asked to evaluate the probability of US occurrence on a 9-point scale (1 = least likely, 5 = moderately likely, 9 = most likely) during this period. The US pictures were displayed for 1000 ms and the inter-trial interval (ITI) varied between 800 and 1000 ms.

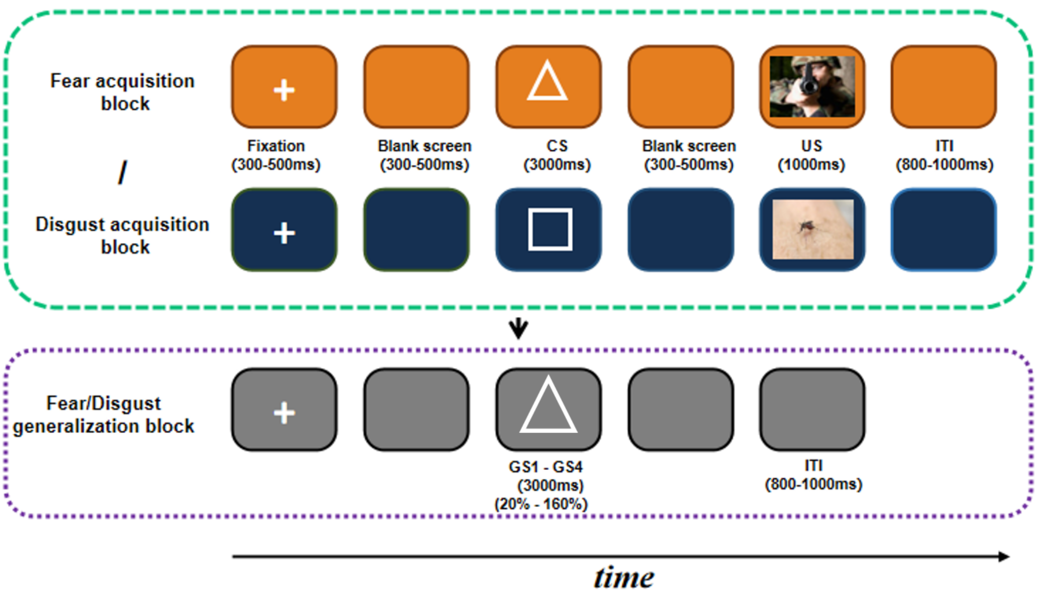

Figure 2. Fear and disgust acquisition and generalization paradigm. A circle, triangle,

square, and parallelogram with systematic size variation were used as CS/GS and each shape was presented in a separate block. Each block included two phases: acquisition and generalization. (A) Aversive acquisition paradigm: the smallest size stimuli served as the CS+ that paired with the US (75% reinforcement rate) and the largest size stimuli served as the CS− and presented alone. The assignment of CS+ was counterbalanced across the participants. (B) Stimuli of +20–160% size from CS were used as GS.
CS = conditioned stimulus; GS = generalized stimulus; US = unconditioned stimulus

2.3.1 ERP recordings and data pre-processing

Continuous electroencephalogram (EEG) data were collected by using a standard 10–20 acquisition EEG cap with a 64-channel Brain Products system (Brain Products GmbH, Munich, Germany; passband: 0.05–100 Hz, sampling rate: 500 Hz). The reference electrodes were placed on the mastoids, with ground electrodes located on the medial frontal line. Electro-oculogram data were collected via facial electrodes located above and below the left eye and the outer canthi of each eye. The impedance was maintained below 10 kΩ during the recordings. ERP data were obtained using the EEGLAB Matlab toolbox (Delorme & Makeig, 2004) and were band pass filtered from 0.1 to 20 Hz. Blinking and eye movements were corrected by using independent component analysis and trials with activities exceeding 80 or below -80 μV were removed. The EEG data were segmented from 100 ms before stimulus onset to 800 ms after onset.

2.4 Statistics

US expectancy ratings and RTs for CSs/GS were computed separately for acquisition and generalization phases. Data of US expectancy ratings and reaction times in the acquisition phase were analyzed by using a two-way repeated measures ANOVA model with Conditioned Stimulus Type (CS+, CS−) as the within-subject factor and, Emotion Type (fear, disgust) as the between-subject factor. A repeated measures 2 × 6 ANOVA was performed with the within-subject factor Conditioned Type (CS+, GS1, GS2, GS3, GS4, CS−) and between-subject factor Emotion Type (fear, disgust). In order to estimate the level of confidence in online ratings, we plotted the participants' reaction times (RTs) during the acquisition phase. RTs was examined using a 2 (Emotion Type: fear, disgust) × 2 (Conditioned Stimulus Type: CS+, CS−) × 4 (Block: Acq1, Acq2, Acq3, Acq4) repeated measures ANOVA. Conditioned Stimulus Type, Block were included as within-subjects factors and Emotion Type was included as a between-subjects factor.

To better describe the generalization gradients, we modeled the responses of US expectancy ratings as Gaussian curve (Ghirlanda and Enquist, 2003). First, we standardized the response data (i.e. CS+, GS1, GS2, GS3, GS4, CS−) by subtracting the CS− value. Then we fitted the response data with a Gaussian function, $f(x) = a*\exp(-(b-x)^2/2c^2)$ by using non-linear least squares (Tuominen et al., 2019), where a corresponds to the height of the curve and c (the standard deviation) responds to the width, and b (fixed at bound, i.e., the CS+) is the location of the peak. The parameter c represents the generalization gradients, indexing the extent of fear generalization.

On the ERP level we scored P2 as the mean response between 200–300 ms (at electrode Fc1, Fcz, Fc2, F1, Fz, F2), CNV as the mean response between 600–800 ms (Fc1, FCz, Fc2, F1, Fz, F2) in acquisition phase, and CNV as the mean response between 400–600 ms (Fz, Cz, FCz) in generalization phase. Repeated measures ANOVAs were performed for the average amplitudes of P2 and CNV, respectively. Throughout our analysis, the *p* value was corrected using Bonferroni correction. All ANOVAs used the Greenhouse-Geisser correction for violations of the assumption of sphericity; in such cases, the corrected *p* value and the corrected degrees of freedom were reported. Effects were considered significant when $p < .05$.

3. Results

3.1 Demographics data

Table 1 displays demographic data (M ± SD) and anxiety and depression levels. The fear and disgust groups were adequately matched with respect to demographic and anxiety/mood data (gender, age, state anxiety, and depression).

Table 1. Demographic data

	Fear group (n = 28)	Disgust group (n = 29)
Gender	14 (50.00%)	13 (44.83%)
Age	21.07 ± 2.92	20.68 ± 2.09
STAI-S	41.41 ± 3.37	40.34 ± 2.86
BDI	6.28 ± 1.32	7.55 ± 1.51

M = mean; SD = standard deviation

Standardized questionnaires were obtained to characterize the sample according to gender, age, their levels of state anxiety (State Trait Anxiety Inventory: STAI-S) and depression (Beck Depression Inventory: BDI), as these factors were previously shown to influence the acquisition and generalization of fear (Peyrot et al., 2020; Glenn et al., 2012; Vriends et al., 2011; Waters et al., 2014).

3.2 Conditioning phase

3.2.1 Subjective expectancy ratings

The results yielded a significant main effect for Conditioned Type ($F_{(1,55)}$ = 699.192; $p < .001$, $\eta p^2 = .927$), however, no differences were observed between the fear and disgust groups (Emotion Type) ($F_{(1,55)}$ = .843; $p = .363$, $\eta p^2 = .015$). Interestingly, the interaction between these two factors was significant ($F_{(1,55)}$ = 5.876;

p = .019, ηp^2 = .097). Bonferroni corrected post-hoc analysis revealed that participants reported higher expectancy ratings of CS+ than those of CS− in both groups (Fear: [The difference of Means (DiffM) was 5.190, 95%CI (4.676; 5.70); p < .001]; Disgust: [DiffM 4.318, 95%CI (3.813; 4.823), p < .001]) . and the expectancy ratings of disgust-related CS− were higher than those of fear-related CS− [DiffM -0.570, 95%CI (-1.042; -.097); p = .019] (Figure 3 #1).

The extent between disgust generalization (c = 2.487 ± 0.224 (M ± SEM)) and fear generalization (c = 2.981 ± 0.201) was not statistically significant (t = -1.635, p = 0.108).

3.2.2. Reaction times

The main effect of Condition Type, $F_{(1,55)}$ = .338; p = .563, ηp^2= .006, the main effect of emotion type, $F_{(1,55)}$ = 1.626; p = .208, ηp^2= .029, and Condition Type × motion type interaction, $F_{(1,55)}$ = 2.133; p = .150, ηp^2= .037, were all non-significant (Figure 3 #2).

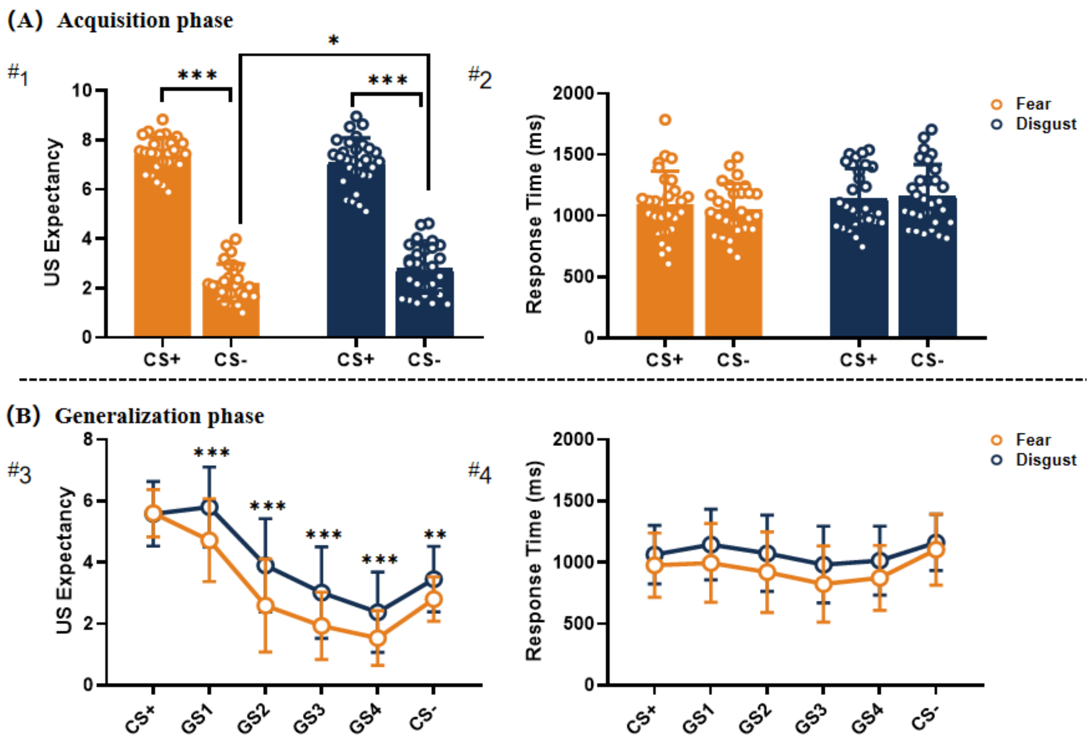

Figure 3. US expectancy ratings and mean response time were collected for each trial in the fear acquisition (A) and generalization tasks (B). Error bars represent standard mean errors. CS = conditioned stimulus; GS = generalized stimulus; US = unconditioned stimulus

On the other hand, a main effect of Block was found, $F_{(2.039,\ 112.118)} = 33.043$; $p < .001$, $\eta^2 = 0.375$. Additionally, the Block × Conditioned Stimulus Type interaction was significant, $F_{(2.505,\ 137.750)} = 5.489$, $p = 0.003$, $\eta^2 = 0.091$. Simple effect analysis showed that, for CS+, the RTs of Acq1 was longer than that of Acq2 ([DiffM 209.170, p < .001; 95%CI (103.405; 314.935)]), Acq3 ([DiffM 181.251, p < .001; 95%CI (72.953; 289.548)]) and Acq4 ([DiffM 165.572, p < .001; 95%CI (60.999; 270.145)]). For CS−, the RTs of Acq1 was larger than that of Acq2 ([DiffM 168.373, p = .001; 95%CI (57.986; 278.761)]), Acq3 ([DiffM 228.738, p < .001; 95%CI (110.017; 347.459)]) and Acq4 ([DiffM 312.096, p < .001; 95%CI (178.267; 445.924)]); Further, the RTs of Acq2 ([DiffM 143.722, p < .001; 95%CI (43.904; 243.541)]) and Acq3 ([DiffM 83.358, p = .004; 95%CI (19.993; 146.722)]) were longer than that of Acq4 (Figure 4).

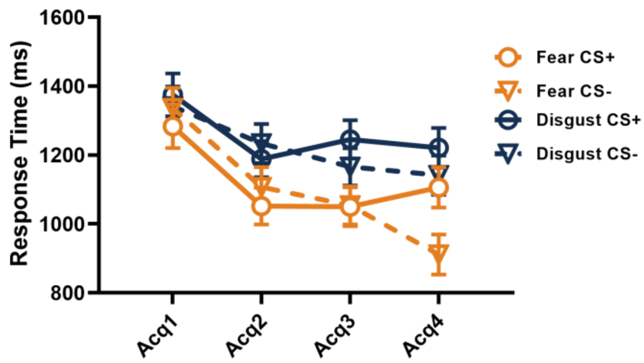

Figure 4. The time course of response time during the fear acquisition (means ± SEMs).

3.3 Generalization phase

3.3.1 Subjective expectancy ratings

The US ratings in both groups in the generalization phase exhibited a significant main effect of Conditioned Type ($F_{(2.279,125.359)} = 230.779$; $p < .001$, $\eta p^2 = .808$). Bonferroni corrected post-hoc analysis revealed that US ratings significantly differed across generalized stimuli ($p < .001$) except CS+ with GS1 and CS− with GS2 ($p > .05$) , exhibiting a gradient of generalization. Furthermore, the US ratings during generalization were characterized by a main effect of Emotion Type ($F_{(1,55)} = 9.699$; $p = .003$, $\eta p^2 = .150$) and their interaction ($F_{(2.279,125.359)} = 5.808$; $p = .003$, $\eta p^2 = .096$). Simple effect analysis showed that the five types of disgust-related GS (GS1 [DiffM .649, $p = .010$; 95%CI (.165; 1.134)]), GS2 ([DiffM 1.084, $p = .003$; 95%CI (0.381; 1.787)]), GS3 ([DiffM 1.311, p = .002; 95%CI (.505; 2.116)]), GS4 ([DiffM 1.085, $p = .003$; 95%CI (.388; 1.782)]) and CS− ([DiffM .840, $p = .007$; 95%CI (0.243; 1.437)]) were larger than those of fear-related GS (Figure 3 [#3]).

3.3.2 Reaction times

The main effects for Conditioned Type ($F_{(2.326,127.911)} = 31.704$; $p < .001$, $\eta p^2 = .366$) reached significance. Apart from GS1 with GS2, and GS4 with CS−, RTs showed an overall downward trend for those followed by Bonferroni corrected post-hoc analysis. The main effect of Emotion Type, $F_{(1,55)} = 3.042$; $p = .087$, $\eta p^2 = .052$, and the Conditioned Type by Emotion Type interaction, $F_{(2.326,127.911)} = 2.005$; $p = .078$, $\eta p^2 = .035$, were both non-significant (Figure 3 [#4]).

3.4 ERPs

3.4.1 Conditioning phase

3.4.1.1 P2

P2 was characterized by a marginal significant main effect of Conditioned Type ($F_{(1,55)} = 3.635$; $p = .062$, $\eta p^2 = .062$). Bonferroni corrected post-hoc analysis indicated that CS+ evoked an enhanced P2 amplitude during the threat learning process compared with CS−. However, the Emotion Type ($F_{(1,55)}$= .030; p = .864, ηp^2 = .001) and Conditioned Type × Emotion Type ($F_{(1,58)}$= 2.090; p = .154, ηp^2 = .037) were not significant (Figure 5).

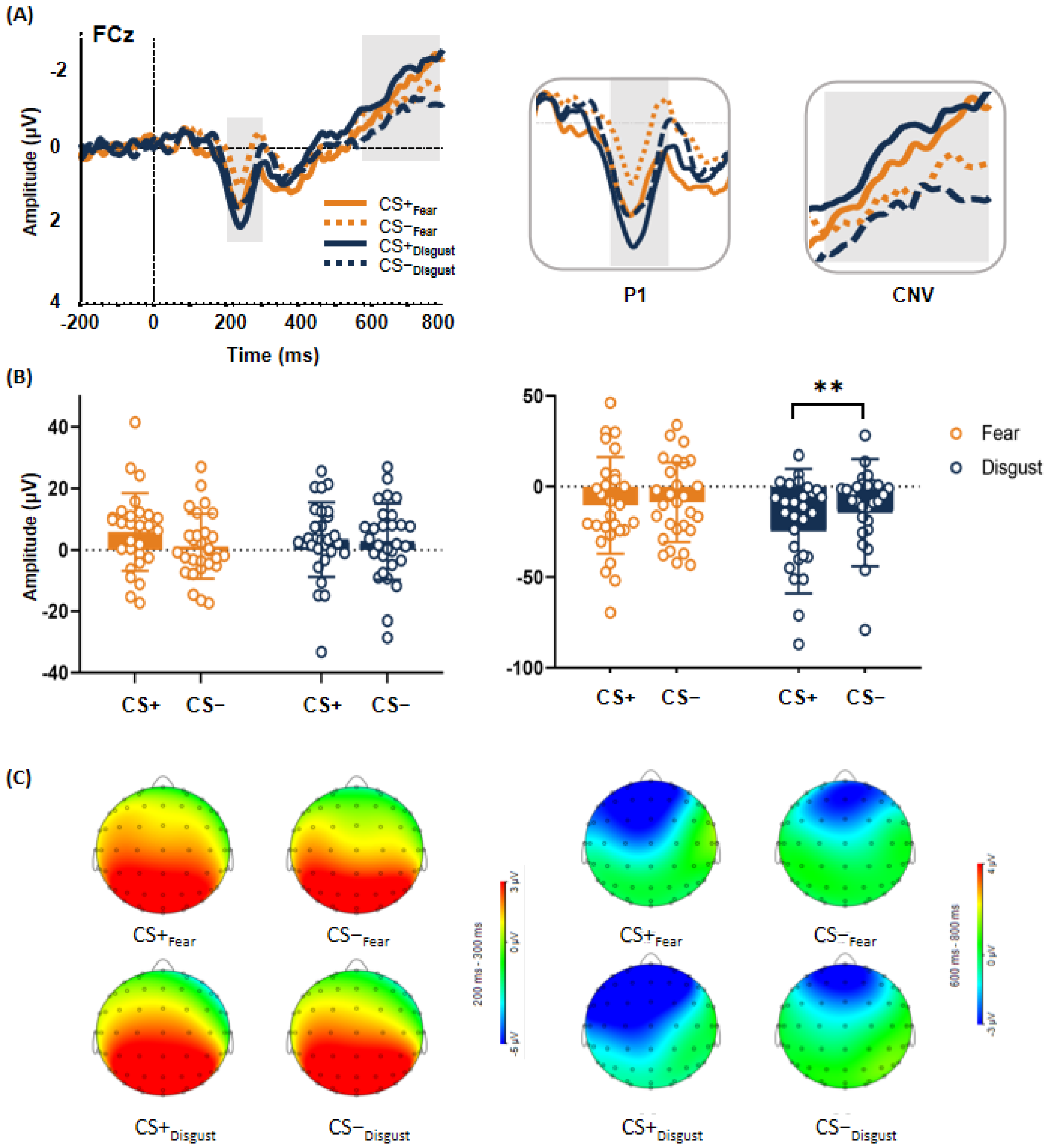

Figure 5. P2 and CNV responses during fear and disgust acquisition. (A) Stimulus-logged ERPs at FCz channels for CS+fear, CS−fear, CS+disgust, and CS−disgust conditions. (B) The averaged ERP (Fc1, Fcz, Fc2, F1, Fz, F2) of the grand average amplitude of P2 and CNV under different emotional conditions. (C) The scalp

topography of the grand average amplitude of P2 and CNV under different emotional conditions.

CNV = contingent negative variation; CS = conditioned stimulus; ERP = event-related potential

3.4.1.2 CNV

We found a significant main effect of Conditioned Type ($F_{(1,55)}$= 7.630; p = .008，ηp^2= .122) and a marginal significant interaction effect ($F_{(1,55)}$= 3.788; p = .057，ηp^2 = .064). Simple effect analysis showed that CNV amplitude was greater in response to Disgust-CS+ compared with Disgust-CS−, whereas CNV amplitudes did not differ in the late time window between the Fear-CS+ and the Fear-CS− conditions. Similarly, the CNV ERP results revealed no significant main effect of Emotion Type with CNV values ($F_{(1,55)}$= 1.932; p = .170，ηp^2= .034) (Figure 5).

3.4.2 Generalization phase

3.4.2.1 CNV

CNV analysis yielded a significant main effect of Conditioned Type ($F_{(3,165)}$= 3.459, p = .018, ηp^2= .059) and a significant interaction effect ($F_{(3,165)}$= 3.573; p = .015，ηp^2= .061). However, we did not find a significant main effect of Emotion Type ($F_{(1,55)}$= .032, p = .859, ηp^2= .001). The simple effect analysis revealed that the CNV amplitudes of GS1, GS2, GS3 and GS4 were not significantly different under the disgust condition (p > .05), but the CNV amplitude of GS1 [DiffM -7.351, p = .003; 95%CI (-12.718; -1.985)] and GS2 [DiffM -4.418, p = .032; 95%CI (-8.592; -.245)] were significantly higher than that of GS4. The difference between GS1 and GS3 was marginally significant in the fear condition. Overall, the CNV amplitude showed a generalization gradient (Figure 6).

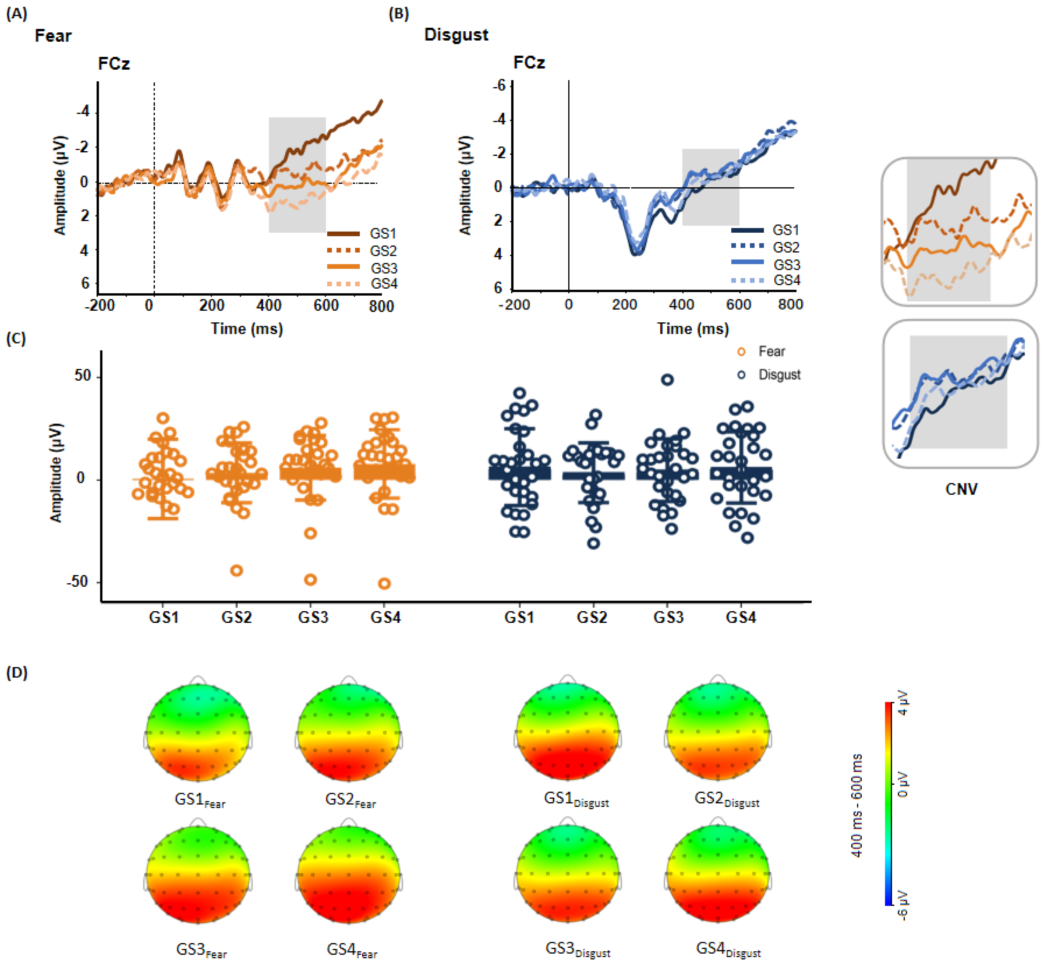

Figure 6. The CNV results during fear generalization. (A) Stimulus-logged ERPs at FCz channels for GS1, GS2, GS3, and GS4 under fear and disgust conditions. (B) The averaged ERP (Fz, Cz, FCz) of the grand average amplitude of CNV under different emotional conditions. (C) The scalp topography of the grand average amplitude of CNV under different emotional conditions.

CNV = contingent negative variation; CS = conditioned stimulus; ERP = event-related potential; GS = generalized stimulus

4. Discussion

The present study aimed at determining common and differential behavioral and neural responses during disgust and fear generalization by means of capitalizing on a multi-CS conditioning and generalization paradigm with concomitant ERP acquisition. On the behavioral level we found greater US expectancy ratings for CS+ than for CS− in both emotional domains, indicating successful acquisition of CS+-US contingencies and an effective experimental manipulation (Koban et al., 2018; Wong & Lovibond, 2017). Individuals reported elevated US expectancy ratings for disgust-CS− as compared to fear-CS−, possibly reflecting that fear induces a stronger discriminative conditioning with respect to the safety signal (CS− , Takemoto & Song, 2019), or alternatively that the fear-related CS− might show a stronger inhibition relative to disgust-relevant CS−.

In the generalization phase, the US expectancy ratings showed a gradual decline as a function of decreasing CS+ similarities across both emotion types. Ratings of US expectancy provide an index of 'subjective CS discrimination' and drive the conditioned response and associated generalization gradients (Lonsdorf et al., 2017; Harvie et al., 2017). Expectancy ratings for disgust generalization stimuli were however generally higher than for the fear generalization stimuli reflecting a stronger ratings of 'risk' for disgust than for fear. Fear may occur in response to immediate threats, perceived as a risk of injury or death, whereas disgust is an emotional response to stimuli considered distasteful or contaminative (Curtis, 2011). Although both represent defensive avoidance reactions characterized by aversive negative arousal and withdrawal, previous studies suggested that it was harder to remember contaminating vs. threatening stimuli since disgust is associated with avoidance and suppressed sensory exposure (Susskind et al., 2008). Thus, one possible explanation for this stronger rating of 'risk' in disgust in turn lead to a relatively poor accuracy of the CS memory representation. Similar stimuli were wrongly categorized to the original one, leading to a border generalization gradient (Zenses et al., 2021). The stronger US expectancy ratings in disgust could reflect an evolutionary adaptive mechanism given the often less explicit indices of pathogen contamination as compared to a direct, e.g. attack-related, threat. Together the findings underscore differential behavioral and neural signatures of fear and disgust generalization which may contribute differentially to psychiatric conditions with dysregulations in aversive avoidance mechanisms, e.g. anxiety or obsessive-compulsive disorders (Armstrong & Olatunji, 2017).

On the behavioral level, we observed that RTs gradually decreased over the learning course during acquisition, which supports the view that RTs may reflect the level of confidence (Lissek et al., 2008) with a higher confidence in the estimation of risks leading to decreasing RTs. Further, we found that decreasing RTs with decreasing similarity with the CS+ in generalization which may be explained in terms of the reinforcement rate, because the CS+-US association was 75% whereas the CS−were always presented alone (Lei et al., 2019). Several associative learning studies employed RTs to assess the associative strength between specific events and outcomes (Craddock et al., 2012). Comparing the stimuli that resemble to CS+, stimuli similar to CS− required less time to make decisions. A short RT to the outcome indicates a strong associative strength, whereas a longer RT may suggest a comparably weaker associative strength between the event and its outcome.

Regarding the ERP results in the acquisition phase, we observed increased P2 amplitude for CS+ relative to CS− irrespective of emotion type. The early modulatory effect on the P2 demonstrates an electrophysiological index of directed selective attention (Ugland et al., 2013). A similar P2 modulation effect was found in the study by Kluge et al. (2011) employing electric shock as US during a fear acquisition paradigm. Previous studies suggested that increased early P2, in response to emotionally aversive stimuli, may reflect automatic attention capture and threat-related attention biases (Lei et al., 2019; Willner et al., 2020). The enhanced P2 amplitudes for conditioned salient stimuli may index motivated attention (Zheng et al., 2019). Together the findings indicate that conditioned fear and disgust engage comparable early attentional resource engagement and salience processes. From a biological perspective, both fear and disgust require rapid defensive avoidance responses in the face of threatening stimuli, and thus early threat detection and deployment of attentional resources towards both classes of stimuli represents a critical initial step of the defensive avoidance response (Buck et al., 2018).

Associative learning describes the acquisition of stimulus-outcome contingencies and conditioned threat CS+ predicts the occurrence of the US. The CS+ could elicit an anticipation of US occurrence due to this predictive relationship (Pittig, et al., 2018). The CNV components are hypothesized to index a processes of cognitive appraisal and contingency evaluation (eg., Proulx & Picton, 1984; Regan & Howard, 1991). The current analyses showed that parietooccipital CNV amplitudes were significantly larger in response to conditioned disgust-CS+ than to disgust-CS−, which might reflect the cognitive processes of anticipation and preparation of defensive responses to a potential disgust triggering stimulus (US).

The current analyses showed that parietooccipital CNV amplitudes were significantly larger in response to conditioned disgust-CS+ than to disgust-CS−, yet interestingly the CNV amplitudes did not significantly differ for the fear-associated CS+ than CS− stimuli. Previous aversive conditioning studies using ERPs found increased CNV amplitude in response to CS+ in response to stimuli which may induce subjective feelings of fear as well as disgust (e.g. small animal pictures Regan & Howard, 1995), suggesting that biological salient threat stimuli can induce a modulation of motivated attention or sustained attention bias. The findings resonate with previous lesion and brain imaging studies suggesting common yet also separable neural responses to fear and disgust-inducing stimuli (e.g. Stark et al., 2003, 2007). Although some features of the defensive avoidance reaction in response to disgust and fear are similar other features such as the specific facial expression or the subjective experience differ. The behavioral responses may specifically differ in terms of the evolutionary function in terms of danger avoidance. Moreover, disgust may manifest in OCD with contamination fears thus suggesting differential underlying biological processes (Knowles et al., 2018). Differentiating temporal dynamics of ERPs that respond to the fear and disgust may thus represent an important neurobiological differentiation between the defensive avoidance reactions and psychiatric conditions characterized by fear versus disgust dysregulations.

Nelson at al. (2014) examined the electrodermal activity of fear generalization by using ERPs. The results revealed that LPP was more enhanced for CS+ relative to CS−, whereas it did not differ among GS, indicating that this component is not sensitive to fear generalization. Our results exhibited an overall CNV fear generalization gradient, furthermore, the GS showed an attenuated CNV effect with decreasing similarity to CS+. One possible explanation for this CNV gradient pattern was that the late-latency periods may index the fear generalization for CS+. These findings may suggest that CNV in particular may reflect anticipation of the GS-US association. As for the CNV in disgust generalization, the CNV amplitude did not differ among the GS (GS1, GS2, GS3, GS4) stimuli. This might suggest that the subtle differences between disgust generalized stimuli could not be detected by CNV. Considering the absence of adequate evidence, caution should be exercised when considering these interpretations, and further research is warranted.

Findings of the present study need to be considered in the context of limitations.

First, we applied a between-subject design to avoid cross-stimulus conditioning or extinction, and the participants were randomly assigned to fear or disgust learning groups. Thus, individual variability between groups might contribute to the findings. If one kind of CS are conditioned to fear and another kind of CS are conditioned to disgust, this limitation may be overcome in future research. Second, eye movement patterns can provide temporal accuracy measures of emotional stimuli processing. Thus, examining how fear and disgust learning affect eye tracking differently could reflect the perceptual and cognitive process in these two learned threats. Future research should consider using eye-movement methodology in conjunction with ERPs to investigate the fear versus disgust generalization pattern. Third, the pictures used in this study to manipulate the type of US were rather weak and might have impacted the results, especially for the CNV electrophysiological index. Unpleasant odors, for example Civette, which smells like feces, could be used to serve as disgust-US, however, might be difficult to match with the fear-associated stimulus. Further studies can use more disgust- or fear-evoking US instead of images to lead to a stronger CS-US association. Finally, the present work may provide implications for clinical research on fear- and disgust-associated disorders such as contamination OCD. Pathology models suggest that both, exaggerated contamination fear and heightened disgust proneness play a role in the development and maintenance of this condition (Eyal, Dar, & Liberman, 2021). The present results indicate that the underlying defensive avoidance mechanisms are – at least in healthy individuals – separable. Despite the limited generalization of the present findings to clinical populations (although see the importance for proof-of-concept studies for clinical OCD (Abramowitz et al., 2021) – future studies may examine common and separable contributions of dysregulations in these domains as potential patho- and vulnerability-mechanism for contamination OCD.

Conclusion

To summarize, both conditioned fear and disgust can create early attentional bias in eliciting P2 potentials that were larger for reinforced CS+ than for CS-, whereas disgust-related CS+ evoked greater CNV reactivity suggesting stronger sustained attention in conditioned disgust. In addition, fear and disgust differed in their generalization pattern: conditioned disgust stimuli were reported with higher US expectancy ratings, showing a stronger ratings of ‘risk’ relative to fear. Importantly, the CNV amplitude elicited in the fear generalization task differed significantly among GS, indicating that CNV components have the potential to predict the generalization of fear. Contrarily, CNV did not vary significantly across disgust-GS. Differentiating temporal dynamics of ERPs that respond to the fear and disgust conditioning process may yield contributions to the understanding of OCD.

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